UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Common and rare genomic risk factors for PTSD with implications for autoimmune disorders and inflammatory biomarkers

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Public Health (Epidemiology)

by

Adam Xavier Maihofer

Committee in Charge:

University of California San Diego
- Professor Caroline M. Nievergelt, Co-chair
- Professor Rany M. Salem
- Professor Jonathan Sebat
- Professor Murray B. Stein

San Diego State University
- Professor Richard A. Shaffer, Chair
- Professor Tianying Wu

2022

The dissertation of Adam Xavier Maihofer is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

_____

_____

_____

_____

_____

_____
Co-chair

_____
Chair

University of California San Diego

San Diego State University

2022

Dedication

This is dedicated to my friends and family.

Epigraph

All generalizations are dangerous, even this one.

Alexandre Dumas

Table of Contents

List of Supplemental Files

maihofer_chapter2_supplementary_note.docx

maihofer_chapter2_supplementary_tables.xlsx

maihofer_chapter3_supplementary_tables.xlsx

maihofer_chapter4_supplementary_tables.xlsx

List of Figures

List of Tables

Acknowledgements

I would like to thank the members of my dissertation committee for their tremendous efforts. I thank Dr. Caroline Nievergelt for inspiring me to begin my doctoral journey, and for her many years of brilliant guidance. I thank Dr. Richard Shaffer for introducing me to epidemiology and sparking my passion for this field. I thank Dr. Murray Stein for the continued encouragement he has provided me and for his stellar intellectual contributions. I thank Dr. Rany Salem for his useful insights for this work, as well as the insights he has provided over the years. I thank Dr. Jonathan Sebat for lending his expertise and in particular introducing me to the world of rare variation. I thank Dr. Tianying Wu for her many bright contributions.

I would like to acknowledge the members of my cohort, Erin Delker, Hope Ettore, Sindana Ilango, and Pedro Kremer, for the good times we shared during this process.

I would like to thank the Psychiatric Genomics Consortium - PTSD consortia for granting me access to the data used in this dissertation. As well, I thank the members of the consortia themselves for the fun, engaging collaborations we have had together.

Chapter 2 is published in Biological Psychiatry. Co-authors include Karmel W. Choi, Jonathan R.I. Coleman, Nikolaos P. Daskalakis, Christy A. Denckla, Elizabeth Ketema, Rajendra A. Morey, Renato Polimanti, Andrew Ratanatharathorn, Katy Torres, Aliza P. Wingo, Clement C. Zai, Allison E. Aiello, Lynn M. Almli, Ananda B. Amstadter, Soren B. Andersen, Ole A. Andreassen, Paul A. Arbisi, Allison E. Ashley-Koch, S. Bryn Austin, Esmina Avdibegovic, Anders D. Borglum, Dragan Babic, Marie Bµkvad-Hansen, Dewleen G. Baker, Jean C. Beckham, Laura J. Bierut, Jonathan I. Bisson, Marco P. Boks, Elizabeth A. Bolger, Bekh Bradley, Meghan Brashear, Gerome Breen, Richard A.

Bryant, Angela C. Bustamante, Jonas Bybjerg-Grauholm, Joseph R. Calabrese, JM Caldas-de-Almeida, Chia-Yen Chen, Anders M. Dale, Shareefa Dalvie, Jürgen Deckert, Douglas L. Delahanty, Michelle F. Dennis, Seth G. Disner, Katharina Domschke, Laramie E. Duncan, Alma Dzubur Kulenovic, Christopher R. Erbes, Alexandra Evans, Lindsay A. Farrer, Norah C. Feeny, Janine D. Flory, David Forbes, Carol E. Franz, Sandro Galea, Melanie E. Garrett, Aarti Gautam, Bizu Gelaye, Joel Gelernter, Elbert Geuze, Charles F. Gillespie, Aferdita Goci, Scott D. Gordon, Guia Guffanti, Rasha Hammamieh, Michael A. Hauser, Andrew C. Heath, Sian M.J. Hemmings, David Michael Hougaard, Miro Jakovljevic, Marti Jett, Eric Otto Johnson, Ian Jones, Tanja Jovanovic, Xue-Jun Qin, Karen-Inge Karstoft, Milissa L. Kaufman, Ronald C. Kessler, Alaptagin Khan, Nathan A. Kimbrel, Anthony P. King, Nastassja Koen, Henry R. Kranzler, William S. Kremen, Bruce R. Lawford, Lauren A. M. Lebois, Catrin Lewis, Israel Liberzon, Sarah D. Linnstaedt, Mark W. Logue, Adriana Lori, Bozo Lugonja, Jurjen J. Luykx, Michael J. Lyons, Jessica L. Maples-Keller, Charles Marmar, Nicholas G Martin, Maurer D, Matig R. Mavissakalian, Alexander McFarlane, Regina E. McGlinchey, Katie A. McLaughlin, Samuel A. McLean, Divya Mehta, Rebecca Mellor, Vasiliki Michopoulos, William Milberg, Mark W. Miller, Charles Phillip Morris, Ole Mors, PB Mortensen, Elliot C. Nelson, Merete Nordentoft, Sonya B. Norman, Meaghan O'Donnell, Holly K. Orcutt, Matthew S. Panizzon, Edward S. Peters, Alan L. Peterson, Matthew Peverill, Robert H. Pietrzak, Melissa A. Polusny, John P. Rice, Victoria B. Risbrough, Andrea L. Roberts, Alex O. Rothbaum, Barbara O. Rothbaum, P. Roy-Byrne, Kenneth J. Ruggiero, Ariane Rung, Bart P. F. Rutten, Nancy L Saccone, Sixto E. Sanchez, Dick Schijven, S. Seedat, Antonia V. Seligowski, Julia S. Seng, Christina M.

Sheerin, Derrick Silove, Alicia K Smith, Jordan W. Smoller, Scott R. Sponheim, Dan J. Stein, Jennifer S. Stevens, Martin H. Teicher, Wesley K. Thompson, Edward Trapido, Monica Uddin, Robert J. Ursano, Leigh Luella van den Heuvel, Miranda Van Hooff, Eric Vermetten, Christiaan Vinkers, Joanne Voisey, Yunpeng Wang, Zhewu Wang, Thomas Werge, Michelle A. Williams, Douglas E. Williamson, Sherry Winternitz, Christiane Wolf, Erika J. Wolf, Rachel Yehuda, Keith A. Young, Ross McD. Young, Hongyu Zhao, Lori A. Zoellner, Magali Haas, Heather Lasseter, Allison C. Provost, Rany M. Salem, Jonathan Sebat, Richard A. Shaffer, Tianying Wu, Stephan Ripke, Mark J. Daly, Kerry J. Ressler, Karestan C. Koenen, Murray B. Stein, and Caroline M. Nievergelt. The dissertation author was the primary investigator and author of this paper.

Chapter 3 is currently being prepared for submission for publication of the material. Co-authors include Worrawat Engchuan, Marieke Klein, Jeffrey R MacDonald, Omar Shanta, Bhooma Thiruvahindrapuram, Guillaume Huguet, Martineau Jean-louis, Zohra Saci, Sebastien Jacquemont, Stephen W Scherer, Elizabeth Ketema, , Allison E Aiello, Ananda B Amstadter, Esmina Avdibegovic, Dragan Babic, Jonathan I Bisson, Elizabeth A Bolger, Richard A Bryant, Jose Miguel Caldas-de-Almeida, Jurgen Deckert, Douglas L Delahanty, Katharina Domschke, Boadie Dunlop, Alma Dzubur-Kulenovic, Alexandra Evans, Norah C Feeny, Carol E Franz, Aarti Gautam, Aferdita Goci Uka, Rasha Hammamieh, Miro Jakovljevic, Marti Jett, Ian Jones, Milissa L Kaufman, Ronald C Kessler, Anthony P King, William S Kremen, Bruce R Lawford, Lauren A M Lebois, Catrin Lewis, Israel Liberzon, Sarah D Linnstaedt ,Bozo Lugonja, Michael J Lyons, Matig R Mavissakalian, Katie A McLaughlin, Samuel A McLean, Divya Mehta, Rebecca Mellor, Charles Phillip Morris, Seid Muhie, Holly K Orcutt, Matthew Peverill, Andrew

Ratanatharathorn, Albert Rizzo, Andrea L Roberts, Alex O Rothbaum, Barbara O Rothbaum, Peter Roy-Byrne, Kenneth J Ruggiero, Julia S Seng, Christina M Sheerin, Martin H Teicher, Robert J Ursano, Joanne Voisey, Heike Weber, Sherry Winternitz, Ruoting Yang, Ross McD Young, Lori A Zoellner, Rany M Salem, Richard Shaffer, Tianying Wu, Kerry J Ressler, Murray B Stein, Karestan C Koenen, Jonathan Sebat, and Caroline M Nievergelt. The dissertation author was the primary investigator and author of this paper.

Chapter 4 is currently being prepared for submission for publication of the material. Co-authors include Andrew Ratanatharathorn, Sian M.J. Hemmings, Vasiliki Michopoulos, Renato Polimanti, Alex O. Rothbaum, Soraya Seedat, Erika J. Wolf, Elizabeth Ketema, Rany M. Salem, Jonathan Sebat, Richard A. Shaffer, Tianying Wu, Psychiatric Genomics Consortium, Kerry J. Ressler, Murray B. Stein, Karestan C. Koenen, Jennifer A. Sumner, and Caroline M. Nievergelt. The dissertation author was the primary investigator and author of this paper.

Vita

Education

2022	**Doctor of Philosophy in Public Health (Epidemiology)** University of California San Diego | San Diego State University Joint Doctoral Program
2012	**Master of Science in Statistics (Concentration Biostatistics)** San Diego State University, San Diego, CA
2010	**Bachelor of Arts in Psychology** San Diego State University, San Diego, CA

Employment

2020-Present	**Senior Research Data Analyst III** University of California San Diego, Department of Psychiatry
2016 - 2020	**Statistician II** University of California San Diego, Department of Psychiatry
2013 - 2016	**Statistician I** University of California San Diego, Department of Psychiatry
2012 - 2013	**Staff Research Associate I** University of California San Diego, Department of Psychiatry

Teaching Experience

Dec. 2016	Instructor, *IRBO-UCT African Advanced School of Neuropsychiatric Genomics*. University of Cape Town
Aug. 2015 - Dec. 2015	Teaching assistant, *Introduction to Epidemiology.* San Diego State University

Training Courses

Jun. 2015 *Psychiatric Genetics Consortium Analyst Training Course*

Kings College, London

Honors and Awards

2021 Staff Appreciation and Recognition (STAR) Award

University of California San Diego

2014 Staff Appreciation and Recognition (STAR) Award

University of California San Diego

Peer Reviewed Publications

1. **Maihofer AX**, Choi KW, Coleman JRI, Daskalakis NP, Denckla CA, Ketema E, Morey RA, Polimanti R, Ratanatharathorn A, Torres K, Wingo AP, Zai CC, Aiello AE, Almli LM, Amstadter AB, Andersen SB, Andreassen OA, Arbisi PA, Ashley-Koch AE, Austin SB, Avdibegovic E, Borglum AD, Babic D, Bμkvad-Hansen M, Baker DG, Beckham JC, Bierut LJ, Bisson JI, Boks MP, Bolger EA, Bradley B, Brashear M, Breen G, Bryant RA, Bustamante AC, Bybjerg-Grauholm J, Calabrese JR, Caldas-de-Almeida JM, Chen C-Y, Dale AM, Dalvie S, Deckert J, Delahanty DL, Dennis MF, Disner SG, Domschke K, Duncan LE, Kulenovic AD, Erbes CR, Evans A, Farrer LA, Feeny NC, Flory JD, Forbes D, Franz CE, Galea S, Garrett ME, Gautam A, Gelaye B, Gelernter J, Geuze E, Gillespie CF, Goci A, Gordon SD, Guffanti G, Hammamieh R, Hauser MA, Heath AC, Hemmings SMJ, Hougaard DM, Jakovljevic M, Jett M, Johnson EO, Jones I, Jovanovic T, Qin X-J, Karstoft K-I, Kaufman ML, Kessler RC, Khan A, Kimbrel NA, King AP, Koen N, Kranzler HR, Kremen WS, Lawford BR, Lebois LAM, Lewis C, Liberzon I, Linnstaedt SD, Logue MW, Lori A, Lugonja B, Luykx JJ, Lyons MJ, Maples-Keller JL, Marmar C, Martin NG, Maurer D, Mavissakalian MR, McFarlane A, McGlinchey RE, McLaughlin KA, McLean SA, Mehta D, Mellor R, Michopoulos V, Milberg W, Miller MW, Morris CP, Mors O, Mortensen PB, Nelson EC, Nordentoft M, Norman SB, O'Donnell M, Orcutt HK, Panizzon MS, Peters ES, Peterson AL, Peverill M, Pietrzak RH, Polusny MA, Rice JP, Risbrough VB, Roberts AL, Rothbaum AO, Rothbaum BO, Roy-Byrne P, Ruggiero KJ, Rung A, Rutten BPF, Saccone NL, Sanchez SE, Schijven D, Seedat S, Seligowski AV, Seng JS, Sheerin CM, Silove D, Smith AK, Smoller JW, Sponheim SR, Stein DJ, Stevens JS, Teicher MH, Thompson WK, Trapido E, Uddin M, Ursano RJ, Luella van den Heuvel L, Van Hooff M, Vermetten E, Vinkers C, Voisey J, Wang Y, Wang Z, Werge T, Williams MA, Williamson DE, Winternitz S, Wolf C, Wolf EJ, Yehuda R, Young KA, Young RM, Zhao H, Zoellner LA, Haas M, Lasseter H, Provost AC, Salem RM, Sebat J, Shaffer RA, Wu T, Ripke S, Daly MJ, Ressler KJ, Koenen

KC, Stein MB, Nievergelt CM. Enhancing discovery of genetic variants for PTSD through integration of quantitative phenotypes and trauma exposure information. Biol Psychiatry. 2021. doi: https://doi.org/10.1016/j.biopsych.2021.09.020.

2. Zheng Y, Garrett ME, Sun D, Clarke-Rubright EK, Haswell CC, **Maihofer AX**, Elman JA, Franz CE, Lyons MJ, Kremen WS, Peverill M, Sambrook K, McLaughlin KA, Davenport ND, Disner S, Sponheim SR, Andrew E, Korgaonkar M, Bryant R, Varkevisser T, Geuze E, Coleman J, Beckham JC, Kimbrel NA, Sullivan D, Miller M, Hayes J, Verfaellie M, Wolf E, Salat D, Spielberg JM, Milberg W, McGlinchey R, Dennis EL, Thompson PM, Medland S, Jahanshad N, Nievergelt CM, Ashley-Koch AE, Logue MW, Morey RA. Trauma and posttraumatic stress disorder modulate polygenic predictors of hippocampal and amygdala volume. Transl Psychiatry. 2021 Dec 16;11(1):637. doi: 10.1038/s41398-021-01707-x. PMID: 34916497; PMCID: PMC8677780.

3. Weber H, **Maihofer AX**, Jaksic N, Bojic EF, Kucukalic S, Dzananovic ES, Uka AG, Hoxha B, Haxhibeqiri V, Haxhibeqiri S, Kravic N, Umihanic MM, Franc AC, Babic R, Pavlovic M, Mehmedbasic AB, Aukst-Margetic B, Kucukalic A, Marjanovic D, Babic D, Bozina N, Jakovljevic M, Sinanovic O, Avdibegović E, Agani F, Warrings B, Domschke K, Nievergelt CM, Deckert J, Dzubur-Kulenovic A, Erhardt A. Association of polygenic risk scores, traumatic life events and coping strategies with war-related PTSD diagnosis and symptom severity in the South Eastern Europe (SEE)-PTSD cohort. J Neural Transm (Vienna). 2021 Nov 27. doi: 10.1007/s00702-021-02446-5. Epub ahead of print. PMID: 34837533.

4. Federoff M, McCarthy MJ, Anand A, Berrettini WH, Bertram H, Bhattacharjee A, Calkin CV, Conroy C, Coryell WH, D'Arcangelo N, DeModena A, Fisher C, Feeder S, Frazier N, Frye MA, Gao K, Garnham J, Gershon ES, Alliey-Rodriguez N, Glazer K, Goes F, Karberg T, Harrington G, Jakobsen P, Kamali M, Kelly M, Leckband SG, Lohoff F, **Maihofer AX**, McInnis MG, Mondimore F, Morken G, Nurnberger JI, Oedegaard KJ, Ritchey M, Ryan K, Schinagle M, Schoeyen H, Schwebel C, Shaw M, Shilling PD, Slaney C, Stautland A, Tarwater B, Calabrese JR, Alda M, Nievergelt CM, Zandi PP, Kelsoe JR. Correction of depression-associated circadian rhythm abnormalities is associated with lithium response in bipolar disorder. Bipolar Disord. 2021 Nov 26. doi: 10.1111/bdi.13162. Epub ahead of print. PMID: 34825444.

5. Muniz Carvalho C, Wendt FR, Pathak GA, **Maihofer AX**, Stein DJ, Sumner JA, Hemmings SMJ, Nievergelt CM, Koenen KC, Gelernter J, Belangero SI, Polimanti R. Disentangling sex differences in the shared genetic architecture of posttraumatic stress disorder, traumatic experiences, and social support with body size and composition. Neurobiol Stress. 2021 Sep 17;15:100400. doi: 10.1016/j.ynstr.2021.100400. PMID: 34611531; PMCID: PMC8477211.

6. Sumner JA, **Maihofer AX**, Michopoulos V, Rothbaum AO, Almli LM, Andreassen OA, Ashley-Koch AE, Baker DG, Beckham JC, Bradley B, Breen G, Coleman JRI, Dale AM, Dennis MF, Feeny NC, Franz CE, Garrett ME, Gillespie CF,

Guffanti G, Hauser MA, Hemmings SMJ, Jovanovic T, Kimbrel NA, Kremen WS, Lawford BR, Logue MW, Lori A, Lyons MJ, Maples-Keller J, Mavissakalian MR, McGlinchey RE, Mehta D, Mellor R, Milberg W, Miller MW, Morris CP, Panizzon MS, Ressler KJ, Risbrough VB, Rothbaum BO, Roy-Byrne P, Seedat S, Smith AK, Stevens JS, van den Heuvel LL, Voisey J, Young RM, Zoellner LA, Nievergelt CM, Wolf EJ. Examining Individual and Synergistic Contributions of PTSD and Genetics to Blood Pressure: A Trans-Ethnic Meta-Analysis. Front Neurosci. 2021 Jun 23;15:678503. doi: 10.3389/fnins.2021.678503. PMID: 34248484; PMCID: PMC8262489.

7. Lin Y, **Maihofer AX**, Stapp E, Ritchey M, Alliey-Rodriguez N, Anand A, Balaraman Y, Berrettini WH, Bertram H, Bhattacharjee A, Calkin CV, Conroy C, Coryell W, D'Arcangelo N, DeModena A, Biernacka JM, Fisher C, Frazier N, Frye M, Gao K, Garnham J, Gershon E, Glazer K, Goes FS, Goto T, Karberg E, Harrington G, Jakobsen P, Kamali M, Kelly M, Leckband SG, Lohoff FW, Stautland A, McCarthy MJ, McInnis MG, Mondimore F, Morken G, Nurnberger JI, Oedegaard KJ, Syrstad VEG, Ryan K, Schinagle M, Schoeyen H, Andreassen OA, Shaw M, Shilling PD, Slaney C, Tarwater B, Calabrese JR, Alda M, Nievergelt CM, Zandi PP, Kelsoe JR. Clinical Predictors of Non-Response to Lithium Treatment in The Pharmacogenomics of Bipolar Disorder (PGBD) Study. Bipolar Disord. 2021 Apr 2. doi: 10.1111/bdi.13078. Epub ahead of print. PMID: 33797828.

8. Atkinson EG, **Maihofer AX**, Kanai M, Martin AR, Karczewski KJ, Santoro ML, Ulirsch JC, Kamatani Y, Okada Y, Finucane HK, Koenen KC, Nievergelt CM, Daly MJ, Neale BM. Tractor uses local ancestry to enable the inclusion of admixed individuals in GWAS and to boost power. Nat Genet. 2021 Feb;53(2):195-204. doi: 10.1038/s41588-020-00766-y. Epub 2021 Jan 18. PMID: 33462486; PMCID: PMC7867648.

9. Smith AK, Ratanatharathorn A, **Maihofer AX**, Naviaux RK, Aiello AE, Amstadter AB, Ashley-Koch AE, Baker DG, Beckham JC, Boks MP, Bromet E, Dennis M, Galea S, Garrett ME, Geuze E, Guffanti G, Hauser MA, Katrinli S, Kilaru V, Kessler RC, Kimbrel NA, Koenen KC, Kuan PF, Li K, Logue MW, Lori A, Luft BJ, Miller MW, Naviaux JC, Nugent NR, Qin X, Ressler KJ, Risbrough VB, Rutten BPF, Stein MB, Ursano RJ, Vermetten E, Vinkers CH, Wang L, Youssef NA; INTRuST Clinical Consortium; VA Mid-Atlantic MIRECC Workgroup; PGC PTSD Epigenetics Workgroup, Uddin M, Nievergelt CM. Epigenome-wide meta-analysis of PTSD across 10 military and civilian cohorts identifies methylation changes in AHRR. Nat Commun. 2020 Nov 24;11(1):5965. doi: 10.1038/s41467-020-19615-x. PMID: 33235198; PMCID: PMC7686485.

10. Clifford RE, **Maihofer AX**, Stein MB, Ryan AF, Nievergelt CM. Novel Risk Loci in Tinnitus and Causal Inference With Neuropsychiatric Disorders Among Adults of European Ancestry. JAMA Otolaryngol Head Neck Surg. 2020 Nov 1;146(11):1015-1025. doi: 10.1001/jamaoto.2020.2920. PMID: 32970095; PMCID: PMC7516809.

11. Huckins LM, Chatzinakos C, Breen MS, Hartmann J, Klengel T, da Silva Almeida AC, Dobbyn A, Girdhar K, Hoffman GE, Klengel C, Logue MW, Lori A, **Maihofer AX**, Morrison FG, Nguyen HT, Park Y, Ruderfer D, Sloofman LG, van Rooij SJH; PTSD Working Group of Psychiatric Genomics Consortium, Baker DG, Chen CY, Cox N, Duncan LE, Geyer MA, Glatt SJ, Im HK, Risbrough VB, Smoller JW, Stein DJ, Yehuda R, Liberzon I, Koenen KC, Jovanovic T, Kellis M, Miller MW, Bacanu SA, Nievergelt CM, Buxbaum JD, Sklar P, Ressler KJ, Stahl EA, Daskalakis NP. Analysis of Genetically Regulated Gene Expression Identifies a Prefrontal PTSD Gene, SNRNP35, Specific to Military Cohorts. Cell Rep. 2020 Jun 2;31(9):107716. doi: 10.1016/j.celrep.2020.107716. PMID: 32492425; PMCID: PMC7359754.

12. Burdick KE, Millett CE, Russo M, Alda M, Alliey-Rodriguez N, Anand A, Balaraman Y, Berrettini W, Bertram H, Calabrese JR, Calkin C, Conroy C, Coryell W, DeModena A, Feeder S, Fisher C, Frazier N, Frye M, Gao K, Garnham J, Gershon ES, Glazer K, Goes FS, Goto T, Harrington GJ, Jakobsen P, Kamali M, Kelly M, Leckband S, Løberg EM, Lohoff FW, **Maihofer AX**, McCarthy MJ, McInnis M, Morken G, Nievergelt CM, Nurnberger J, Oedegaard KJ, Ortiz A, Ritchey M, Ryan K, Schinagle M, Schwebel C, Shaw M, Shilling P, Slaney C, Stapp E, Tarwater B, Zandi P, Kelsoe JR. The association between lithium use and neurocognitive performance in patients with bipolar disorder. Neuropsychopharmacology. 2020 Sep;45(10):1743-1749. doi: 10.1038/s41386-020-0683-2. Epub 2020 Apr 29. PMID: 32349118; PMCID: PMC7419515.

13. Lind MJ, Brick LA, Gehrman PR, Duncan LE, Gelaye B, **Maihofer AX**, Nievergelt CM, Nugent NR, Stein MB, Amstadter AB; Psychiatric Genomics Consortium Posttraumatic Stress Disorder. Molecular genetic overlap between posttraumatic stress disorder and sleep phenotypes. Sleep. 2020 Apr 15;43(4):zsz257. doi: 10.1093/sleep/zsz257. PMID: 31802129; PMCID: PMC7157187.

14. Sheerin CM, Bountress KE, Meyers JL, Saenz de Viteri SS, Shen H, **Maihofer AX**, Duncan LE, Amstadter AB. Shared molecular genetic risk of alcohol dependence and posttraumatic stress disorder (PTSD). Psychol Addict Behav. 2020 Mar 19. doi:10.1037/adb0000568. [Epub ahead of print] PubMed PMID: 32191043.

15. Muniz Carvalho C, Wendt FR, **Maihofer AX**, Stein DJ, Stein MB, Sumner JA, Hemmings SMJ, Nievergelt CM, Koenen KC, Gelernter J, Belangero SI, Polimanti R.Dissecting the genetic association of C-reactive protein with PTSD, traumatic events, and social support. Neuropsychopharmacology. 2020 Mar 16. doi: 10.1038/s41386-020-0655-6. [Epub ahead of print] PubMed PMID: 32179874.

16. Logue MW, Miller MW, Wolf EJ, Huber BR, Morrison FG, Zhou Z, Zheng Y, Smith AK, Daskalakis NP, Ratanatharathorn A, Uddin M, Nievergelt CM, Ashley-Koch AE, Baker DG, Beckham JC, Garrett ME, Boks MP, Geuze E, Grant GA, Hauser MA, Kessler RC, Kimbrel NA, **Maihofer AX,** Marx CE, Qin XJ, Risbrough

VB, Rutten BPF, Stein MB,Ursano RJ, Vermetten E, Vinkers CH, Ware EB, Stone A, Schichman SA, McGlinchey RE, Milberg WP, Hayes JP, Verfaellie M; Traumatic Stress Brain Study Group. An epigenome-wide association study of posttraumatic stress disorder in US veterans implicates several new DNA methylation loci. Clin Epigenetics. 2020 Mar 14;12(1):46. doi: 10.1186/s13148-020-0820-0. PubMed PMID: 32171335; PubMed Central PMCID: PMC7071645.

17. Dalvie S, **Maihofer AX**, Coleman JRI, Bradley B, Breen G, Brick LA, Chen CY,Choi KW, Duncan LE, Guffanti G, Haas M, Harnal S, Liberzon I, Nugent NR, Provost AC, Ressler KJ, Torres K, Amstadter AB, Bryn Austin S, Baker DG, Bolger EA,Bryant RA, Calabrese JR, Delahanty DL, Farrer LA, Feeny NC, Flory JD, Forbes D, Galea S, Gautam A, Gelernter J, Hammamieh R, Jett M, Junglen AG, Kaufman ML, Kessler RC, Khan A, Kranzler HR, Lebois LAM, Marmar C, Mavissakalian MR, McFarlane A, Donnell MO, Orcutt HK, Pietrzak RH, Risbrough VB, Roberts AL, Rothbaum AO, Roy-Byrne P, Ruggiero K, Seligowski AV, Sheerin CM, Silove D, Smoller JW, Stein MB, Teicher MH, Ursano RJ, Van Hooff M, Winternitz S, Wolff JD, Yehuda R, Zhao H, Zoellner LA, Stein DJ, Koenen KC, Nievergelt CM. Genomic influences on self-reported childhood maltreatment. Transl Psychiatry. 2020 Jan 27;10(1):38. doi: 10.1038/s41398-020-0706-0. PubMed PMID: 32066696; PubMed Central PMCID: PMC7026037.

18. Snijders C, **Maihofer AX**, Ratanatharathorn A, Baker DG, Boks MP, Geuze E, Jain S, Kessler RC, Pishva E, Risbrough VB, Stein MB, Ursano RJ, Vermetten E, Vinkers CH; PGC PTSD EWAS Consortium, Smith AK, Uddin M, Rutten BPF, Nievergelt CM. Longitudinal epigenome-wide association studies of three male military cohorts reveal multiple CpG sites associated with post-traumatic stress disorder. ClinEpigenetics. 2020 Jan 13;12(1):11. doi: 10.1186/s13148-019-0798-7. PubMed PMID:31931860; PubMed Central PMCID: PMC6958602.

19. **Maihofer AX**, Shadyab AH, Wild RA, LaCroix AZ. Associations between Serum Levels of Cholesterol and Survival to Age 90 in Postmenopausal Women. J Am Geriatr Soc. 2020 Feb;68(2):288-296. doi: 10.1111/jgs.16306. Epub 2020 Jan 13.PubMed PMID: 31930739.

20. Lind MJ, Brick LA, Gehrman PR, Duncan LE, Gelaye B, **Maihofer AX**, Nievergelt CM, Nugent NR, Stein MB, Amstadter AB; Psychiatric Genomics Consortium Posttraumatic Stress Disorder . Molecular genetic overlap between posttraumatic stress disorder and sleep phenotypes. Sleep. 2019 Dec 5. pii: zsz257. doi:10.1093/sleep/zsz257. [Epub ahead of print] PubMed PMID: 31802129.

21. Kilaru V, Knight AK, Katrinli S, Cobb D, Lori A, Gillespie CF, **Maihofer AX**, Nievergelt CM, Dunlop AL, Conneely KN, Smith AK. Critical evaluation of copy number variant calling methods using DNA methylation. Genet Epidemiol. 2019 Nov 18. doi: 10.1002/gepi.22269. [Epub ahead of print] PubMed PMID: 31737926.

22. Nievergelt CM, **Maihofer AX**, Klengel T, Atkinson EG, Chen CY, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, Levey DF, Logue MW, Polimanti R, Provost AC, Ratanatharathorn A, Stein MB, Torres K, Aiello AE, Almli LM, Amstadter AB,Andersen SB, Andreassen OA, Arbisi PA, Ashley-Koch AE, Austin SB, Avdibegovic E, Babić D, Bækvad-Hansen M, Baker DG, Beckham JC, Bierut LJ, Bisson JI, Boks MP,Bolger EA, Børglum AD, Bradley B, Brashear M, Breen G, Bryant RA, Bustamante AC, Bybjerg-Grauholm J, Calabrese JR, Caldas-de-Almeida JM, Dale AM, Daly MJ,Daskalakis NP, Deckert J, Delahanty DL, Dennis MF, Disner SG, Domschke K,Dzubur-Kulenovic A, Erbes CR, Evans A, Farrer LA, Feeny NC, Flory JD, Forbes D,Franz CE, Galea S, Garrett ME, Gelaye B, Geuze E, Gillespie C, Uka AG, Gordon SD,Guffanti G, Hammamieh R, Harnal S, Hauser MA, Heath AC, Hemmings SMJ, HougaardDM, Jakovljevic M, Jett M, Johnson EO, Jones I, Jovanovic T, Qin XJ, Junglen AG, Karstoft KI, Kaufman ML, Kessler RC, Khan A, Kimbrel NA, King AP, Koen N,Kranzler HR, Kremen WS, Lawford BR, Lebois LAM, Lewis CE, Linnstaedt SD, Lori A, Lugonja B, Luykx JJ, Lyons MJ, Maples-Keller J, Marmar C, Martin AR, Martin NG,Maurer D, Mavissakalian MR, McFarlane A, McGlinchey RE, McLaughlin KA, McLean SA,McLeay S, Mehta D, Milberg WP, Miller MW, Morey RA, Morris CP, Mors O, Mortensen PB, Neale BM, Nelson EC, Nordentoft M, Norman SB, O'Donnell M, Orcutt HK,Panizzon MS, Peters ES, Peterson AL, Peverill M, Pietrzak RH, Polusny MA, RiceJP, Ripke S, Risbrough VB, Roberts AL, Rothbaum AO, Rothbaum BO, Roy-Byrne P,Ruggiero K, Rung A, Rutten BPF, Saccone NL, Sanchez SE, Schijven D, Seedat S,Seligowski AV, Seng JS, Sheerin CM, Silove D, Smith AK, Smoller JW, Sponheim SR, Stein DJ, Stevens JS, Sumner JA, Teicher MH, Thompson WK, Trapido E, Uddin M,Ursano RJ, van den Heuvel LL, Van Hooff M, Vermetten E, Vinkers CH, Voisey J,Wang Y, Wang Z, Werge T, Williams MA, Williamson DE, Winternitz S, Wolf C, WolfEJ, Wolff JD, Yehuda R, Young RM, Young KA, Zhao H, Zoellner LA, Liberzon I,Ressler KJ, Haas M, Koenen KC. International meta-analysis of PTSD genome-wideassociation studies identifies sex- and ancestry-specific genetic risk loci. Nat Commun. 2019 Oct 8;10(1):4558. doi: 10.1038/s41467-019-12576-w. PubMed PMID:31594949; PubMed Central PMCID: PMC6783435.

23. Acheson DT, Kwan B, **Maihofer AX**, Risbrough VB, Nievergelt CM, Clark JW, Tu XM, Irwin MR, Baker DG. Sleep disturbance at pre-deployment is a significant predictor of post-deployment re-experiencing symptoms. Eur J Psychotraumatol.2019 Oct 29;10(1):1679964. doi: 10.1080/20008198.2019.1679964. eCollection 2019. PubMed PMID: 31723377; PubMed Central PMCID: PMC6830277.

24. Greenwood TA, Lazzeroni LC, **Maihofer AX**, Swerdlow NR, Calkins ME, Freedman R, Green MF, Light GA, Nievergelt CM, Nuechterlein KH, Radant AD, Siever LJ,Silverman JM, Stone WS, Sugar CA, Tsuang DW, Tsuang MT, Turetsky BI, Gur RC, Gur RE, Braff DL. Genome-wide Association of Endophenotypes for Schizophrenia From the Consortium on the Genetics of Schizophrenia (COGS) Study. JAMA Psychiatry.2019 Oct 9. doi:

10.1001/jamapsychiatry.2019.2850. [Epub ahead of print] PubMedPMID: 31596458; PubMed Central PMCID: PMC6802253.

25. Stein MB, Choi KW, Jain S, Campbell-Sills L, Chen CY, Gelernter J, He F, Heeringa SG, **Maihofer AX**, Nievergelt C, Nock MK, Ripke S, Sun X, Kessler RC, Smoller JW, Ursano RJ. Genome-wide analyses of psychological resilience in U.S. Army soldiers. Am J Med Genet B Neuropsychiatr Genet. 2019 Jul;180(5):310-319. doi: 10.1002/ajmg.b.32730. Epub 2019 May 13. PubMed PMID: 31081985.

26. Wang Y, Karstoft KI, Nievergelt CM, **Maihofer AX**, Stein MB, Ursano RJ, Bybjerg-Grauholm J, Bækvad-Hansen M, Hougaard DM, Andreassen OA, Werge T, Thompson WK, Andersen SB. Post-traumatic stress following military deployment: Genetic associations and cross-disorder genetic correlations. J Affect Disord. 2019 Jun 1;252:350-357. doi: 10.1016/j.jad.2019.04.070. Epub 2019 Apr 9. PubMed PMID: 30999091.

27. Nudell V, Wei H, Nievergelt C, **Maihofer AX**, Shilling P, Alda M, Berrettini WH, Brennand KJ, Calabrese JR, Coryell WH, Covault JM, Frye MA, Gage F, Gershon E,McInnis MG, Nurnberger JI, Oedegaard KJ, Shekhtman T, Zandi PP, Kelsoe JR,McCarthy MJ. Entrainment of Circadian Rhythms to Temperature Reveals Amplitude Deficits in Fibroblasts from Patients with Bipolar Disorder and Possible Links to Calcium Channels. Mol Neuropsychiatry. 2019 Apr;5(2):115-124. doi:10.1159/000497354. Epub 2019 Apr 4. PubMed PMID: 31192224; PubMed Central PMCID: PMC6528084.

28. Polimanti R, Ratanatharathorn A, **Maihofer AX**, Choi KW, Stein MB, Morey RA,Logue MW, Nievergelt CM, Stein DJ, Koenen KC, Gelernter J; Psychiatric Genomics Consortium Posttraumatic Stress Disorder Working Group. Association of Economic Status and Educational Attainment With Posttraumatic Stress Disorder: A Mendelian Randomization Study. JAMA Netw Open. 2019 May 3;2(5):e193447. doi: 10.1001/jamanetworkopen.2019.3447. PubMed PMID: 31050786.

29. McCarthy MJ, Wei H, Nievergelt CM, Stautland A, **Maihofer AX**, Welsh DK,Shilling P, Alda M, Alliey-Rodriguez N, Anand A, Andreasson OA, Balaraman Y,Berrettini WH, Bertram H, Brennand KJ, Calabrese JR, Calkin CV, Claasen A, Conroy C, Coryell WH, Craig DW, D'Arcangelo N, Demodena A, Djurovic S, Feeder S, Fisher C, Frazier N, Frye MA, Gage FH, Gao K, Garnham J, Gershon ES, Glazer K, Goes F, Goto T, Harrington G, Jakobsen P, Kamali M, Karberg E, Kelly M, Leckband SG, Lohoff F, McInnis MG, Mondimore F, Morken G, Nurnberger JI, Obral S, Oedegaard KJ, Ortiz A, Ritchey M, Ryan K, Schinagle M, Schoeyen H, Schwebel C, Shaw M, Shekhtman T, Slaney C, Stapp E, Szelinger S, Tarwater B, Zandi PP, Kelsoe JR. Chronotype and cellular circadian rhythms predict the clinical response to lithium maintenance treatment in patients with bipolar disorder.Neuropsychopharmacology. 2018 Nov 16. doi: 10.1038/s41386-018-0273-8. [Epub ahead of print] PubMed PMID: 30487653.

30. Boks MP, Houtepen LC, Xu Z, He Y, Ursini G, **Maihofer AX**, Rajarajan P, Yu Q, XuH, Wu Y, Wang S, Shi JP, Hulshoff Pol HE, Strengman E, Rutten BPF, Jaffe AE,Kleinman JE, Baker DG, Hol EM, Akbarian S, Nievergelt CM, De Witte LD, Vinkers CH, Weinberger DR, Yu J, Kahn RS. Genetic vulnerability to DUSP22 promoter hypermethylation is involved in the relation between in utero famine exposure and schizophrenia. NPJ Schizophr. 2018 Aug 21;4(1):16. doi:10.1038/s41537-018-0058-4.

31. Reijnen A, Geuze E, Eekhout I, **Maihofer AX**, Nievergelt CM, Baker DG, Vermetten E. Biological profiling of plasma neuropeptide Y in relation to posttraumatic stress symptoms in two combat cohorts. Biol Psychol. 2018 Apr;134:72-79. doi: 10.1016/j.biopsycho.2018.02.008.

32. Wolf EJ, Maniates H, Nugent N, **Maihofer AX**, Armstrong D, Ratanatharathorn A, Ashley-Koch AE, Garrett M, Kimbrel NA, Lori A, Va Mid-Atlantic Mirecc Workgroup, Aiello AE, Baker DG, Beckham JC, Boks MP, Galea S, Geuze E, Hauser MA, Kessler RC, Koenen KC, Miller MW, Ressler KJ, Risbrough V, Rutten BPF, Stein MB, Ursano RJ, Vermetten E, Vinkers CH, Uddin M, Smith AK, Nievergelt CM, Logue MW. Traumatic stress and accelerated DNA methylation age: A meta-analysis. Psychoneuroendocrinology. 2017 Dec 27. pii: S0306-4530(17)31260-X. doi:10.1016/j.psyneuen.2017.12.007.

33. Moore TM, Risbrough VB, Baker DG, Larson GE, Glenn DE, Nievergelt CM, **Maihofer A**, Port AM, Jackson CT, Ruparel K, Gur RC. Effects of military service and deployment on clinical symptomatology: The role of trauma exposure and social support. J Psychiatr Res. 2017 Dec;95:121-128. doi: 10.1016/j.jpsychires.2017.08.013.

34. Polimanti R, Amstadter AB, Stein MB, Almli LM, Baker DG, Bierut LJ, Bradley B, Farrer LA, Johnson EO, King A, Kranzler HR, **Maihofer AX**, Rice JP, Roberts AL, Saccone NL, Zhao H, Liberzon I, Ressler KJ, Nievergelt CM, Koenen KC, Gelernter J; Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup. A putative causal relationship between genetically determined female body shape and posttraumatic stress disorder. Genome Med. 2017 Nov 27;9(1):99. doi:10.1186/s13073-017-0491-4.

35. Almli LM, Lori A, Meyers JL, Shin J, Fani N, **Maihofer AX**, Nievergelt CM, Smith AK, Mercer KB, Kerley K, Leveille JM, Feng H, Abu-Amara D, Flory JD, Yehuda R, Marmar CR, Baker DG, Bradley B, Koenen KC, Conneely KN, Ressler KJ. Problematic alcohol use associates with sodium channel and clathrin linker 1 (SCLT1) in trauma-exposed populations. Addict Biol. 2017 Oct 30. doi: 10.1111/adb.12569.

36. Breen MS, Tylee DS, **Maihofer AX**, Neylan TC, Mehta D, Binder E, Chandler SD, Hess JL, Kremen WS, Risbrough VB, Woelk CH, Baker DG, Nievergelt CM, Tsuang MT, Buxbaum JD, Glatt SJ. PTSD Blood Transcriptome Mega-Analysis:

Shared Inflammatory Pathways Across Biological Sex and Modes of Trauma. Neuropsychopharmacology. 2017 Sep 19. doi:10.1038/npp.2017.220.

37. Ratanatharathorn A, Boks MP, **Maihofer AX**, Aiello AE, Amstadter AB, Ashley-Koch AE, Baker DG, Beckham JC, Bromet E, Dennis M, Garrett ME, Geuze E, Guffanti G, Hauser MA, Kilaru V, Kimbrel NA, Koenen KC, Kuan PF, Logue MW, Luft BJ, Miller MW, Mitchell C, Nugent NR, Ressler KJ, Rutten BPF, Stein MB, Vermetten E, Vinkers CH, Youssef NA; VA Mid-Atlantic MIRECC Workgroup; PGC PTSD Epigenetics Workgroup, Uddin M, Nievergelt CM, Smith AK. Epigenome-wide association of PTSD from heterogeneous cohorts with a common multi-site analysis pipeline. Am J Med Genet B Neuropsychiatr Genet. 2017 Sep;174(6):619-630. doi: 10.1002/ajmg.b.32568.

38. Deslauriers J, Acheson DT, **Maihofer AX**, Nievergelt CM, Baker DG, Geyer MA, Risbrough VB; Marine Resiliency Study Team. COMT val158met polymorphism links to altered fear conditioning and extinction are modulated by PTSD and childhood trauma. Depress Anxiety. 2017 Aug 18. doi: 10.1002/da.22678.

39. Nolte IM, Munoz ML, Tragante V, Amare AT, Jansen R, Vaez A, von der Heyde B, Avery CL, Bis JC, Dierckx B, van Dongen J, Gogarten SM, Goyette P, Hernesniemi J, Huikari V, Hwang S-J, Jaju D, Kerr KF, Kluttig A, Krijthe BP, Kumar J, van der Laan SW, Lyytikäinen L-P, **Maihofer AX**, Minassian A, van der Most PJ, Müller-Nurasyid M, Nivard M, Salvi E, Stewart JD, Thayer JF, Verweij N, Wong A, Zabaneh D, Zafarmand MH, Abdellaoui A, Albarwani S, Albert C, Alonso A, Ashar F, Auvinen J, Axelsson T, Baker DG, de Bakker PIW, Barcella M, Bayoumi R, Bieringa RJ, Boomsma D, Boucher G, Britton AR, Christophersen I, Dietrich A, Ehret GB, Ellinor PT, Eskola M, Felix JF, Floras JS, Franco OH, Friberg P, Gademan MGJ, Geyer MA, Giedraitis V, Hartman CA, Hemerich D, Hofman A, Hottenga J-J, Huikuri H, Hutri-Kähönen N, Jouven X, Junttila J, Juonala M, Kiviniemi AM, Kors JA, Kumari M, Kuznetsova T, Laurie CC, Lefrandt JD, Li Y, Li Y, Liao D, Limacher MC, Lin HJ, Lindgren CM, Lubitz SA, Mahajan A, McKnight B, zu Schwabedissen HM, Milaneschi Y, Mononen N, Morris AP, Nalls MA, Navis G, Neijts M, Nikus K, North KE, O'Connor DT, Ormel J, Perz S, Peters A, Psaty BM, Raitakari OT, Risbrough VB, Sinner MF, Siscovick D, Smit JH, Smith NL, Soliman EZ, Sotoodehnia N, Staessen JA, Stein PK, Stilp AM, Stolarz-Skrzypek K, Strauch K, Sundström J, Swenne CA, Syvänen A-C, Tardif J-C, Taylor KD, Teumer A, Thornton TA, Tinker LE, Uitterlinden AG, van Setten J, Voss A, Waldenberger M, Wilhelmsen KC, Willemsen G, Wong Q, Zhang Z-M, Zonderman AB, Cusi D, Evans MK, Greiser HK, van der Harst P, Hassan M, Ingelsson E, Järvelin M-R, Kääb S, Kähönen M, Kivimaki M, Kooperberg C, Kuh D, Lehtimäki T, Lind L, Nievergelt CM, O'Donnell CJ, Oldehinkel AJ, Penninx B, Reiner AP, Riese H, van Roon AM, Rioux JD, Rotter JI, Sofer T, Stricker BH, Tiemeier H, Vrijkotte TGM, Asselbergs FW, Brundel BJJM, Heckbert SR, Whitsel EA, den Hoed M, Snieder H, de Geus EJC. Genetic loci associated with heart rate variability and their effects on cardiac disease risk. Nature Communications. 2017;8:15805. doi: 10.1038/ncomms15805

40. Rutten BPF, Vermetten E, Vinkers CH, Ursini G, Daskalakis NP, Pishva E, de Nijs L, Houtepen LC, Eijssen L, Jaffe AE, Kenis G, Viechtbauer W, van de Hove D, Schraut KG, Lesch KP, Kleinman JE, Hyde TM, Weinberger DR, Schalkwyk L, Lunnon K, Mill J, Cohen H, Yehuda R, Baker DG, **Maihofer AX**, Nievergelt CM, Geuze E, Boks MPM (2017). Longitudinal analyses of the DNA methylome in deployed military servicemen identify susceptibility loci for Post-Traumatic Stress Disorder. *Molecular Psychiatry* (accepted).

41. Duncan LE, Ratanatharathorn A, Aiello AE, Almli LM, Amstadter AB, Ashley-Koch AE, Baker DG, Beckham JC, Bierut LJ, Bisson J, Bradley B, Chen CY, Dalvie S, Farrer LA, Galea S, Garrett ME, Gelernter JE, Guffanti G, Hauser MA, Johnson EO, Kessler RC, Kimbrel NA, King A, Koen N, Kranzler HR, Logue MW, **Maihofer AX**, Martin AR, Miller MW, Morey RA, Nugent NR, Rice JP, Ripke S, Roberts AL, Saccone NL, Smoller JW, Stein DJ, Stein MB, Sumner JA, Uddin M, Ursano RJ, Wildman DE, Yehuda R, Zhao H, Daly MJ, Liberzon I, Ressler KJ, Nievergelt CM, Koenen KC. Largest GWAS of PTSD (N=20[thinsp]070) yields genetic overlap with schizophrenia and sex differences in heritability. *Mol Psychiatry*. 2017. doi: 10.1038/mp.2017.77.

42. Stein MB, Chen CY, Jain S, Jensen KP, He F, Heeringa SG, Kessler RC, **Maihofer A**, Nock MK, Ripke S, Sun X, Thomas ML, Ursano RJ, Smoller JW, Gelernter J; Army STARRS Collaborators.. Genetic risk variants for social anxiety. *Am J Med Genet B Neuropsychiatr Genet*. 2017 Mar;174(2):120-131.

43. Benyamin B, **Maihofer AX**, Schork AJ, Hamilton BA, Rao F, Schmid-Schönbein GW, Zhang K, Mahata M, Stridsberg M, Schork NJ, Biswas N, Hook VY, Wei Z, Montgomery GW, Martin NG, Nievergelt CM, Whitfield JB, O'Connor DT. Identification of novel loci affecting circulating chromogranins and related peptides. *Hum Mol Genet*. 2016 Dec 22.

44. Spector SA, Brummel SS, Nievergelt CM, **Maihofer AX**, Singh KK, Purswani MU, Williams PL, Hazra R, Van Dyke R, Seage GR 3rd; Pediatric HIVAIDS Cohort Study (PHACS). Genetically determined ancestry is more informative than self-reported race in HIV-infected and -exposed children. Medicine (Baltimore). 2016 Sep;95(36):e4733.

45. Bhatnagar V, Richard EL, Wu W, Nievergelt CM, Lipkowitz MS, Jeff J, **Maihofer AX**, Nigam SK. Analysis of ABCG2 and other urate transporters in uric acid homeostasis in chronic kidney disease: potential role of remote sensing and signaling. Clin Kidney J. 2016 Jun;9(3):444-53.

46. Biswas N, **Maihofer AX**, Mir SA, Rao F, Zhang K, Khandrika S, Mahata M, Friese RS, Hightower CM, Mahata SK, Baker DG, Nievergelt CM, Vaingankar S, O'Connor DT (2016). Polymorphisms at the F12 and KLKB1 loci have significant trait association with activation of the renin-angiotensin system. *BMC Medical Genetics.* 2016 Mar 11;17:21.

47. Stein MB, C-Y Chen, Ursano RJ, Cai T, Gelernter J, Heeringa S, Jain S, Jensen KP, **Maihofer AX**, Mitchell C, Nievergelt CM, Nock MK, Neale BM, Polimanti R, Ripke S, Sun X, Thomas ML, Wang Q, Ware EB, Borja S, Kessler RC, Smoller JW, On behalf of the Army STARRS Collaborators (2016). Genomewide Association Studies of Posttraumatic Stress Disorder in Two Cohorts of US Army Soldiers. *JAMA Psychiatry*. 2016 May 11, Published online.

48. Brummel SS, Singh KK, **Maihofer AX**, Farhad M, Qin M, Fenton T, Nievergelt CM, Spector SA. Associations of Genetically Determined Continental Ancestry with CD4+ Count and Plasma HIV-1 RNA beyond Self-Reported Race and Ethnicity. *J Acquir Immune Defic Syndr*. 2016 Apr 15;71(5):544-50.

49. Minassian A, **Maihofer AX**, Baker DG, Nievergelt CM, Geyer MA, Risbrough VB; Marine Resiliency Study Team. Association of Predeployment Heart Rate Variability With Risk of Postdeployment Posttraumatic Stress Disorder in Active-Duty Marines. *JAMA Psychiatry*. 2015 Sep 9:1-8.

50. Rao F, Schork AJ, **Maihofer AX**, Nievergelt CM, Marcovina S, Miller ER, Witztum JL, O'Connor DT, Tsimikas S (2015). Heritability of Biomarkers of Oxidized Lipoproteins: A Twin Pair Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2015 Jul:35(7):1704-11.

51. Oedegaard KJ, Alda M, Anand A, Andreassen OA, Balaraman Y, Berrettini WH,Bhattacharjee A, Brennand KJ, Burdick KE, Calabrese JR, Calkin CV, Claasen A,Coryell WH, Craig D, DeModena A, Frye M, Gage FH, Gao K, Garnham J, Gershon E,Jakobsen P, Leckband SG, McCarthy MJ, McInnis MG, **Maihofer AX**, Mertens J, Morken G, Nievergelt CM, Nurnberger J, Pham S, Schoeyen H, Shekhtman T, Shilling PD, Szelinger S, Tarwater B, Yao J, Zandi PP, Kelsoe JR. The Pharmacogenomics of Bipolar Disorder study (PGBD): identification of genes for lithium response in a prospective sample. *BMC Psychiatry*. 2016 May 5;16:129.

52. Girkin CA, Nievergelt CM, Kuo JZ, **Maihofer AX**, Carrie H, Liebmann JM, Ayyagari R, Weinreb RN, Ritch R, Zangwill LM, ADAGES Study Group (2015). Biogeographic Ancestry in the African Descent and Glaucoma Evaluation Study (ADAGES): Association with Corneal and Optic Nerve Structure. *IOVS*. 2015 Mar 5; 56(3):2043-9.

53. Breen MS, **Maihofer AX**, Glatt SJ, Tylee DS, Chandler SD, Tsuang MT, Risbrough VB, Baker DG, O'Connor DT, Nievergelt CM, Woelk CH. Gene networks specific for innate immunity define post-traumatic stress disorder. *Molecular Psychiatry*. 2015 Mar 10.

54. Zhang K, Mir SA, Hightower CM, Miramontes-Gonzalez JP, **Maihofer AX**, Chen Y, Mahata SK, Nievergelt CM, Schork NJ, Freedman BI, Vaingankar SM, O'Connor DT. Molecular mechanism for hypertensive renal disease: differential

regulation of chromogranin A expression at 3'-untranslated region polymorphism C+87T by microRNA-107. *J Am Soc Nephrol.* 2014 Nov 12.

55. Nievergelt CM, **Maihofer AX**, Mustapic M, Yurgil KA, Schork NJ, Miller MW, Logue MW, Geyer MA, Risbrough VB, O'Connor DT, Baker DG. Genomic predictors of combat stress vulnerability and resilience in U.S. Marines: a genome-wide association study across multiple ancestries implicates PRTFDC1 as a potential PTSD gene. *Psychoneuroendocrinology.* 2015 Jan;51:459-71

56. Mustapic M, **Maihofer AX,** Mahata M, Chen Y, Baker DG, O'Connor DT, and Nievergelt CM. The catecholamine biosynthetic enzyme dopamine β-hydroxylase (DBH): first genome-wide search positions trait-determining variants acting additively in the proximal promoter. *Human Molecular Genetics.* 2014.

57. Eraly SA, Nievergelt CM, **Maihofer AX,** Barkauskas DA, Biswas N, Agorastos A, O'Connor DT, Baker DG and MRS Team. Assessment of Plasma C-Reactive Protein as a Biomarker of PTSD Risk. *JAMA Psychiatry.* 2014; 71(4):423-431.

58. Nievergelt CM, **Maihofer AX,** Shekhtman T, Libiger O, Wang X, Kidd KK, Kidd JR. Inference of human continental origin and admixture proportions using a highly discriminative ancestry informative 41-SNP panel. *Investigative Genetics.* 2013; 4:13.

Symposia Presentations

- **Maihofer A** (Speaker), Choi K, Coleman J, Daskalakis N, Polimanti R, Ratanatharathorn A, Stein M, Ressler K, Koenen K, Nievergelt C. (2021). PTSD Genome-Wide Association Study Identifies Novel Loci and Informs Future Expectations. Biological Psychiatry. 89. S69-S70. 10.1016/j.biopsych.2021.02.188.

- **Maihofer A** (Speaker), Strom N, Mattheisen M, Torres K, Stein M, Ressler K, Koenen K, Nievergelt C. (2020). Refined PTSD Phenotyping Identifies Additional GWAS Risk Variants and Broader Domains Underlying Risk to Psychopathology. Biological Psychiatry. 87. S51-S52. 10.1016/j.biopsych.2020.02.156.

- **Maihofer A** (Speaker), Ratanatharathorn A, Dalvie S, Duncan L, Daly M, Ressler K, Liberzon I, Koenen K, Nievergelt C, PGC PTSD Workgroup. 'Beyond Lumping and Splitting: Leveraging Granularity in Large Scale Consortia Data to Improve Signal in PTSD' Symposium conducted at the 2019 World Congress of Psychiatric Genetics, Anaheim, CA

- **Maihofer AX** (Speaker), Coleman JRI, Duncan LE, Ratanatharathorn A, Liberzon I, Ressler KJ, Koenen KC, Nievergelt CM. 152. Taking a Closer Look at PTSD Genomics: Rare Copy Number Variants and Extended Phenotyping. Biological Psychiatry. 2019;85(10):S63. doi: 10.1016/j.biopsych.2019.03.166.

- Nievergelt C, **Maihofer A** (Speaker), Ratanatharathorn A, Dalvie S, Duncan L, Daly M, Ressler K, Liberzon I, Koenen K, PGC PTSD Workgroup. Large-scale genetic characterization of PTSD: addressing heterogeneity across ancestry, sex, and trauma. Symposium conducted at the 2018 Society of Biological Psychiatry, New York, NY.

- **Maihofer A** (Speaker), Ratanatharathorn A, Dalvie S, Duncan L, Daly M, Ressler K, Liberzon I, Koenen K, Nievergelt C, PGC PTSD Workgroup. Large scale Genome Wide Association Studies (GWAS) in PTSD across Gender, Ancestry and Trauma-type. Symposium conducted at the 2017 International Society for Traumatic Stress Studies, Chicago, Illinois.

- Nievergelt CM, **Maihofer AX,** Dalvie S, Ratanatharathorn A, Duncan L, Daly M, Ressler K, Liberzon I, Koenen K, PGC PTSD. Large-Scale Genetic Characterization of PTSD Across Ancestry, Gender and Trauma-Type. Symposium conducted at the 2017 World Congress of Psychiatric Genetics, Orlando, Florida.

- **Maihofer AX** (Speaker)**,** Duncan L, Ratanatharathorn A, Dalvie S, Martin A, Daly M, Ressler K, Liberzon I, Koenen K, Nievergelt C, PGC PTSD. SNP-Based Dissection of PTSD from Large-Scale Genome-Wide Association Studies (GWAS) across Military and Civilian Cohorts. Symposium conducted at the 2017 meeting of the Society of Biological Psychiatry, San Diego, California.

- **Maihofer A** (Speaker)**,** Shadyab A, Kritz-Silverstein D, LaCroix A**.** Are LDL and HDL cholesterol levels associated with healthy longevity in postmenopausal women? Presented at the 2017 Epidemiology Research Exchange in San Diego, California

Poster Presentations

- **Maihofer AX**, Mustapic M, Baker DG, O'Connor DT, Nievergelt CM. First GWAS in DBH confirms strong cis-acting variants and lends support for its role as an intermediate phenotype in post-traumatic stress disorder. Poster presented at the 2014 meeting of the American Society of Human Genetics, San Diego, CA.

Abstract of the dissertation

Common and rare genomic risk factors for PTSD, with implications for autoimmune disorders and inflammatory biomarkers

by

Adam Xavier Maihofer

Doctor of Philosophy in Public Health (Epidemiology)

University of California San Diego, 2022
San Diego State University, 2022

Professor Richard A. Shaffer, Chair
Professor Caroline M. Nievergelt, Co-Chair

Background: Posttraumatic stress disorder (PTSD) is a potential consequence of exposure to traumatic stress. PTSD has severe psychological, physical, interpersonal, and societal costs. The development of PTSD following traumatic stress is heritable. Studies of genetic risk factors have focused on common single nucleotide polymorphisms. The overwhelming majority of risk PTSD loci have yet to be identified.

The integration of detailed PTSD phenotyping has shown promise to increase power to identify PTSD risk loci. Rare genetic variation has only been sparsely examined in the context of PTSD, yet evidence is emerging that rare variation such as copy number variation (CNV) is relevant to psychiatric disorders. Findings of large genetic studies of PTSD and co-morbid disorders make it possible to make causal inferences and provide mechanistic insights using Mendelian Randomization (MR).

Methods: This dissertation includes three studies, all of which were conducted among participants from the Psychiatric Genomics Consortium-PTSD data collection, a consortia made to investigate genomic risk factors for PTSD through meta-analysis of PTSD cohorts. Study 1 was a GWAS of PTSD symptom scores and lifetime trauma exposure phenotypes to identify common genetic risk variation for PTSD. Study 2 was an investigation of rare CNV and PTSD. Study 3 leverages GWAS summary statistics from PTSD and inflammatory phenotypes related to PTSD, using MR to make causal inferences about PTSD and inflammatory diseases.

Results: In study one, multiple genetic risk loci were identified for PTSD and for lifetime trauma exposure, with the two traits having a substantial degree of genetic overlap. In study two, PTSD risk was elevated in CNVs that crossed over known neurodevelopmental CNV regions and pathways related to the function of the nervous system and brain. In study three, PTSD had evidence of causal effect on asthma and psoriasis, as well as inflammatory biomarkers.

Conclusion: This dissertation enhances the general field of PTSD genetics, having identified novel common and rare risk variation, and supports hypotheses that

PTSD has a causal relationship with certain comorbid diseases with an inflammatory component.

Chapter 1: Introduction

1.1 Post traumatic stress disorder (PTSD)

PTSD is a psychiatric illness that develops in response to exposure to extreme traumatic stress [1]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), PTSD is characterized by multiple symptoms that are clustered into four categories: intrusive memories, avoidance, negative changes in thinking and mood, and changes in physical and emotional reactions [2]. Diagnosis of PTSD requires exposure to a traumatic event, as well as one or more symptoms of intrusion, one or more symptoms of avoidance, two or more symptoms of negative changes in thinking and mood, and two or more symptoms of changes in arousal [2]. Symptoms must last for longer than one month, and cause considerable distress or interference with multiple areas of life [2]. While PTSD is coded as a binary diagnosis, the wide variety of symptoms imply a potentially considerable heterogeneity of PTSD [3]. As well, there is significant potential variation in symptom severity, which importantly influences the clinical trajectory of the disorder [4]. Many tools exist for PTSD assessment [5], such as the gold standard Clinician Administered PTSD Scale [6] (CAPS-5), and self-reported measures such as the PTSD checklist (PCL-5)[7].

1.2 Treatment of PTSD

There are clinical treatments for PTSD [8]. Trauma-focused therapies are a widely used, evidence based treatment option [8, 9] . Currently recommended pharmacological treatment options include anti-depressants, anti-psychotics, and alpha-adrenergic receptor blockers [9 10]. Other pharmacological treatments including anticonvulsants,

benzodiazepines, and other agents such as ketamine and cannabis, have been proposed but are not as well studied [10]. The complex relationship between PTSD and co-morbid psychiatric conditions poses challenges in the treatment of PTSD [11]. In terms of efficacy of treatments, survey data suggests that the mean time to remission is shorter for treatment seeking cases relative to those who do not seek treatment [12]. However, not all cases attain a full remission of symptoms [9]. It has been suggested that more efficacious PTSD treatments may rely on deeper understanding of the biological mechanisms of the disorder [13].

1.3 Epidemiology of PTSD

The estimated lifetime prevalence of PTSD in the United States is 5-10% [1]. Prevalence is higher in lower income countries [14]. Prevalence is widely conditional on the nature of trauma exposure [15]. Risk is modified by demographic [16], social, [16], personality [17], and biological [18] factors, which can operate at pre, peri, or post-trauma levels [19]. Importantly, interventions targeted at modifiable risk factors such as pain [20] and lack of social support [21] can reduce the likelihood of developing PTSD. Biological risk factors, including psychophysiological response, brain structure and functioning, the neuroendocrine system, and genetics, are widely studied [18] .

1.4 Co-morbidities and consequences of PTSD

PTSD is often co-morbid with one or more other psychiatric disorders [12], most commonly with affective disorders such as major depressive disorder [11]. Relative to other mental disorders, PTSD has a notably strong association with suicidal behavior [19]. PTSD is also linked to increased rates of age related chronic diseases [22], worse

physical functioning [22], and elevated rates of diseases that involve immune dysregulation [23]. In addition, there are social consequences of PTSD, such as educational failure, marital instability, and unemployment [24] [19], where PTSD related work impairments translate into billions of dollars of lost productivity [24, 25].

1.5 The link between autoimmune disorders and PTSD

Longitudinal and cross sectional association studies suggest that individuals with PTSD are at increased risk of developing autoimmune disease [26-28]. The overlap of PTSD and autoimmune diseases is hypothesized to be related to the immune dysregulation seen in PTSD cases [23]. Indeed, longitudinal studies show that inflammatory biomarkers are elevated in PTSD cases [29, 30]. However, the causal relationship between PTSD and autoimmune conditions remains unclear [31]. Determining this would enhance our general understanding of PTSD [32] and potentially lead to enhanced treatment options [33]. For instance, it has been noted that early treatment for PTSD with antidepressants is associated with attenuated risk of developing certain autoimmune diseases[27].

1.6 Genetic contributions to PTSD

Studying the genetic basis of PTSD has the potential to enhance biological understanding, as well as to guide the development of treatments for PTSD and it's comorbidities [32, 34, 35]. The genetics of PTSD has been studied for over 25 years [36]. Twin studies [36-38] suggested that genes are a major contributing factor to the development of PTSD, with heritability estimates ranging from 24%-71% across studies. This

considerable range of estimates may be due to limited sample sizes of some studies, but also perhaps due to the environment context specific nature of heritability [39].

The first consistently replicable risk loci and genetic signals for PTSD have only recently emerged, from large scale meta-analysis across multiple cohorts, and analyses of biobank-scale data [40-45]. Some of the loci identified in GWAS have been implicated in other mental disorders, possibly indicating a general shared liability across psychiatric disorders [40, 43]. The genetic pathways found to be enriched in GWAS include inflammatory pathways [41] and genes heavily expressed in the central nervous system [40]. However, the several loci identified by current PTSD GWAS only explain a small fraction of the total genetic contribution to PTSD risk, where several thousand PTSD associated genetic variants are yet to be identified by GWAS[44]. Increasing sample size is expected to lead to more loci being identified by GWAS and more biological insights being delivered [45]. It has been proposed that well powered GWAS will have a direct translational impact in the near future, as there are prospective clinical applications [46] of the polygenic risk score, i.e. the estimate of individual genetic liability to disease [47].

1.7 Further enhancing discovery power of PTSD GWAS

Detailed characterization of the PTSD phenotype is expected to enhance discovery power and elucidate biological insights [48, 49]. For example, evaluation of PTSD as a quantitative severity score led to the successful identification of risk loci, beyond what had been identified in GWAS based on a binary diagnosis [40]. Thus, this information is important to integrate into GWAS of PTSD. Less is known about how trauma exposure phenotyping affects the power of a PTSD GWAS, yet this is also a

crucial component: by definition, individuals will not develop PTSD unless they are exposed to trauma, regardless of their genetic vulnerability to PTSD. In most GWAS, trauma exposure information has not been incorporated much beyond having restricted study participants to include only trauma exposed controls [42, 50-53]. However, despite restricting controls to trauma-exposed subjects, most studies persistently have reported higher average trauma exposure in cases relative to controls. Thus, it remains to be seen what the genetics of PTSD look like, once thoroughly conditioned on trauma exposure.

In consideration of trauma exposure in the context of PTSD GWAS, there is evidence from twin studies and GWAS of a genetic basis of trauma exposure itself [37, 54-56]. The type of trauma related to PTSD vary greatly in nature, including witnessing death, sexual assault, combat exposure, suffering an accident, being in a natural disaster, et cetera [1], such that genetic influence on the different types of trauma may vary. Indeed, the estimate of the heritability of combat exposure by Lyons et al. ranged from 35 to 47% [55], but Stein et al. observed somewhat different heritabilities for assaultive and non-assaultive traumas [37]. Nevertheless, given a genetic basis for trauma exposure, trauma represents a potential intermediate factor in how genetic variants alter PTSD risk. Two recent GWAS focused on childhood trauma exposure [54, 57], and identified loci related to mental health, risky behavior, substance use, and physical health. Similarly, PTSD has substantial genetic correlations with traits in these domains [41]. Despite this evident genetic overlap, to my knowledge, there is no comparative investigation of the common variant genetics of PTSD and trauma exposure.

1.8 Rare variant contribution to PTSD

Rare and structural forms of genetic variation make considerable contributions to the genetic liability of psychiatric disorders [45]. An often studied form of rare genetic variation in this context is copy number variation (CNV) [58]. CNVs have been thoroughly implicated in relation to neurodevelopmental disorders [59], but also autism [60] and schizophrenia [61], where variants of high penetrance have been identified. For example, there is the well-known 22q11.2 deletion, where approximately 25% of individuals born with this deletion will develop schizophrenia [62], thus accounting for up to 2% of schizophrenia cases in the general population [63]. More recently, CNVs have been examined in other psychiatric disorders such as attention deficit hyperactive disorder, obsessive compulsive disorder, and major depressive disorder [64-66]. One factor that has facilitated the study of CNV for psychiatric disorders is that rare CNVs can be reliably called by applying specialized calling algorithms to the signal intensity data gathered by standard single nucleotide polymorphism arrays [67]. Thus, given the wide availability of psychiatric GWAS data, CNV is a form of rare variation that can be studied without requiring additional, potentially quite cost prohibitive sequencing efforts. Analyses of CNVs called in this manner have provided novel insights into psychiatric disorders such as major depressive disorder [66] and schizophrenia [61].

1.9 The Psychiatric Genomics Consortium (PGC) PTSD data collection

This dissertation was conducted using early-access data from the PGC-PTSD, a global collaborative effort to study the genetic basis of PTSD through meta-analysis of diverse cohorts genotyped and assessed for PTSD [34]. Data access and authorship policies follow PGC guidelines. The contributing PTSD cohorts have been described in

great detail [41]. Briefly, within each cohort, participants were assessed for PTSD via clinical assessment, clinician administered inventory, self-reported inventory, or via diagnostic codes in a medical database. Participants were genotyped using single nucleotide polymorphism arrays. Study principal investigators provided the participant PTSD phenotype and DNA or genotype data to the PGC-PTSD, or alternatively, summary statistics from GWAS. Where genotype data was provided to the PGC-PTSD, genotype data was quality controlled using a standardized pipeline [68] to insure data compatibility across cohorts. Where individual level data was not provided, investigators followed similar protocols for QC and analysis. The data from contributing cohorts was analyzed in a meta-analytic framework.

1.10 Dissertation overview

The availability of genotype and dense phenotype data in the PGC-PTSD, including continuous symptom scores and trauma exposure measures, means that several of the aforementioned topics relevant to PTSD can be investigated: First, the deep phenotyping allows for a more statistically powered investigation of common variant genetics, beyond what could be obtained by a binary case definition. The availability of trauma exposure measures in the same subjects allows for trauma exposure informed analysis of PTSD. Furthermore, it allows for the evaluation of the genetic contribution to trauma exposure itself, as well as the subsequent comparison of the genetic overlap of PTSD and trauma exposure. Second, the available genotype data, so far only used for GWAS, can also be used to estimate the contribution of CNVs to PTSD risk with unprecedented power. Lastly, risk variants identified in well-powered GWAS of PTSD can be used as genetic instruments (i.e. Mendelian Randomization

analysis [69]), allowing for the evaluation of a potential causal association between PTSD and disorders involving immune dysregulation.

The goal of this dissertation is to perform novel analyses to provide insight into the genetic architecture of PTSD, and to test mechanistic hypotheses related to the observed comorbidities between PTSD and disorders involving immune dysregulation. These analyses will be organized across three chapters. Chapter 2 includes GWAS of PTSD in PGC-PTSD cohorts. Quantitative symptom scores that measure the severity of PTSD are used to enhance discovery power beyond binary diagnosis. In addition, lifetime trauma exposure is incorporated as a phenotype to measure PTSD associations conditional on trauma exposure. Comparative evaluations of the genetics of PTSD and trauma are made. Finally, trauma exposure is leveraged in a multivariate approach to identify additional common genetic variant risk for PTSD. Chapter 3 examines the impact of rare CNV burden on PTSD in what is the first large scale study of this topic. Genotype array data is used to determine CNV carrier status. Rare CNVs are tested for association with PTSD at a variety of scales of burden, including genome-wide, across gene-sets, genes, and in individual neurodevelopmental CNVs. Chapter 4 evaluates the causal relationship between PTSD and immune related conditions and inflammatory biomarkers, via two sample Mendelian Randomization analyses of GWAS data from PTSD and these traits [70].

1.11 References

1. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, Hobfoll SE, Koenen KC, Neylan TC, Hyman SE. Post-traumatic stress disorder. Nature Reviews Disease Primers. 2015;1(1):15057. doi: 10.1038/nrdp.2015.57.

2. Diagnostic and statistical manual of mental disorders : DSM-5. American Psychiatric A, American Psychiatric Association DSMTF, editors. Arlington, VA: American Psychiatric Association; 2013.

3. Galatzer-Levy IR, Bryant RA. 636,120 Ways to Have Posttraumatic Stress Disorder. Perspectives on Psychological Science. 2013;8(6):651-62. doi: 10.1177/1745691613504115.

4. Bonanno GA, Mancini AD, Horton JL, Powell TM, LeardMann CA, Boyko EJ, Wells TS, Hooper TI, Gackstetter GD, Smith TC. Trajectories of trauma symptoms and resilience in deployed US military service members: Prospective cohort study. British Journal of Psychiatry. 2012;200(4):317-23. Epub 2018/01/02. doi: 10.1192/bjp.bp.111.096552.

5. Spoont M, Arbisi P, Fu S, Greer N, Kehle-Forbes S, Meis L, Rutks I, Wilt TJ. VA Evidence-based Synthesis Program Reports. Screening for Post-Traumatic Stress Disorder (PTSD) in Primary Care: A Systematic Review. Washington (DC): Department of Veterans Affairs (US); 2013.

6. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, Keane TM, Marx BP. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol Assess. 2018;30(3):383-95. Epub 2017/05/12. doi: 10.1037/pas0000486. PubMed PMID: 28493729 PMCID: PMCPMC5805662.

7. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Development and Initial Psychometric Evaluation. Journal of traumatic stress. 2015;28(6):489-98. Epub 2015/11/26. doi: 10.1002/jts.22059. PubMed PMID: 26606250.

8. Schrader C, Ross A. A Review of PTSD and Current Treatment Strategies. Mo Med. 2021;118(6):546-51. PubMed PMID: 34924624.

9. Watkins LE, Sprang KR, Rothbaum BO. Treating PTSD: A Review of Evidence-Based Psychotherapy Interventions. Frontiers in Behavioral Neuroscience. 2018;12(258). doi: 10.3389/fnbeh.2018.00258.

10. Ravindran LN, Stein MB. Pharmacotherapy of PTSD: Premises, principles, and priorities. Brain Research. 2009;1293:24-39. doi: https://doi.org/10.1016/j.brainres.2009.03.037.

11. Brady KT, Killeen TK, Brewerton T, Lucerini S. Comorbidity of psychiatric disorders and posttraumatic stress disorder. J Clin Psychiatry. 2000;61 Suppl 7:22-32. Epub 2000/05/05. PubMed PMID: 10795606.

12. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Archives of general psychiatry. 1995;52(12):1048-60. Epub 1995/12/01. doi: 10.1001/archpsyc.1995.03950240066012. PubMed PMID: 7492257.

13. Kelmendi B, Adams TG, Yarnell S, Southwick S, Abdallah CG, Krystal JH. PTSD: from neurobiology to pharmacological treatments. Eur J Psychotraumatol. 2016;7(1):31858. doi: 10.3402/ejpt.v7.31858.

14. Atwoli L, Stein DJ, Koenen KC, McLaughlin KA. Epidemiology of posttraumatic stress disorder: prevalence, correlates and consequences. Curr Opin Psychiatry. 2015;28(4):307-11. doi: 10.1097/YCO.0000000000000167. PubMed PMID: 26001922.

15. Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, Degenhardt L, de Girolamo G, Dinolova RV, Ferry F, Florescu S, Gureje O, Haro JM, Huang Y, Karam EG, Kawakami N, Lee S, Lepine J-P, Levinson D, Navarro-Mateu F, Pennell B-E, Piazza M, Posada-Villa J, Scott KM, Stein DJ, Ten Have M, Torres Y, Viana MC, Petukhova MV, Sampson NA, Zaslavsky AM, Koenen KC. Trauma and PTSD in the WHO World Mental Health Surveys. Eur J Psychotraumatol. 2017;8(sup5):1353383-. doi: 10.1080/20008198.2017.1353383. PubMed PMID: 29075426.

16. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. Journal of Consulting and Clinical Psychology. 2000;68(5):748-66. doi: 10.1037/0022-006X.68.5.748.

17. Ogle CM, Siegler IC, Beckham JC, Rubin DC. Neuroticism Increases PTSD Symptom Severity by Amplifying the Emotionality, Rehearsal, and Centrality of Trauma Memories. J Pers. 2017;85(5):702-15. Epub 2016/09/17. doi: 10.1111/jopy.12278. PubMed PMID: 27517170.

18. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, Milad MR, Liberzon I. Biological studies of post-traumatic stress disorder. Nature Reviews Neuroscience. 2012;13(11):769-87. doi: 10.1038/nrn3339.

19. Sareen J. Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. Can J Psychiatry. 2014;59(9):460-7. doi: 10.1177/070674371405900902. PubMed PMID: 25565692.

20. Holbrook TL, Galarneau MR, Dye JL, Quinn K, Dougherty AL. Morphine use after combat injury in Iraq and post-traumatic stress disorder. N Engl J Med. 2010;362(2):110-7. Epub 2010/01/15. doi: 10.1056/NEJMoa0903326. PubMed PMID: 20071700.

21. Zatzick D, Roy-Byrne P, Russo J, Rivara F, Droesch R, Wagner A, Dunn C, Jurkovich G, Uehara E, Katon W. A randomized effectiveness trial of stepped collaborative care for acutely injured trauma survivors. Archives of general psychiatry. 2004;61(5):498-506. Epub 2004/05/05. doi: 10.1001/archpsyc.61.5.498. PubMed PMID: 15123495.

22. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Physical health conditions associated with posttraumatic stress disorder in U.S. older adults: results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. J Am Geriatr

Soc. 2012;60(2):296-303. Epub 2012/01/27. doi: 10.1111/j.1532-5415.2011.03788.x. PubMed PMID: 22283516.

23. Hori H, Kim Y. Inflammation and post-traumatic stress disorder. Psychiatry and Clinical Neurosciences. 2019;73(4):143-53. doi: https://doi.org/10.1111/pcn.12820.

24. Brunello N, Davidson JRT, Deahl M, Kessler RC, Mendlewicz J, Racagni G, Shalev AY, Zohar J. Posttraumatic Stress Disorder: Diagnosis and Epidemiology, Comorbidity and Social Consequences, Biology and Treatment. Neuropsychobiology. 2001;43(3):150-62. doi: 10.1159/000054884.

25. McCrone P, Knapp M, Cawkill P. Posttraumatic Stress Disorder (PTSD) in the Armed Forces: Health Economic Considerations. Journal of traumatic stress. 2003;16(5):519-22. doi: 10.1023/A:1025722930935.

26. Hung YH, Cheng CM, Lin WC, Bai YM, Su TP, Li CT, Tsai SJ, Pan TL, Chen TJ, Chen MH. Post-traumatic stress disorder and asthma risk: A nationwide longitudinal study. Psychiatry Res. 2019;276:25-30. Epub 2019/04/17. doi: 10.1016/j.psychres.2019.04.014. PubMed PMID: 30991276.

27. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, Almqvist C, Fall K, Valdimarsdóttir UA. Association of Stress-Related Disorders With Subsequent Autoimmune Disease. JAMA. 2018;319(23):2388-400. doi: 10.1001/jama.2018.7028.

28. Bookwalter DB, Roenfeldt KA, LeardMann CA, Kong SY, Riddle MS, Rull RP. Posttraumatic stress disorder and risk of selected autoimmune diseases among US military personnel. BMC Psychiatry. 2020;20(1):23. doi: 10.1186/s12888-020-2432-9.

29. Lindqvist D, Mellon SH, Dhabhar FS, Yehuda R, Grenon SM, Flory JD, Bierer LM, Abu-Amara D, Coy M, Makotkine I, Reus VI, Aschbacher K, Bersani FS, Marmar CR, Wolkowitz OM. Increased circulating blood cell counts in combat-related PTSD: Associations with inflammation and PTSD severity. Psychiatry Res. 2017;258:330-6. Epub 2017/09/26. doi: 10.1016/j.psychres.2017.08.052. PubMed PMID: 28942957.

30. Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, Agorastos A, O'Connor DT, Baker DG. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA Psychiatry. 2014;71(4):423-31. Epub 2014/03/01. doi: 10.1001/jamapsychiatry.2013.4374. PubMed PMID: 24576974 PMCID: PMCPMC4032578.

31. Sumner JA, Nishimi KM, Koenen KC, Roberts AL, Kubzansky LD. Posttraumatic Stress Disorder and Inflammation: Untangling Issues of Bidirectionality. Biological Psychiatry. 2020;87(10):885-97. doi: https://doi.org/10.1016/j.biopsych.2019.11.005.

32. Neigh GN, Ali FF. Co-morbidity of PTSD and immune system dysfunction: opportunities for treatment. Curr Opin Pharmacol. 2016;29:104-10. Epub 2016/07/29. doi: 10.1016/j.coph.2016.07.011. PubMed PMID: 27479489.

33. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann N Y Acad Sci. 2004;1032:141-53. Epub 2005/01/29. doi: 10.1196/annals.1314.011. PubMed PMID: 15677401.

34. Logue MW, Amstadter AB, Baker DG, Duncan L, Koenen KC, Liberzon I, Miller MW, Morey RA, Nievergelt CM, Ressler KJ, Smith AK, Smoller JW, Stein MB, Sumner JA, Uddin M. The Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup: Posttraumatic Stress Disorder Enters the Age of Large-Scale Genomic Collaboration. Neuropsychopharmacology. 2015;40(10):2287-97. Epub 2015/04/23. doi: 10.1038/npp.2015.118. PubMed PMID: 25904361.

35. Bui E. Pharmacological treatments for PTSD: where are we in 2020? Eur J Psychotraumatol. 2021;12(sup1):1866411. doi: 10.1080/20008198.2020.1866411.

36. Duncan LE, Cooper BN, Shen H. Robust Findings From 25 Years of PTSD Genetics Research. Curr Psychiatry Rep. 2018;20(12):115-. doi: 10.1007/s11920-018-0980-1. PubMed PMID: 30350223.

37. Stein MB, Jang KL, Taylor S, Vernon PA, Livesley WJ. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. The American journal of psychiatry. 2002;159(10):1675-81. Epub 2002/10/03. doi: 10.1176/appi.ajp.159.10.1675. PubMed PMID: 12359672.

38. Sartor CE, Grant JD, Lynskey MT, McCutcheon VV, Waldron M, Statham DJ, Bucholz KK, Madden PA, Heath AC, Martin NG, Nelson EC. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. Archives of general psychiatry. 2012;69(3):293-9. Epub 2012/03/07. doi: 10.1001/archgenpsychiatry.2011.1385. PubMed PMID: 22393221 PMCID: PMCPMC3594801.

39. Haworth C, Davis O. From observational to dynamic genetics. Frontiers in Genetics. 2014;5. doi: 10.3389/fgene.2014.00006.

40. Stein MB, Levey DF, Cheng Z, Wendt FR, Harrington K, Pathak GA, Cho K, Quaden R, Radhakrishnan K, Girgenti MJ, Ho YA, Posner D, Aslan M, Duman RS, Zhao H, Polimanti R, Concato J, Gelernter J. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. Nat Genet. 2021;53(2):174-84. Epub 2021/01/30. doi: 10.1038/s41588-020-00767-x. PubMed PMID: 33510476 PMCID: PMCPMC7972521.

41. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, Levey DF, Logue MW, Polimanti R, Provost AC, Ratanatharathorn A, Stein MB, Torres K, Aiello AE, Almli LM, Amstadter AB, Andersen SB, Andreassen OA, Arbisi PA, Ashley-Koch AE, Austin SB, Avdibegovic E, Babić D, Bækvad-Hansen M, Baker DG, Beckham JC, Bierut LJ, Bisson JI, Boks MP, Bolger EA, Børglum AD, Bradley B, Brashear M, Breen G, Bryant RA, Bustamante AC, Bybjerg-Grauholm J, Calabrese JR, Caldas- de- Almeida JM, Dale AM, Daly MJ, Daskalakis NP, Deckert J, Delahanty DL, Dennis MF, Disner SG, Domschke K, Dzubur-Kulenovic A, Erbes CR, Evans A, Farrer LA, Feeny NC, Flory JD, Forbes D, Franz CE,

Galea S, Garrett ME, Gelaye B, Geuze E, Gillespie C, Uka AG, Gordon SD, Guffanti G, Hammamieh R, Harnal S, Hauser MA, Heath AC, Hemmings SMJ, Hougaard DM, Jakovljevic M, Jett M, Johnson EO, Jones I, Jovanovic T, Qin X-J, Junglen AG, Karstoft K-I, Kaufman ML, Kessler RC, Khan A, Kimbrel NA, King AP, Koen N, Kranzler HR, Kremen WS, Lawford BR, Lebois LAM, Lewis CE, Linnstaedt SD, Lori A, Lugonja B, Luykx JJ, Lyons MJ, Maples-Keller J, Marmar C, Martin AR, Martin NG, Maurer D, Mavissakalian MR, McFarlane A, McGlinchey RE, McLaughlin KA, McLean SA, McLeay S, Mehta D, Milberg WP, Miller MW, Morey RA, Morris CP, Mors O, Mortensen PB, Neale BM, Nelson EC, Nordentoft M, Norman SB, O'Donnell M, Orcutt HK, Panizzon MS, Peters ES, Peterson AL, Peverill M, Pietrzak RH, Polusny MA, Rice JP, Ripke S, Risbrough VB, Roberts AL, Rothbaum AO, Rothbaum BO, Roy-Byrne P, Ruggiero K, Rung A, Rutten BPF, Saccone NL, Sanchez SE, Schijven D, Seedat S, Seligowski AV, Seng JS, Sheerin CM, Silove D, Smith AK, Smoller JW, Sponheim SR, Stein DJ, Stevens JS, Sumner JA, Teicher MH, Thompson WK, Trapido E, Uddin M, Ursano RJ, van den Heuvel LL, Van Hooff M, Vermetten E, Vinkers CH, Voisey J, Wang Y, Wang Z, Werge T, Williams MA, Williamson DE, Winternitz S, Wolf C, Wolf EJ, Wolff JD, Yehuda R, Young RM, Young KA, Zhao H, Zoellner LA, Liberzon I, Ressler KJ, Haas M, Koenen KC. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nature Communications. 2019;10(1):4558. doi: 10.1038/s41467-019-12576-w.

42. Duncan LE, Ratanatharathorn A, Aiello AE, Almli LM, Amstadter AB, Ashley-Koch AE, Baker DG, Beckham JC, Bierut LJ, Bisson J, Bradley B, Chen CY, Dalvie S, Farrer LA, Galea S, Garrett ME, Gelernter JE, Guffanti G, Hauser MA, Johnson EO, Kessler RC, Kimbrel NA, King A, Koen N, Kranzler HR, Logue MW, Maihofer AX, Martin AR, Miller MW, Morey RA, Nugent NR, Rice JP, Ripke S, Roberts AL, Saccone NL, Smoller JW, Stein DJ, Stein MB, Sumner JA, Uddin M, Ursano RJ, Wildman DE, Yehuda R, Zhao H, Daly MJ, Liberzon I, Ressler KJ, Nievergelt CM, Koenen KC. Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. Molecular Psychiatry. 2018;23(3):666-73. doi: 10.1038/mp.2017.77.

43. Selzam S, Coleman JRI, Caspi A, Moffitt TE, Plomin R. A polygenic p factor for major psychiatric disorders. Translational Psychiatry. 2018;8(1):205. doi: 10.1038/s41398-018-0217-4.

44. Holland D, Frei O, Desikan R, Fan C-C, Shadrin AA, Smeland OB, Sundar VS, Thompson P, Andreassen OA, Dale AM. Beyond SNP heritability: Polygenicity and discoverability of phenotypes estimated with a univariate Gaussian mixture model. PLOS Genetics. 2020;16(5):e1008612. doi: 10.1371/journal.pgen.1008612.

45. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Børglum AD, Breen G, Cichon S, Edenberg HJ, Faraone SV, Gelernter J, Mathews CA, Nievergelt CM, Smoller JW, O'Donovan MC, Psychiatric Genomics C. Psychiatric Genomics: An Update and an Agenda. Am J Psychiatry. 2018;175(1):15-27. Epub 10/03. doi: 10.1176/appi.ajp.2017.17030283. PubMed PMID: 28969442.

46. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. Genome Medicine. 2020;12(1):44. doi: 10.1186/s13073-020-00742-5.

47. Choi SW, Mak TS-H, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc. 2020;15(9):2759-72. doi: 10.1038/s41596-020-0353-1.

48. Lee SH, Wray NR. Novel genetic analysis for case-control genome-wide association studies: quantification of power and genomic prediction accuracy. PloS one. 2013;8(8):e71494-e. doi: 10.1371/journal.pone.0071494. PubMed PMID: 23977056.

49. Cai N, Choi KW, Fried EI. Reviewing the genetics of heterogeneity in depression: operationalizations, manifestations and etiologies. Human Molecular Genetics. 2020;29(R1):R10-R8. doi: 10.1093/hmg/ddaa115.

50. Logue MW, Baldwin C, Guffanti G, Melista E, Wolf EJ, Reardon AF, Uddin M, Wildman D, Galea S, Koenen KC, Miller MW. A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. Molecular Psychiatry. 2013;18(8):937-42. doi: 10.1038/mp.2012.113.

51. Nievergelt CM, Maihofer AX, Mustapic M, Yurgil KA, Schork NJ, Miller MW, Logue MW, Geyer MA, Risbrough VB, O'Connor DT, Baker DG. Genomic predictors of combat stress vulnerability and resilience in U.S. Marines: A genome-wide association study across multiple ancestries implicates PRTFDC1 as a potential PTSD gene. Psychoneuroendocrinology. 2015;51:459-71. Epub 2014/12/03. doi: 10.1016/j.psyneuen.2014.10.017. PubMed PMID: 25456346.

52. Xie P, Kranzler HR, Yang C, Zhao H, Farrer LA, Gelernter J. Genome-wide association study identifies new susceptibility loci for posttraumatic stress disorder. Biological psychiatry. 2013;74(9):656-63. Epub 2013/05/28. doi: 10.1016/j.biopsych.2013.04.013. PubMed PMID: 23726511.

53. Guffanti G, Galea S, Yan L, Roberts AL, Solovieff N, Aiello AE, Smoller JW, De Vivo I, Ranu H, Uddin M, Wildman DE, Purcell S, Koenen KC. Genome-wide association study implicates a novel RNA gene, the lincRNA AC068718.1, as a risk factor for post-traumatic stress disorder in women. Psychoneuroendocrinology. 2013;38(12):3029-38. Epub 2013/10/02. doi: 10.1016/j.psyneuen.2013.08.014. PubMed PMID: 24080187 PMCID: PMCPMC3844079.

54. Dalvie S, Maihofer AX, Coleman JRI, Bradley B, Breen G, Brick LA, Chen C-Y, Choi KW, Duncan LE, Guffanti G, Haas M, Harnal S, Liberzon I, Nugent NR, Provost AC, Ressler KJ, Torres K, Amstadter AB, Bryn Austin S, Baker DG, Bolger EA, Bryant RA, Calabrese JR, Delahanty DL, Farrer LA, Feeny NC, Flory JD, Forbes D, Galea S, Gautam A, Gelernter J, Hammamieh R, Jett M, Junglen AG, Kaufman ML, Kessler RC, Khan A, Kranzler HR, Lebois LAM, Marmar C, Mavissakalian MR, McFarlane A, Donnell MO, Orcutt HK, Pietrzak RH, Risbrough VB, Roberts AL, Rothbaum AO, Roy-Byrne P, Ruggiero K, Seligowski AV, Sheerin CM, Silove D, Smoller JW, Stein MB, Teicher MH, Ursano RJ, Van Hooff M, Winternitz S, Wolff JD, Yehuda R, Zhao H, Zoellner LA, Stein DJ, Koenen KC, Nievergelt CM. Genomic influences on self-reported childhood

maltreatment. Translational Psychiatry. 2020;10(1):38. doi: 10.1038/s41398-020-0706-0.

55. Lyons MJ, Goldberg J, Eisen SA, True W, Tsuang MT, Meyer JM, Henderson WG. Do genes influence exposure to trauma? A twin study of combat. Am J Med Genet. 1993;48(1):22-7. Epub 1993/05/01. doi: 10.1002/ajmg.1320480107. PubMed PMID: 8357033.

56. Peel AJ, Purves KL, Baldwin JR, Breen G, Coleman JRI, Pingault JB, Skelton M, Ter Kuile AR, Danese A, Eley TC. Genetic and early environmental predictors of adulthood self-reports of trauma. Br J Psychiatry. 2022:1-8. Epub 2022/02/03. doi: 10.1192/bjp.2021.207. PubMed PMID: 35105391.

57. Warrier V, Kwong ASF, Luo M, Dalvie S, Croft J, Sallis HM, Baldwin J, Munafò MR, Nievergelt CM, Grant AJ, Burgess S, Moore TM, Barzilay R, McIntosh A, van Ijzendoorn MH, Cecil CAM. Gene–environment correlations and causal effects of childhood maltreatment on physical and mental health: a genetically informed approach. The Lancet Psychiatry. 2021;8(5):373-86. doi: https://doi.org/10.1016/S2215-0366(20)30569-1.

58. Ask H, Cheesman R, Jami ES, Levey DF, Purves KL, Weber H. Genetic contributions to anxiety disorders: where we are and where we are heading. Psychological Medicine. 2021;51(13):2231-46. Epub 2021/02/09. doi: 10.1017/S0033291720005486.

59. Merikangas AK, Corvin AP, Gallagher L. Copy-number variants in neurodevelopmental disorders: promises and challenges. Trends in Genetics. 2009;25(12):536-44. doi: https://doi.org/10.1016/j.tig.2009.10.006.

60. Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, Almeida J, Bacchelli E, Bader GD, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bölte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Bryson SE, Carson AR, Casallo G, Casey J, Chung BHY, Cochrane L, Corsello C, Crawford EL, Crossett A, Cytrynbaum C, Dawson G, de Jonge M, Delorme R, Drmic I, Duketis E, Duque F, Estes A, Farrar P, Fernandez BA, Folstein SE, Fombonne E, Freitag CM, Gilbert J, Gillberg C, Glessner JT, Goldberg J, Green A, Green J, Guter SJ, Hakonarson H, Heron EA, Hill M, Holt R, Howe JL, Hughes G, Hus V, Igliozzi R, Kim C, Klauck SM, Kolevzon A, Korvatska O, Kustanovich V, Lajonchere CM, Lamb JA, Laskawiec M, Leboyer M, Le Couteur A, Leventhal BL, Lionel AC, Liu X-Q, Lord C, Lotspeich L, Lund SC, Maestrini E, Mahoney W, Mantoulan C, Marshall CR, McConachie H, McDougle CJ, McGrath J, McMahon WM, Merikangas A, Migita O, Minshew NJ, Mirza GK, Munson J, Nelson SF, Noakes C, Noor A, Nygren G, Oliveira G, Papanikolaou K, Parr JR, Parrini B, Paton T, Pickles A, Pilorge M, Piven J, Ponting CP, Posey DJ, Poustka A, Poustka F, Prasad A, Ragoussis J, Renshaw K, Rickaby J, Roberts W, Roeder K, Roge B, Rutter ML, Bierut LJ, Rice JP, Salt J, Sansom K, Sato D, Segurado R, Sequeira AF, Senman L, Shah N, Sheffield VC, Soorya L, Sousa I, Stein O, Sykes N, Stoppioni V, Strawbridge C, Tancredi R, Tansey K, Thiruvahindrapduram B, Thompson AP, Thomson S, Tryfon A, Tsiantis J, Van Engeland H, Vincent JB,

Volkmar F, Wallace S, Wang K, Wang Z, Wassink TH, Webber C, Weksberg R, Wing K, Wittemeyer K, Wood S, Wu J, Yaspan BL, Zurawiecki D, Zwaigenbaum L, Buxbaum JD, Cantor RM, Cook EH, Coon H, Cuccaro ML, Devlin B, Ennis S, Gallagher L, Geschwind DH, Gill M, Haines JL, Hallmayer J, Miller J, Monaco AP, Nurnberger JI, Jr., Paterson AD, Pericak-Vance MA, Schellenberg GD, Szatmari P, Vicente AM, Vieland VJ, Wijsman EM, Scherer SW, Sutcliffe JS, Betancur C. Functional impact of global rare copy number variation in autism spectrum disorders. Nature. 2010;466(7304):368-72. Epub 2010/06/09. doi: 10.1038/nature09146. PubMed PMID: 20531469.

61. Marshall CR, Howrigan DP, Merico D, Thiruvahindrapuram B, Wu W, Greer DS, Antaki D, Shetty A, Holmans PA, Pinto D, Gujral M, Brandler WM, Malhotra D, Wang Z, Fajarado KVF, Maile MS, Ripke S, Agartz I, Albus M, Alexander M, Amin F, Atkins J, Bacanu SA, Belliveau RA, Bergen SE, Bertalan M, Bevilacqua E, Bigdeli TB, Black DW, Bruggeman R, Buccola NG, Buckner RL, Bulik-Sullivan B, Byerley W, Cahn W, Cai G, Cairns MJ, Campion D, Cantor RM, Carr VJ, Carrera N, Catts SV, Chambert KD, Cheng W, Cloninger CR, Cohen D, Cormican P, Craddock N, Crespo-Facorro B, Crowley JJ, Curtis D, Davidson M, Davis KL, Degenhardt F, Del Favero J, DeLisi LE, Dikeos D, Dinan T, Djurovic S, Donohoe G, Drapeau E, Duan J, Dudbridge F, Eichhammer P, Eriksson J, Escott-Price V, Essioux L, Fanous AH, Farh K-H, Farrell MS, Frank J, Franke L, Freedman R, Freimer NB, Friedman JI, Forstner AJ, Fromer M, Genovese G, Georgieva L, Gershon ES, Giegling I, Giusti-Rodríguez P, Godard S, Goldstein JI, Gratten J, de Haan L, Hamshere ML, Hansen M, Hansen T, Haroutunian V, Hartmann AM, Henskens FA, Herms S, Hirschhorn JN, Hoffmann P, Hofman A, Huang H, Ikeda M, Joa I, Kähler AK, Kahn RS, Kalaydjieva L, Karjalainen J, Kavanagh D, Keller MC, Kelly BJ, Kennedy JL, Kim Y, Knowles JA, Konte B, Laurent C, Lee P, Lee SH, Legge SE, Lerer B, Levy DL, Liang K-Y, Lieberman J, Lönnqvist J, Loughland CM, Magnusson PKE, Maher BS, Maier W, Mallet J, Mattheisen M, Mattingsdal M, McCarley RW, McDonald C, McIntosh AM, Meier S, Meijer CJ, Melle I, Mesholam-Gately RI, Metspalu A, Michie PT, Milani L, Milanova V, Mokrab Y, Morris DW, Müller-Myhsok B, Murphy KC, Murray RM, Myin-Germeys I, Nenadic I, Nertney DA, Nestadt G, Nicodemus KK, Nisenbaum L, Nordin A, O'Callaghan E, O'Dushlaine C, Oh S-Y, Olincy A, Olsen L, O'Neill FA, Van Os J, Pantelis C, Papadimitriou GN, Parkhomenko E, Pato MT, Paunio T, Perkins DO, Pers TH, Pietiläinen O, Pimm J, Pocklington AJ, Powell J, Price A, Pulver AE, Purcell SM, Quested D, Rasmussen HB, Reichenberg A, Reimers MA, Richards AL, Roffman JL, Roussos P, Ruderfer DM, Salomaa V, Sanders AR, Savitz A, Schall U, Schulze TG, Schwab SG, Scolnick EM, Scott RJ, Seidman LJ, Shi J, Silverman JM, Smoller JW, Söderman E, Spencer CCA, Stahl EA, Strengman E, Strohmaier J, Stroup TS, Suvisaari J, Svrakic DM, Szatkiewicz JP, Thirumalai S, Tooney PA, Veijola J, Visscher PM, Waddington J, Walsh D, Webb BT, Weiser M, Wildenauer DB, Williams NM, Williams S, Witt SH, Wolen AR, Wormley BK, Wray NR, Wu JQ, Zai CC, Adolfsson R, Andreassen OA, Blackwood DHR, Bramon E, Buxbaum JD, Cichon S, Collier DA, Corvin A, Daly MJ, Darvasi A, Domenici E, Esko T, Gejman PV, Gill M, Gurling H, Hultman CM, Iwata N, Jablensky AV, Jönsson EG, Kendler KS, Kirov G, Knight J, Levinson DF, Li QS, McCarroll SA, McQuillin A, Moran JL, Mowry BJ, Nöthen MM, Ophoff RA, Owen MJ, Palotie A, Pato CN, Petryshen TL, Posthuma D, Rietschel M, Riley BP, Rujescu D, Sklar P, St Clair D, Walters JTR, Werge T, Sullivan PF, O'Donovan MC, Scherer SW, Neale BM, Sebat J, Psychosis Endophenotypes

International C, Cnv, Schizophrenia Working Groups of the Psychiatric Genomics C. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nature genetics. 2017;49(1):27-35. doi: 10.1038/ng.3725.

62. Van L, Boot E, Bassett AS. Update on the 22q11.2 deletion syndrome and its relevance to schizophrenia. Curr Opin Psychiatry. 2017;30(3).

63. Bassett AS, Scherer SW, Brzustowicz LM. Copy number variations in schizophrenia: critical review and new perspectives on concepts of genetics and disease. Am J Psychiatry. 2010;167(8):899-914. Epub 2010/05/03. doi: 10.1176/appi.ajp.2009.09071016. PubMed PMID: 20439386.

64. Zarrei M, Burton CL, Engchuan W, Young EJ, Higginbotham EJ, MacDonald JR, Trost B, Chan AJS, Walker S, Lamoureux S, Heung T, Mojarad BA, Kellam B, Paton T, Faheem M, Miron K, Lu C, Wang T, Samler K, Wang X, Costain G, Hoang N, Pellecchia G, Wei J, Patel RV, Thiruvahindrapuram B, Roifman M, Merico D, Goodale T, Drmic I, Speevak M, Howe JL, Yuen RKC, Buchanan JA, Vorstman JAS, Marshall CR, Wintle RF, Rosenberg DR, Hanna GL, Woodbury-Smith M, Cytrynbaum C, Zwaigenbaum L, Elsabbagh M, Flanagan J, Fernandez BA, Carter MT, Szatmari P, Roberts W, Lerch J, Liu X, Nicolson R, Georgiades S, Weksberg R, Arnold PD, Bassett AS, Crosbie J, Schachar R, Stavropoulos DJ, Anagnostou E, Scherer SW. A large data resource of genomic copy number variation across neurodevelopmental disorders. npj Genomic Medicine. 2019;4(1):26. doi: 10.1038/s41525-019-0098-3.

65. Martin J, Tammimies K, Karlsson R, Lu Y, Larsson H, Lichtenstein P, Magnusson PKE. Copy number variation and neuropsychiatric problems in females and males in the general population. Am J Med Genet B Neuropsychiatr Genet. 2019;180(6):341-50. Epub 2018/10/11. doi: 10.1002/ajmg.b.32685. PubMed PMID: 30307693.

66. Kendall KM, Rees E, Bracher-Smith M, Legge S, Riglin L, Zammit S, O'Donovan MC, Owen MJ, Jones I, Kirov G, Walters JTR. Association of Rare Copy Number Variants With Risk of Depression. JAMA Psychiatry. 2019;76(8):818-25. doi: 10.1001/jamapsychiatry.2019.0566.

67. Lin C-F, Naj AC, Wang L-S. Analyzing copy number variation using SNP array data: protocols for calling CNV and association tests. Curr Protoc Hum Genet. 2013;79:Unit-1.27. doi: 10.1002/0471142905.hg0127s79. PubMed PMID: 24510649.

68. Lam M, Awasthi S, Watson HJ, Goldstein J, Panagiotaropoulou G, Trubetskoy V, Karlsson R, Frei O, Fan CC, De Witte W, Mota NR, Mullins N, Brügger K, Lee SH, Wray NR, Skarabis N, Huang H, Neale B, Daly MJ, Mattheisen M, Walters R, Ripke S. RICOPILI: Rapid Imputation for COnsortias PIpeLIne. Bioinformatics. 2020;36(3):930-3. Epub 2019/08/09. doi: 10.1093/bioinformatics/btz633. PubMed PMID: 31393554.

69. Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. Journal of the American Society of Nephrology. 2016;27(11):3253. doi: 10.1681/ASN.2016010098.

70. Ye J, Gillespie KM, Rodriguez S. Unravelling the Roles of Susceptibility Loci for Autoimmune Diseases in the Post-GWAS Era. Genes. 2018;9(8). doi: 10.3390/genes9080377.

Chapter 2. Enhancing discovery of genetic variants for PTSD through integration of quantitative phenotypes and trauma exposure information

2.1 Abstract

Background: Posttraumatic stress disorder (PTSD) is heritable and a potential consequence of exposure to traumatic stress. Evidence suggests that a quantitative approach to PTSD phenotype measurement and incorporation of lifetime trauma exposure (LTE) information could enhance the discovery power of PTSD genome-wide association studies (GWAS).

Methods: GWAS on PTSD symptoms was performed in 51 cohorts followed by a fixed-effects meta-analysis (N = 182,199 European Ancestry participants). A GWAS of LTE burden was performed in the UK Biobank cohort (N = 132,988). Genetic correlations were evaluated with LD-score regression. Multivariate analysis was performed using Multi-Trait Analysis of GWAS. Functional mapping and annotation of leading loci was performed with FUMA. Replication was evaluated using the Million Veteran Program (MVP) GWAS of PTSD total symptoms.

Results: GWAS of PTSD symptoms and LTE burden identified 5 and 6 independent genome-wide significant loci, respectively. There was a 72% genetic correlation between PTSD and LTE. PTSD and LTE showed largely similar patterns of genetic correlation with other traits, albeit with some distinctions. Adjusting PTSD for LTE reduced PTSD heritability by 31%. Multivariate analysis of PTSD and LTE increased the effective sample size of the PTSD GWAS by 20% and identified 4 additional loci. Four out of these 9 PTSD loci were independently replicated in MVP.

Conclusion: Through using a quantitative trait measure of PTSD, we identify novel risk loci not previously identified using prior case/control analyses. PTSD and LTE have a high genetic overlap that can be leveraged to increase discovery power through multivariate methods.

2.2 Introduction

Posttraumatic stress disorder (PTSD) may develop after exposure to traumatic life events. PTSD can severely impact the mental and physical health of affected individuals and impair their interpersonal relationships[1]. While the estimated community prevalence of PTSD in the United States is 5-10%[2], the rate of PTSD differs based on the nature of trauma exposure[3], and other environmental[4] and genetic factors[5-7]. Identifying the biological mechanisms associated with the etiology of PTSD will facilitate the discovery of biomarkers for screening and diagnostic purposes[7] and the development of new treatments.

Genome-wide association studies (GWAS) facilitate biological understanding of PTSD [8, 9], but are well known to be limited by statistical power to identify risk variation[10]. Quantitative measures of PTSD enhance discovery power over binary trait definitions [9,11]. Appropriately accounting for trauma exposure hypothetically enhances power, as individuals will not develop the disorder unless they are exposed to trauma, irrespective of high genetic vulnerability for PTSD [12, 13]. Moreover, the notion that genetic variants can predispose to trauma exposure is only starting to be explored [14]. As trauma exposure is a prerequisite for the development and manifestation of PTSD, investigating the genetics of trauma exposure will hypothetically lead to a clearer picture of PTSD genetics.

The Psychiatric Genomics Consortium (PGC) PTSD is a global collaborative effort to study the genetic basis of PTSD through meta-analysis of diverse cohorts[13]. Subsequent to a case-control GWAS[8], our collaborators have provided quantitative measures of PTSD and lifetime trauma exposure (LTE). To obtain genomic insights

from the quantitative PTSD phenotyping, we perform GWAS of PTSD symptoms in 182,199 participants from PGC-PTSD Freeze 2. To determine if accounting for LTE would provide the hypothesized increase in discovery power, we perform GWAS of PTSD with covariate adjustment for LTE, showing that it *lowers* PTSD signal. We investigate the possibility that multicollinearity arising from high genetic correlation (r_g) of PTSD and LTE was responsible for this result. To perform this investigation, we perform GWAS of LTE in most powered and unbiased [15] subsample of the data, 132,988 participants from the UK Biobank (UKBB) [16], then evaluate the r_g of PTSD and LTE. To explore the r_g further, we contrast the r_gs PTSD and LTE have with other traits. We show the high r_g of PTSD and LTE can be leveraged to enhance the power of PTSD GWAS using multivariate methods. We replicate PTSD GWAS findings in the Million Veteran Program GWAS of total PTSD symptoms (MVP_{TOT}). We contextualize genomic findings through functional annotation, tissue expression analyses, and phenome-wide association study (PheWAS).

2.3 Methods

2.3.1 Study population and phenotyping

Participants were drawn from a collection of 51 cohorts within the PGC-PTSD freeze 2 dataset, as previously described in Nievergelt et al.[8]. All participants included in the present study were of genetically estimated European ancestry. PTSD symptoms and LTE were measured within each cohort using structured clinical interviews, self-reported inventories, or by clinical evaluation. A summary of the assessment and scoring methods for the various studies is in Supplementary Table 2.1 and a complete description is available in Nievergelt et al.[8]. All participants provided written informed

consent and studies were approved by the relevant institutional review boards and the UCSD Human Research Protection Program (protocol #16097×).

2.3.2 GWAS Quality Control

Genotyping, QC, and imputation methods for the included studies have been described in detail[8]. In brief, participating cohorts provided phenotype and genotype data or GWAS summary statistics to the PGC-PTSD for quality control and analysis. For studies in which the PGC-PTSD analyst had direct access to genotype data, the RICOPILI pipeline[17] was used to perform QC and imputation. QC included standard filters for SNP call rates (exclusion of SNPs with call rate <98% or a missing difference > 0.02 between cases and controls), call rate for participant genotypes (samples with <98% call rate excluded), Hardy-Weinberg equilibrium (HWE $p < 1 \times 10^{-6}$ in controls), and heterozygosity (FHET within +/- 0.2). Datasets were phased using SHAPEIT[18] and imputed using IMPUTE2[19] with the 1000 Genomes Phase 3 reference panel data[20]. For the UKBB, quality control and imputation were carried out centrally by UKBB investigators as previous described[16] and GWAS was carried out by the PGC-PTSD analyst. For cohorts with data sharing restrictions, analyses were performed using similar protocols by the study team that had individual level data access and GWAS summary statistics were provided to the PGC-PTSD.

2.3.3 GWAS

Only unrelated ($\pi < 0.2$) participants were retained for analysis. Principal components were calculated within each cohort using EIGENSOFT v6.3.4[21]. PTSD GWAS was performed within cohorts using PLINK 2.0 alpha with the --glm option, with the exception of UKBB and VETSA data, which were analyzed using BOLT LMM

v2.3.4[22]. Where available, PTSD symptom scores were analyzed using linear regression (N = 36 cohorts); PTSD case/control status was used if symptom scores were not available, using logistic regression (N = 15 cohorts). In both cases, 5 principal components (PCs) were included as covariates to account for population stratification and genotyping artifacts. The UKBB PTSD GWAS included an additional PC as well as batch and assessment center covariates. Studies providing summary data used similar analytic strategies, as previously described [8]. For each GWAS, SNPs with minor allele frequency < 1% or imputation information score < 0.6 were excluded. To perform GWAS of PTSD conditioned on LTE, GWAS was performed with LTE included as an additional covariate where, depending on data availability, as either a count of LTEs or a binary variable. GWAS of the LTE count phenotype in the UKBB sample was performed in BOLT-LMM using 6 PCs, batch, and assessment center as covariates.

2.3.4 PTSD meta-analysis

Sample-size weighted fixed effects meta-analysis was performed using METAL[23]. To account for different analytic methods and measure scales, effect estimates were converted into z-scores by dividing effect sizes by standard errors [24]. Case/control and quantitative GWAS subsets were evaluated for r_g to determine if they could be meta-analyzed. To account for differences in ascertainment, heritability, and power between case/control and quantitative subsets, modified sample size weights were derived as previously described [25], assuming 10% population prevalence of PTSD, the estimates of SNP-based heritability (h^2_{SNP}), r_g, and sample PTSD prevalence. Meta-analysis was conducted on the reweighted z-scores. Only SNPs available in >90% of all

samples (N $\geq$ 163,979) were included in analyses. Regional annotation plots of genome-wide significant loci were produced using LocusZoom[26].

2.3.5 Heritability and genetic correlation estimation with LD Score Regression (LDSC)

Trait h^2_{SNP} and r_g were estimated from GWAS summary statistics using LDSC[27]. The LDSC intercept was used to test for inflation of test statistics due to residual population stratification or other artefacts and the attenuation factor ((Intercept - 1)/(mean(χ^2)-1) was used to determine the proportion of inflation of test statistics due to residual population stratification (Supplementary Table 2.2). Heritabilities were contrasted using a z-test where standard errors were estimated using the block-jackknife approach. To estimate r_g with other disorders, the LDhub web-interface was used[28]. To identify genetic differences between PTSD and LTE, the r_gs observed for PTSD and LTE were contrasted using z-tests, where significance level was determined using Bonferroni correction for the 772 traits tested ($p < 6.47x10^{-5}$).

2.3.6 Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA)

FUMA version v1.3.6a[29] was used with the default settings (Supplementary Text) to visualize and annotate GWAS results. The FUMA pipeline integrates the MAGMA[30] tool to perform gene-based, gene-pathway, and tissue enrichment analyses, with significance based on Bonferroni correction. 1000 Genomes Europeans were used as reference genotypes. Tissue enrichment analysis included GTEx v8 expression data[31].

2.3.7 Cis Quantitative Trait Locus (QTL) mapping

The effects of GWAS loci on transcriptomic regulation of surrounding genes (locus within ± 1 Mb of the gene transcription starting site) were tested for 49 tissues in

GTEx v8 with genome-wide false discovery rate correction applied. Using the same criteria, GTEx v8 data were also used to investigate the effects of GWAS loci on the regulation of alternative splicing isoforms. A detailed description regarding GTEx v8 QTL mapping data is available at[32]. Briefly, cis-eQTL and cis-splicing QTL mapping was performed using FastQTL[33] including top-five genotyping PCs, PEER (Probabilistic Estimation of Expression Residuals) factors[34], sequencing platform, sequencing protocol, and sex as covariates.

2.3.8 Replication analysis

Summary data from MVP_{TOT} (dbGaP Study Accession phs001672.v4.p1) was used to replicate GWAS results. MVP_{TOT} included 186,689 European ancestry participants who completed the PCL-C and passed quality control. Details of MVP_{TOT} have been published[35]. SNPs were deemed replicated in MVP_{TOT} if they had matching effect direction and were nominally significant after Bonferroni correction for the 9 SNPs tested ($p < 0.006$).

2.3.9 Multi-Trait Analysis for GWAS (MTAG)

MTAG[36] performs multivariate analysis of genetically correlated traits to increase discovery power for each input trait, providing trait-specific effect estimates and p-values. MTAG was used to perform multivariate analysis with PTSD and LTE GWAS. The maxFDR statistic was used to test for MTAG model assumptions (supplementary text).

2.3.10 Phenome Wide Association Study (PheWAS)

To understand further how functional changes of significant loci are associated with human traits and diseases, we conducted a PheWAS of leading SNPs from PTSD

and LTE loci using data from the GWAS Atlas[37] (available at https://atlas.ctglab.nl/). Bonferroni correction was applied to account for the 4,756 phenotypes available that were tested ($p < 1.05 \times 10^{-5}$).

2.4 Results

The PTSD GWAS meta-analysis included 182,199 participants of European ancestry from 51 cohorts (Supplementary Table 2.1). The largest cohort was the UKBB (N = 134,586 participants). Across the cohorts, PTSD was assessed using a variety of different methods (N=19 methods), the most common methods were versions of the Clinician Administered PTSD scale (N=18 studies) and PTSD Checklist (N=14 studies). The majority of participants (91%, N = 165,825, 36 studies) were analyzed based on PTSD symptom scores; the remaining participants (9%, N = 16,374, 15 studies) did not have symptom scores available and were analyzed based on PTSD case/control status.

2.4.1 PGC PTSD GWAS meta-analysis

The h^2_{SNP} of meta-analysis of cohorts analyzed by symptom scores was 0.0547 (se = 0.0042, p = 8.9e-39) (Supplementary Table 2.2). The h^2_{SNP} was similar, albeit not significant, in the smaller meta-analysis of case/control cohorts (observed scale h^2_{SNP} = 0.0580, se = 0.0259, p = 0.17). The r_g between the symptom score and case/control analyses was very high (r_g = 0.9646, se = 0.36, p = 0.0074). Thus, symptom score and case/control GWAS were meta-analyzed. We identified 5 genome-wide significant loci (Table 2.1, Figure 2.1 panel A). Leading variants in significant loci mapped to an intergenic locus on chromosome 1, the intronic region of the *GABBR1* gene on chromosome 6, the intronic regions of *MPP6* and *DFNA5* on chromosome 7, an intron of *FOXP2* on chromosome 7, and the intronic region of *FAM120A* on chromosome 9.

Gene-based analysis identified 6 significant genes (*DCAF5, EXD2, FAM120A, FOXP2, GALNT16,* and *PHF2*) (Supplementary Table 2.3).

2.4.2 PGC PTSD GWAS covariate adjusted for LTE

We repeated the GWAS of PTSD with covariate adjustment for LTE. h^2_{SNP} was 0.0389 (se = 0.00340, p = 2.6×10^{-30}), 31% lower than the PTSD GWAS without LTE covariate adjustment (p = 8.6×10^{-20}). There was a genome-wide significant locus in uncharacterized region, CTC-340A15.2, on chromosome 5 that was not identified in the PTSD GWAS (Supplementary Table 2.4). Effects changed slightly for the loci previously identified in the unadjusted PTSD GWAS (Supplementary Table 2.4). Gene based analysis identified no significant genes.

2.4.3 UKBB LTE GWAS

We performed GWAS of LTE count in the UKBB subset of the PGC-PTSD GWAS data (132,988 UKBB participants). 30.9% of participants reported 1 LTE, 14.8% reported 2 LTEs, 6.3% reported 3 LTEs, and 3.3% reported 4 or more LTEs (Supplementary Table 2.5). The SNP-based heritability of LTE count was 0.0734 (se = 0.005, p = 8.7×10^{-49}). Six loci were genome-wide significant (Figure 2.1, panel B, Table 2.2). Leading variants in significant loci mapped to an intron of *PRUNE* on chromosome 1, the intron of non-coding RNA AC068490.2 on chromosome 2, the intron of *SGCD* on chromosome 5, an intron of *FOXP2* on chromosome 7 (also identified in the PGC-PTSD GWAS), an intergenic region in chromosome 14 near *MDGA*, and upstream of *CCDC8* on chromosome 19. Gene-based analysis identified *SGCD* (chr5:155297354-156194799 BP, 2965 SNPs, 99 parameters, z = 5.53, p = 1.5×10^{-8}) and *C20orf112* (chr20:31030862-31172876 BP, 296 SNPs, 21 parameters, z = 4.73, p = 1.13×10^{-6}).

GWAS of LTE count weighted by trauma specific PTSD prevalences gave highly similar results, being highly genetically correlated to the unweighted count (rg = 1, se=0.0016 p=<1.13x10-100).

2.4.4 Genetic overlap between LTE and PTSD

r_g between PTSD and LTE was high, (r_g = 0.7239, p < $1x10^{-100}$). To explore this genetic overlap, we contrasted patterns of r_g of PTSD and LTE to other traits. Testing 772 human traits and diseases, we observed 269 and 217 r_gs that survived Bonferroni multiple testing correction (p<6.47x10-5) for PTSD and LTE, respectively (Supplementary Table 2.6). There was a complete directional concordance between PTSD and LTE among the 187 r_gs that were significant in both analyses. For several traits, while the effect direction was concordant, the magnitude of correlation with PTSD was significantly different from the correlation with LTE (p < $6.47x10^{-5}$) (Figure 2). Fifteen traits showed significantly higher genetic correlation with PTSD than with LTE (e.g., neuroticism score p = $2.74x10^{-24}$; fed-up feelings p = $1.83x10^{-15}$; mood swings p = $9.92x10^{-15}$; loneliness p = $8.07x10^{-8}$; depressive symptoms p =$1.94x10^{-7}$; irritability p = $2.27x10^{-7}$). Conversely, risk taking showed a significantly higher genetic correlation with LTE (r_g= 0.55, p = $2.71x10^{-55}$) compared to PTSD (r_g = 0.33, p = $3.9x10^{-20}$; p =$8.09x10^{-6}$).

2.4.5 Multivariate analysis of PTSD and trauma exposure

MTAG analysis that combined PTSD GWAS meta-analysis and UKBB LTE GWAS reported an effective sample size increase of PTSD GWAS from 182,199 to 217,491. There were 8 genome-wide-significant loci for the MTAG PTSD analysis, including 4 loci not identified in the PTSD GWAS meta-analysis (Table 2.1, Figure 2.1

panel C). Leading variants from additional loci mapped to an intergenic region in chromosome 2, the intron of *SGCD* on chromosome 5, an intergenic region on chromosome 16 near *ZKSCAN2* and *AQP8*, and the intron of *STAU1* on chromosome 20. In gene-based analysis, there were 8 significant genes, including five genes not identified from the original GWAS gene-based analysis (*CSE1L, DFNA5, FOXP1, SGCD, TRIM26*) (Supplementary Table 2.3).

2.4.6 Cross-replication in MVP_{TOT}

Of the 9 loci identified across the PTSD GWAS (5 PGC GWAS and 4 MTAG loci), 4 replicated significantly in MVP_{TOT} ($p < 0.006$) (Table 2.1) (Supplementary Figures 2-10). Of the 11 genes identified in gene-based analyses (6 GWAS + 5 MTAG), 7 replicated at least at a nominally significant level in MVP_{TOT} (Supplementary Table 2.3). Additionally, of 15 loci identified in MVP_{TOT} GWAS, 9 nominally replicated in PGC-PTSD (Supplementary Table 2.7). Overall, r_g between PGC PTSD and MVP_{TOT} was high($rg = 0.8359$, $se = 0.0376$, $p = 2.5x10^{-109}$).

2.4.7 Functional consequences of risk loci

We examined the functional impact of the 9 GWS variants associated with PTSD (5 from GWAS and 4 from MTAG; Table 2.1). We observed that 7 loci were related to multiple tissue-specific expression quantitative trait loci (eQTL; Supplementary Table 2.8), where 11% of FDR-significant eQTLs were in brain regions. A similar trend was present for splicing QTLs (Supplementary Table 2.9), where only 7% of gene-tissue combinations were related to brain regions. Further details of the eQTL analysis are in the supplementary text.

We found enrichment of genes involved in brain transcriptomic regulation in PTSD (Supplementary Table 2.10). All brain regions tested were at least nominally significant, with several remaining significant after Bonferroni correction (MTAG-analysis: cortex p = 2.9 x 10^{-5}, frontal cortex BA9 p = 3.53e-5, cerebellum p = 1.09e-4, anterior cingulate cortex BA24 p = 1.29 x 10^{-4}, cerebellar hemisphere p = 1.43 x 10^{-3}, nucleus accumbens/basal ganglia p = 3.6 x 10^{-4}). There was no significant enrichment detected in any sets from the list of curated gene-sets and GO terms (Supplementary Table 2.11).

2.4.8 PheWAS

We identified 200 phenome-wide significant associations (Supplementary Table 2.12), with more than half of the significant associations related to two domains: psychiatry (34%) and metabolism (18%). The strongest PheWAS associations with PTSD and LTE loci included: height and body mass phenotypes, educational attainment, social interaction, sexual activity, risk tolerance, and sleep phenotypes (Supplementary Text). Several PTSD loci showed widespread pleiotropy across multiple psychiatric traits: rs10266297 (35 significant associations, 40% psychiatric domain, top psychiatric result: risk taking p=1.27e-11), rs10821140 (37 significant associations, 38% psychiatric domain, top psychiatric result: loneliness p=1.11e-11), rs146918648 (44 significant associations, 48% psychiatric domain, top psychiatric result: tenseness/restlessness p=2.13e-9).

2.5 Discussion

Our GWAS study aimed to advance understanding of PTSD genetics by integrating quantitative PTSD phenotypes and LTE exposure information in 182,199 participants of European ancestry from 51 cohorts. Overall, quantitative PTSD phenotyping captured similar genetic signal to our prior case/control analysis (r_g = 0.92 – 1.14) [8], but with substantially higher power. However, by using LTE as a covariate, which hypothetically accounts for unexpressed genetic vulnerability among unexposed participants[12], we found a significant reduction in heritability and gene discovery. As high r_g between PTSD and LTE would be one hypothetical explanation for this result (i.e. multicollinearity), we performed GWAS of LTE and contrasted it to GWAS results for PTSD. We found that LTE has h^2_{SNP} comparable to PTSD and high r_g with PTSD. We leveraged the r_g to significantly enhance PTSD discovery power using a multivariate approach [36].

One explanation for h^2_{SNP} of PTSD adjusted for LTE being lower than the unadjusted estimate is that it may have removed genetic effects on PTSD mediated by trauma exposure [12, 13]. Given that trauma is a prerequisite for PTSD, genetic effects on trauma exposure can have mediated (i.e. indirect) effects on PTSD. Indeed this seems plausible, as our LTE GWAS suggested a substantial amount of h^2_{SNP} related to trauma exposure. Therefore, the estimated h^2_{SNP} of PTSD conditional on LTE would theoretically reflect only non-mediated (i.e. direct) effects and thus would be smaller.

We used r_g to quantify the genetic overlap between LTE and PTSD, finding similar magnitude to findings from twin studies[5, 6]. At the same time, incomplete r_g

between these two phenotypes also suggested meaningful genetic differences. To investigate this, we contrasted the magnitudes of r_g that PTSD and LTE shared with other traits. For most traits, r_g with PTSD was quite similar in magnitude to r_g with LTE. However, we also found that negative affect traits like neuroticism and irritability were more strongly correlated with PTSD than LTE, whereas risk-taking behavior showed higher correlation with LTE than PTSD. This suggests that some variants influence PTSD and LTE through somewhat distinct psychological and behavioral mechanisms[5].

The high r_g between PTSD and LTE facilitates the application of multivariate approaches to PTSD GWAS. Whereas the r_g between PTSD and LTE induces loss of power in the PTSD analysis when conditioned on LTE, a multivariate approach can benefit from it. Our multivariate[36] analysis resulted in a 19% increase in the effective sample size by adding LTE count data from the UKBB, and identified replicable loci and patterns of tissue expression not identified in a standard PTSD GWAS.

The biological mechanisms associated with several of the protein products of identified genes have been linked to PTSD pathophysiology in animal and cell models: amygdala-mediated fear extinction (FAM120A[38]), neuronal transcriptional regulation (FOXP2[39]), brain excitatory/inhibitory balance (ARFGEF2, GABBR1, STAUI1[40]), intracellular vesicular trafficking and other synaptic activities (ARFGEF2[41], MPP6[42], SEMA6C[43], SGCD[44]), and inflammation (HIATL1, TRIM26[45], TRIM27[46], ZMYM4, ZNF165[47]). Blood and brain transcription-wide association and differential gene expression studies of PTSD have also implicated some of these genes, including a blood-based prediction of downregulation of *ARFGEF2* in the dorsolateral pre-frontal cortex[48] , and a postmortem study of human PTSD cortex indicating downregulation of

CTSS expression in the dorsal anterior cingulate cortex and downregulation of *OSBPL3* expression in the dorsolateral pre-frontal cortex[49].

Interestingly, PTSD loci show widespread pleiotropic associations in PheWAS [32, 50-52]. Some loci point to factors associated with existing clinical presentations of PTSD (e.g. sleep), while others point to potential risk/protective factors for PTSD like educational attainment and cognitive functioning. Loci may affect PTSD through their direct influence on these risk/protective factors. Alternatively, the high degree of pleiotropy shown by these loci suggests that they could influence PTSD risk through a more general alteration of biological function[37], such as general predisposition to psychiatric illness [53]. In particular, metabolic phenotypes such as height and body mass also appeared to be enriched in our PheWAS. This could be the influence of these loci on previously implicated inflammatory mechanisms for PTSD [8] or simply an artifact of their overrepresentation in the GWAS Atlas. Nevertheless, the broad variety of behavioral and clinical domains associated with these loci suggest complex etiologic heterogeneity of PTSD that could relate to subtypes [54].

Further characterization of significant loci via eQTL analyses identified expression across a variety of tissue types. Given the high degree of shared eQTL architecture between tissues, the presence of some of these tissues might not be directly related to PTSD pathogenesis. Indeed, on the genome-wide level, our tissue enrichment analysis only suggests that brain tissues are relevant. The brain regions implicated are consistent with functional MRI and structural MRI findings of PTSD. Brodmann area 24 (as part of the ventral anterior cingulate cortex) is implicated in PTSD response to trauma-, fear-, and threat-related stimuli[55, 56]. Brodmann area 9 (as

part of the dorsomedial prefrontal cortex), reflects response to self-referential thought, theory of mind, empathy, and moral judgements, and shows greater engagement in PTSD and trauma-exposed individuals[55, 57, 58]. Nucleus accumbens expression is consistent with the neuroimaging evidence of its role in the reward system, which is prominently affected with emotional numbing symptoms of PTSD[59-62].

2.5.1 Limitations

Stress-related disorders are phenotypically complex and heterogeneous[63], which limits discovery power and complicates translation to clinical application. The strategies proposed for understanding and addressing heterogeneity in major depressive disorder such as harmonization of measures, additional phenotypic measures, and investigations of subtypes, could be applied to PTSD as additional avenues to enhance discovery power[64]. Sex differences may also contribute a significant source of heterogeneity[8, 65-68] Our analyses were restricted to participants of European ancestry given power limitations for other ancestry groups. However urgent scientific and ethical reasons call for extending analyses to individuals of non-European ancestry[69]. The PGC-PTSD group has actively been gathering data to increase representation from diverse ancestry and developing methods to optimize analyses in admixed populations[70]. As sample sizes increase, future investigations will be powered to investigate ancestry and sex-specific genetic influences on PTSD and trauma exposure. In performing a GWAS of cumulative LTE, we identified several significant loci, including those previously identified in GWAS of childhood trauma exposure[14]. A full investigation of the genetic basis of LTE is clearly warranted. Future work could also examine the relationship between PTSD and specific types or numbers of trauma exposure, as they plausibly

have different relationships with PTSD [6], and may therefore be more informative than our cumulative measure for LTE. Finally, trauma was assessed via participant self-report, which may vary with mood and PTSD symptoms at the time of reporting[71], and could inflate genetic associations with PTSD.

2.5.2 Conclusions

Novel replicable risk loci for PTSD identified by incorporating quantitative symptom data and trauma exposure information into GWAS offer us new insights into the genetic architecture of PTSD. Beyond the nature of LTE as an environmental exposure, there is a heritable component to LTE that overlaps highly with PTSD to impart an enhanced understanding of PTSD genetics. In future investigations, the genetic architectures of PTSD and LTE could be further delineated using causal mediation analysis [72], which can provide estimates of LTE related mediation and gene-by-environment interaction. Our results reinforce the notion that in addition to larger samples, more detailed phenotyping and sophisticated modeling are needed to account for the role of environmental exposure in developing PTSD, as these influence GWAS discovery power. Widespread pleiotropy of significant loci suggests that cross-disorder analysis with PTSD [73, 74] will enhance our understanding of how these loci modify risk for PTSD and related disorders.

2.6 Acknowledgements

This work was funded by NIMH/U.S. Army Medical Research and Development Command Grant R01MH106595 to CMN, IL, MBS, KJR, and KCK, and supported by 5U01MH109539. KWC is supported in part by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation. Genotyping of samples was provided

in part through the Stanley Center for Psychiatric Genetics at the Broad Institute supported by Cohen Veterans Bioscience. Statistical analyses were carried out on the NL Genetic Cluster computer (https://userinfo.surfsara.nl/systems/lisa) hosted by SURFsara. This research has been conducted using the UK Biobank resource under application number 41209.

This work would have not been possible without the financial support provided by Cohen Veterans Bioscience, the Stanley Center for Psychiatric Genetics at the Broad Institute, and One Mind. We are very grateful to the investigators who comprise the PGC-PTSD working group, and especially the more than 206,000 research participants worldwide who shared their life experiences and biological samples with PGC-PTSD investigators. We thank Mark Zervas for his critical input. Full acknowledgements are in the Supplementary Note.

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense.

Chapter 2 is published in Biological Psychiatry. Co-authors include Karmel W. Choi, Jonathan R.I. Coleman, Nikolaos P. Daskalakis, Christy A. Denckla, Elizabeth Ketema, Rajendra A. Morey, Renato Polimanti, Andrew Ratanatharathorn, Katy Torres, Aliza P. Wingo, Clement C. Zai, Allison E. Aiello, Lynn M. Almli, Ananda B. Amstadter, Soren B. Andersen, Ole A. Andreassen, Paul A. Arbisi, Allison E. Ashley-Koch, S. Bryn Austin, Esmina Avdibegovic, Anders D. Borglum, Dragan Babic, Marie Bµkvad-Hansen,

Dewleen G. Baker, Jean C. Beckham, Laura J. Bierut, Jonathan I. Bisson, Marco P. Boks, Elizabeth A. Bolger, Bekh Bradley, Meghan Brashear, Gerome Breen, Richard A. Bryant, Angela C. Bustamante, Jonas Bybjerg-Grauholm, Joseph R. Calabrese, JM Caldas-de-Almeida, Chia-Yen Chen, Anders M. Dale, Shareefa Dalvie, Jürgen Deckert, Douglas L. Delahanty, Michelle F. Dennis, Seth G. Disner, Katharina Domschke, Laramie E. Duncan, Alma Dzubur Kulenovic, Christopher R. Erbes, Alexandra Evans, Lindsay A. Farrer, Norah C. Feeny, Janine D. Flory, David Forbes, Carol E. Franz, Sandro Galea, Melanie E. Garrett, Aarti Gautam, Bizu Gelaye, Joel Gelernter, Elbert Geuze, Charles F. Gillespie, Aferdita Goci, Scott D. Gordon, Guia Guffanti, Rasha Hammamieh, Michael A. Hauser, Andrew C. Heath, Sian M.J. Hemmings, David Michael Hougaard, Miro Jakovljevic, Marti Jett, Eric Otto Johnson, Ian Jones, Tanja Jovanovic, Xue-Jun Qin, Karen-Inge Karstoft, Milissa L. Kaufman, Ronald C. Kessler, Alaptagin Khan, Nathan A. Kimbrel, Anthony P. King, Nastassja Koen, Henry R. Kranzler, William S. Kremen, Bruce R. Lawford, Lauren A. M. Lebois, Catrin Lewis, Israel Liberzon, Sarah D. Linnstaedt, Mark W. Logue, Adriana Lori, Bozo Lugonja, Jurjen J. Luykx, Michael J. Lyons, Jessica L. Maples-Keller, Charles Marmar, Nicholas G Martin, Maurer D, Matig R. Mavissakalian, Alexander McFarlane, Regina E. McGlinchey, Katie A. McLaughlin, Samuel A. McLean, Divya Mehta, Rebecca Mellor, Vasiliki Michopoulos, William Milberg, Mark W. Miller, Charles Phillip Morris, Ole Mors, PB Mortensen, Elliot C. Nelson, Merete Nordentoft, Sonya B. Norman, Meaghan O'Donnell, Holly K. Orcutt, Matthew S. Panizzon, Edward S. Peters, Alan L. Peterson, Matthew Peverill, Robert H. Pietrzak, Melissa A. Polusny, John P. Rice, Victoria B. Risbrough, Andrea L. Roberts, Alex O. Rothbaum, Barbara O. Rothbaum, P. Roy-

Byrne, Kenneth J. Ruggiero, Ariane Rung, Bart P. F. Rutten, Nancy L Saccone, Sixto E. Sanchez, Dick Schijven, S. Seedat, Antonia V. Seligowski, Julia S. Seng, Christina M. Sheerin, Derrick Silove, Alicia K Smith, Jordan W. Smoller, Scott R. Sponheim, Dan J. Stein, Jennifer S. Stevens, Martin H. Teicher, Wesley K. Thompson, Edward Trapido, Monica Uddin, Robert J. Ursano, Leigh Luella van den Heuvel, Miranda Van Hooff, Eric Vermetten, Christiaan Vinkers, Joanne Voisey, Yunpeng Wang, Zhewu Wang, Thomas Werge, Michelle A. Williams, Douglas E. Williamson, Sherry Winternitz, Christiane Wolf, Erika J. Wolf, Rachel Yehuda, Keith A. Young, Ross McD. Young, Hongyu Zhao, Lori A. Zoellner, Magali Haas, Heather Lasseter, Allison C. Provost, Rany M. Salem, Jonathan Sebat, Richard A. Shaffer, Tianying Wu, Stephan Ripke, Mark J. Daly, Kerry J. Ressler, Karestan C. Koenen, Murray B. Stein, and Caroline M. Nievergelt. The dissertation author was the primary investigator and author of this paper.

2.7 Disclosures

Murray B. Stein has in the past 3 years received consulting income from Actelion, Acadia Pharmaceuticals, Aptinyx, Bionomics, BioXcel Therapeutics, Clexio, EmpowerPharm, GW Pharmaceuticals, Janssen, Jazz Pharmaceuticals, and Roche/Genentech. Dr. Stein has stock options in Oxeia Biopharmaceuticals and Epivario. In the past 3 years, NPD has held a part-time paid position at Cohen Veterans Bioscience, has been a consultant for Sunovion Pharmaceuticals and is on the scientific advisory board for Sentio Solutions for unrelated work. In the past 3 years, Dr. Kessler was a consultant for Datastat, Inc., RallyPoint Networks, Inc., Sage Pharmaceuticals, and Takeda. Dr. Maples-Keller has funding from COMPASS Pathways and has received a speaking fee from COMPASS Pathways. Dr. Uddin was a consultant for

systemanalytic. Henry Kranzler is a member of a Dicerna scientific advisory board and a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which during the past 3 years was supported by Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Dicerna, Ethypharm, Indivior, Lundbeck, Mitsubishi, and Otsuka. He and Joel Gelernter are named as inventors on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018. Renato Polimanti and Joel Gelernter are paid for their editorial work on the journal Complex Psychiatry. Dr Andreasen is a consultant to HealthLytix. The remaining authors report no disclosures.

2.8 Figures

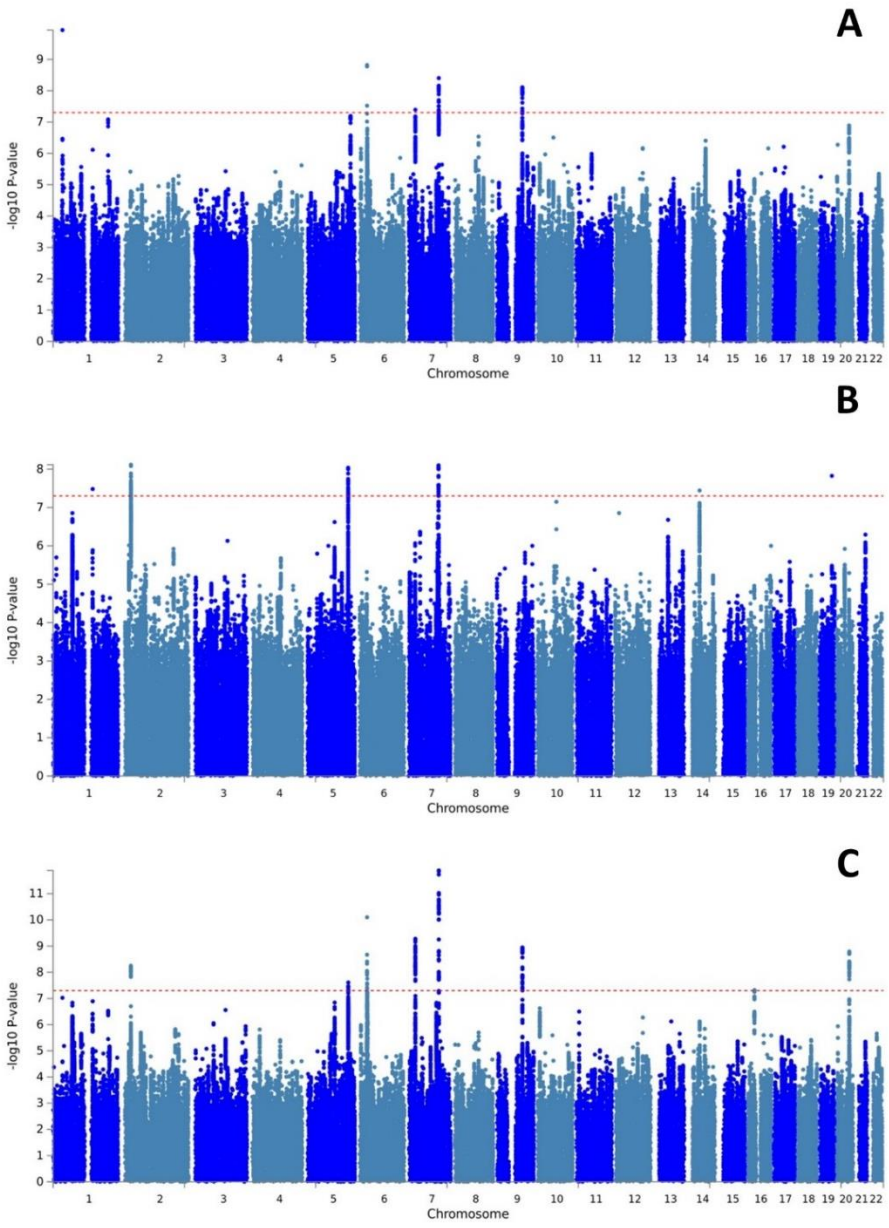

Figure 2.1. Manhattan plots of GWAS associations.

Footnote: The X-axis is the position on the genome, ordered by chromosome and base-pair position. The Y-axis is the -$\log_{10}$ p-value of association. Each dot represents the association between a given SNP and the trait. Colors alternate between chromosomes, with odd chromosomes colored blue, even chromosomes colored teal. Panel A) results of PTSD GWAS. Panel B) Results of LTE GWAS). Panel C) PTSD specific results of MTAG analysis of PTSD and LTE.

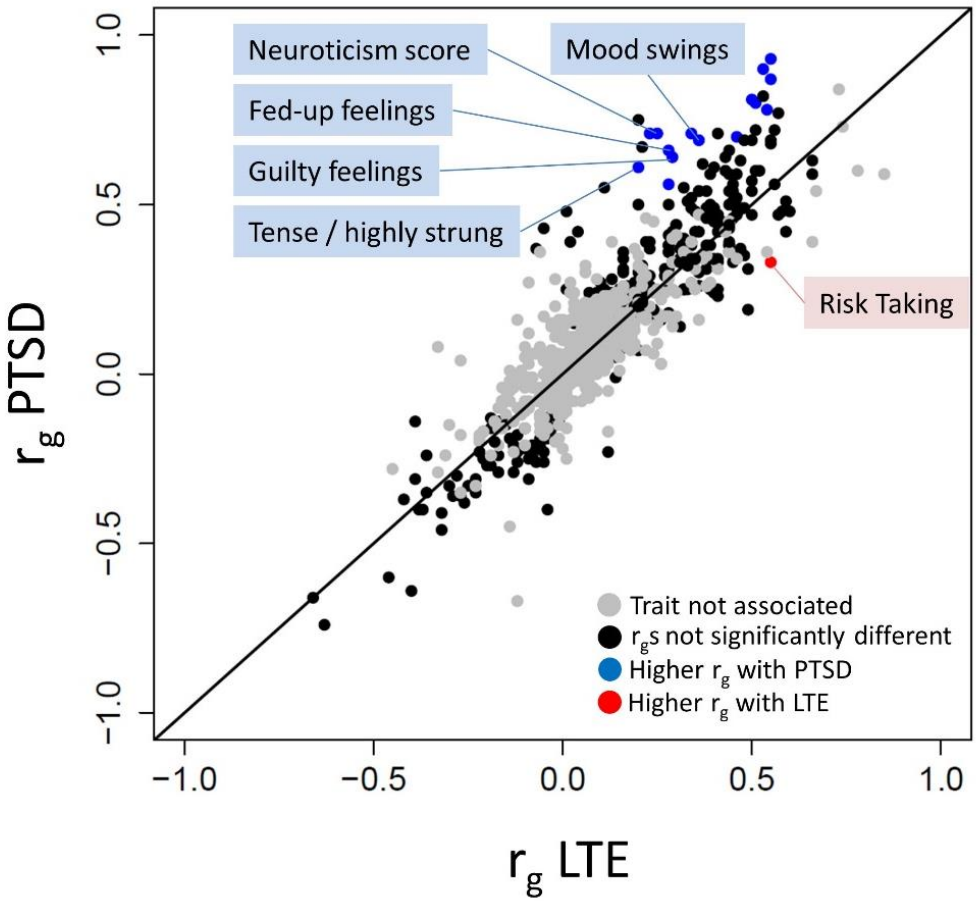

Figure 2.2. Comparison of the genetic correlations of PTSD and LTE to other traits.

Footnote: The X-axis is the genetic correlation between LTE and a given trait from LD hub. The Y-axis is the genetic correlation between PTSD and a given trait. Each dot depicts a given trait. Colored (black, red, or blue) dots indicate traits with significant genetic correlation to both PTSD and LTE after Bonferroni adjustment. Non-colored (grey) dots indicate traits where genetic correlation is not significant after Bonferroni adjustment. Blue dots indicate traits with significantly higher genetic correlation with PTSD than with LTE. Red dots indicate traits with significantly higher correlation with LTE than with PTSD. The top five traits with a significantly higher correlation to PTSD than LTE and top trait with significantly higher correlation to LTE than PTSD have been labeled.

Table 2.1. Genome-Wide Significant Loci from PTSD GWAS and MTAG with Replication in the MVP_{TOT} GWAS

						PGC-PTSD GWAS			PGC-PTSD MTAG		MVP_{TOT}		
Analysis	**rsID**	**Chr**	**Position**	**A1**	**A2**	**A1 freq**	**Z**	***p*-value**	**Z**	***p*-value**	**A1 freq**	**Z**	***p*-value** [a]
a)	rs72657988	1	35,688,541	T	G	0.08	6.44	1.2E-10	5.34	9.4E-08	0.07	2.18	0.029
Identified	rs146918648	6	28,548,674	A	G	0.04	6.04	1.5E-09	6.50	8.0E-11	0.04	2.00	0.045
in GWAS	rs2721816[b]	7	24,699,329	A	G	0.82	-5.27	1.4E-07	-5.80	6.5E-09	0.82	-1.45	0.15
	rs10266297	7	114,143,407	T	C	0.59	5.38	7.4E-08	6.72	1.8E-11	0.59	4.97	6.7E-07
	rs10821140	9	96,253,169	A	C	0.35	-5.71	1.2E-08	-6.02	1.8E-09	0.34	-3.89	1.0E-04
b)	rs4557006	2	22,443,840	A	G	0.45	4.26	2.0E-05	5.83	5.7E-09	0.45	5.53	3.2E-08
Identified	rs1504930	5	155,852,066	T	C	0.62	-4.26	2.0E-05	-5.58	2.5E-08	0.62	-4.20	2.7E-05
in MTAG	rs8059002	16	25,417,390	T	G	0.86	-4.43	9.3E-06	-5.46	4.8E-08	0.85	-1.50	0.13
	rs7264419	20	47,701,309	A	G	0.75	-5.06	4.1E-07	-5.85	5.0E-09	0.76	0.55	0.58

Abbreviations: Chr, chromosome; Position, base pair position on chromosome (hg19/GR37 Human Genome Build). A1, Allele 1 (coded); A2, Allele 2; A1 freq, frequency; Z, Z-score; C, cytosine; A, adenosine; T, thymidine; G, guanidine;

[a]Significant in MVP if $p < 0.006$ (Bonferroni-corrected for 9 loci).

[b] LD Proxy for rs2721817, the leading SNP in this locus

Table 2.2. Genome-Wide Significant Loci from GWAS of LTE

rsID	Chr	Position	A1	A2	A1 freq	Z-score	*p*-value
rs6661135	1	150999414	C	T	0.93	-5.52	3.3E-08
rs4665501	2	22546151	G	T	0.44	-5.77	7.7E-09
rs4704792	5	155757946	A	T	0.26	5.75	9.2E-09
rs1476535	7	114071035	C	T	0.44	-5.77	8.0E-09
rs2933196	14	47285917	G	A	0.59	-5.51	3.6E-08
rs770444611	19	46917381	INS[a]	T	0.59	5.66	1.5E-08

[a]Insertion of TGAGGCCAGGAGTTC

Abbreviations: Chr, chromosome; Position, base pair position on chromosome (hg19/GR37 Human Genome Build). A1, Allele 1 (coded); A2, Allele 2; A1 freq, frequency; C, cytosine; A, adenosine; T, thymidine; G, guanidine;

2.10 References

1. Sareen J. Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. Can J Psychiatry. 2014;59(9):460-7. doi: 10.1177/070674371405900902. PubMed PMID: 25565692.

2. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, Hobfoll SE, Koenen KC, Neylan TC, Hyman SE. Post-traumatic stress disorder. Nature Reviews Disease Primers. 2015;1(1):15057. doi: 10.1038/nrdp.2015.57.

3. Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, Degenhardt L, de Girolamo G, Dinolova RV, Ferry F, Florescu S, Gureje O, Haro JM, Huang Y, Karam EG, Kawakami N, Lee S, Lepine J-P, Levinson D, Navarro-Mateu F, Pennell B-E, Piazza M, Posada-Villa J, Scott KM, Stein DJ, Ten Have M, Torres Y, Viana MC, Petukhova MV, Sampson NA, Zaslavsky AM, Koenen KC. Trauma and PTSD in the WHO World Mental Health Surveys. Eur J Psychotraumatol. 2017;8(sup5):1353383-. doi: 10.1080/20008198.2017.1353383. PubMed PMID: 29075426.

4. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. Journal of Consulting and Clinical Psychology. 2000;68(5):748-66. doi: 10.1037/0022-006X.68.5.748.

5. Stein MB, Jang KL, Taylor S, Vernon PA, Livesley WJ. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. The American journal of psychiatry. 2002;159(10):1675-81. Epub 2002/10/03. doi: 10.1176/appi.ajp.159.10.1675. PubMed PMID: 12359672.

6. Sartor CE, Grant JD, Lynskey MT, McCutcheon VV, Waldron M, Statham DJ, Bucholz KK, Madden PA, Heath AC, Martin NG, Nelson EC. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. Archives of general psychiatry. 2012;69(3):293-9. Epub 2012/03/07. doi: 10.1001/archgenpsychiatry.2011.1385. PubMed PMID: 22393221 PMCID: PMCPMC3594801.

7. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, Milad MR, Liberzon I. Biological studies of post-traumatic stress disorder. Nature Reviews Neuroscience. 2012;13(11):769-87. doi: 10.1038/nrn3339.

8. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, Levey DF, Logue MW, Polimanti R, Provost AC, Ratanatharathorn A, Stein MB, Torres K, Aiello AE, Almli LM, Amstadter AB, Andersen SB, Andreassen OA, Arbisi PA, Ashley-Koch AE, Austin SB, Avdibegovic E, Babić D, Bækvad-Hansen M, Baker DG, Beckham JC, Bierut LJ, Bisson JI, Boks MP, Bolger EA, Børglum AD, Bradley B, Brashear M, Breen G, Bryant RA, Bustamante AC, Bybjerg-Grauholm J, Calabrese JR, Caldas- de- Almeida JM, Dale AM, Daly MJ, Daskalakis NP, Deckert J, Delahanty DL, Dennis MF, Disner SG, Domschke K, Dzubur-Kulenovic A, Erbes CR, Evans A, Farrer LA, Feeny NC, Flory JD, Forbes D, Franz CE,

Galea S, Garrett ME, Gelaye B, Geuze E, Gillespie C, Uka AG, Gordon SD, Guffanti G, Hammamieh R, Harnal S, Hauser MA, Heath AC, Hemmings SMJ, Hougaard DM, Jakovljevic M, Jett M, Johnson EO, Jones I, Jovanovic T, Qin X-J, Junglen AG, Karstoft K-I, Kaufman ML, Kessler RC, Khan A, Kimbrel NA, King AP, Koen N, Kranzler HR, Kremen WS, Lawford BR, Lebois LAM, Lewis CE, Linnstaedt SD, Lori A, Lugonja B, Luykx JJ, Lyons MJ, Maples-Keller J, Marmar C, Martin AR, Martin NG, Maurer D, Mavissakalian MR, McFarlane A, McGlinchey RE, McLaughlin KA, McLean SA, McLeay S, Mehta D, Milberg WP, Miller MW, Morey RA, Morris CP, Mors O, Mortensen PB, Neale BM, Nelson EC, Nordentoft M, Norman SB, O'Donnell M, Orcutt HK, Panizzon MS, Peters ES, Peterson AL, Peverill M, Pietrzak RH, Polusny MA, Rice JP, Ripke S, Risbrough VB, Roberts AL, Rothbaum AO, Rothbaum BO, Roy-Byrne P, Ruggiero K, Rung A, Rutten BPF, Saccone NL, Sanchez SE, Schijven D, Seedat S, Seligowski AV, Seng JS, Sheerin CM, Silove D, Smith AK, Smoller JW, Sponheim SR, Stein DJ, Stevens JS, Sumner JA, Teicher MH, Thompson WK, Trapido E, Uddin M, Ursano RJ, van den Heuvel LL, Van Hooff M, Vermetten E, Vinkers CH, Voisey J, Wang Y, Wang Z, Werge T, Williams MA, Williamson DE, Winternitz S, Wolf C, Wolf EJ, Wolff JD, Yehuda R, Young RM, Young KA, Zhao H, Zoellner LA, Liberzon I, Ressler KJ, Haas M, Koenen KC. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nature Communications. 2019;10(1):4558. doi: 10.1038/s41467-019-12576-w.

9. Stein MB, Levey DF, Cheng Z, Wendt FR, Harrington K, Pathak GA, Cho K, Quaden R, Radhakrishnan K, Girgenti MJ, Ho YA, Posner D, Aslan M, Duman RS, Zhao H, Department of Veterans Affairs Cooperative Studies P, Program VAMV, Polimanti R, Concato J, Gelernter J. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. Nat Genet. 2021;53(2):174-84. doi: 10.1038/s41588-020-00767-x. PubMed PMID: 33510476.

10. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Børglum AD, Breen G, Cichon S, Edenberg HJ, Faraone SV, Gelernter J, Mathews CA, Nievergelt CM, Smoller JW, O'Donovan MC, Psychiatric Genomics C. Psychiatric Genomics: An Update and an Agenda. Am J Psychiatry. 2018;175(1):15-27. Epub 10/03. doi: 10.1176/appi.ajp.2017.17030283. PubMed PMID: 28969442.

11. Lee SH, Wray NR. Novel genetic analysis for case-control genome-wide association studies: quantification of power and genomic prediction accuracy. PloS one. 2013;8(8):e71494-e. doi: 10.1371/journal.pone.0071494. PubMed PMID: 23977056.

12. Cornelis MC, Nugent NR, Amstadter AB, Koenen KC. Genetics of post-traumatic stress disorder: review and recommendations for genome-wide association studies. Curr Psychiatry Rep. 2010;12(4):313-26. doi: 10.1007/s11920-010-0126-6. PubMed PMID: 20549395.

13. Logue MW, Amstadter AB, Baker DG, Duncan L, Koenen KC, Liberzon I, Miller MW, Morey RA, Nievergelt CM, Ressler KJ, Smith AK, Smoller JW, Stein MB, Sumner JA, Uddin M. The Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup: Posttraumatic Stress Disorder Enters the Age of Large-Scale Genomic

Collaboration. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2015;40(10):2287-97. Epub 04/23. doi: 10.1038/npp.2015.118. PubMed PMID: 25904361.

14. Dalvie S, Maihofer AX, Coleman JRI, Bradley B, Breen G, Brick LA, Chen C-Y, Choi KW, Duncan LE, Guffanti G, Haas M, Harnal S, Liberzon I, Nugent NR, Provost AC, Ressler KJ, Torres K, Amstadter AB, Bryn Austin S, Baker DG, Bolger EA, Bryant RA, Calabrese JR, Delahanty DL, Farrer LA, Feeny NC, Flory JD, Forbes D, Galea S, Gautam A, Gelernter J, Hammamieh R, Jett M, Junglen AG, Kaufman ML, Kessler RC, Khan A, Kranzler HR, Lebois LAM, Marmar C, Mavissakalian MR, McFarlane A, Donnell MO, Orcutt HK, Pietrzak RH, Risbrough VB, Roberts AL, Rothbaum AO, Roy-Byrne P, Ruggiero K, Seligowski AV, Sheerin CM, Silove D, Smoller JW, Stein MB, Teicher MH, Ursano RJ, Van Hooff M, Winternitz S, Wolff JD, Yehuda R, Zhao H, Zoellner LA, Stein DJ, Koenen KC, Nievergelt CM. Genomic influences on self-reported childhood maltreatment. Translational Psychiatry. 2020;10(1):38. doi: 10.1038/s41398-020-0706-0.

15. Schifano ED. A review of analysis methods for secondary outcomes in case-control studies. CSAM. 2019;26(2):103-29. Epub 03/31. doi: 10.29220/CSAM.2019.26.2.103.

16. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203-9. Epub 2018/10/12. doi: 10.1038/s41586-018-0579-z. PubMed PMID: 30305743 PMCID: PMCPMC6786975.

17. Lam M, Awasthi S, Watson HJ, Goldstein J, Panagiotaropoulou G, Trubetskoy V, Karlsson R, Frei O, Fan CC, De Witte W, Mota NR, Mullins N, Brügger K, Lee SH, Wray NR, Skarabis N, Huang H, Neale B, Daly MJ, Mattheisen M, Walters R, Ripke S. RICOPILI: Rapid Imputation for COnsortias PIpeLIne. Bioinformatics. 2020;36(3):930-3. Epub 2019/08/09. doi: 10.1093/bioinformatics/btz633. PubMed PMID: 31393554.

18. Delaneau O, Coulonges C, Zagury J-F. Shape-IT: new rapid and accurate algorithm for haplotype inference. BMC Bioinformatics. 2008;9(1):540. doi: 10.1186/1471-2105-9-540.

19. Howie B, Marchini J, Stephens M. Genotype Imputation with Thousands of Genomes. G3: Genes|Genomes|Genetics. 2011;1(6):457. doi: 10.1534/g3.111.001198.

20. Clarke L, Zheng-Bradley X, Smith R, Kulesha E, Xiao C, Toneva I, Vaughan B, Preuss D, Leinonen R, Shumway M, Sherry S, Flicek P, The Genomes Project C. The 1000 Genomes Project: data management and community access. Nature Methods. 2012;9(5):459-62. doi: 10.1038/nmeth.1974.

21. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nature Genetics. 2006;38(8):904-9. doi: 10.1038/ng1847.

22. Loh P-R, Kichaev G, Gazal S, Schoech AP, Price AL. Mixed-model association for biobank-scale datasets. Nature genetics. 2018;50(7):906-8. doi: 10.1038/s41588-018-0144-6. PubMed PMID: 29892013.

23. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26(17):2190-1. Epub 2010/07/10. doi: 10.1093/bioinformatics/btq340. PubMed PMID: 20616382 PMCID: PMCPMC2922887.

24. Lee CH, Cook S, Lee JS, Han B. Comparison of Two Meta-Analysis Methods: Inverse-Variance-Weighted Average and Weighted Sum of Z-Scores. Genomics Inform. 2016;14(4):173-80. Epub 12/30. doi: 10.5808/GI.2016.14.4.173. PubMed PMID: 28154508.

25. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, Baldursson G, Belliveau R, Bybjerg-Grauholm J, Bækvad-Hansen M, Cerrato F, Chambert K, Churchhouse C, Dumont A, Eriksson N, Gandal M, Goldstein JI, Grasby KL, Grove J, Gudmundsson OO, Hansen CS, Hauberg ME, Hollegaard MV, Howrigan DP, Huang H, Maller JB, Martin AR, Martin NG, Moran J, Pallesen J, Palmer DS, Pedersen CB, Pedersen MG, Poterba T, Poulsen JB, Ripke S, Robinson EB, Satterstrom FK, Stefansson H, Stevens C, Turley P, Walters GB, Won H, Wright MJ, Andreassen OA, Asherson P, Burton CL, Boomsma DI, Cormand B, Dalsgaard S, Franke B, Gelernter J, Geschwind D, Hakonarson H, Haavik J, Kranzler HR, Kuntsi J, Langley K, Lesch KP, Middeldorp C, Reif A, Rohde LA, Roussos P, Schachar R, Sklar P, Sonuga-Barke EJS, Sullivan PF, Thapar A, Tung JY, Waldman ID, Medland SE, Stefansson K, Nordentoft M, Hougaard DM, Werge T, Mors O, Mortensen PB, Daly MJ, Faraone SV, Børglum AD, Neale BM. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51(1):63-75. Epub 2018/11/28. doi: 10.1038/s41588-018-0269-7. PubMed PMID: 30478444 PMCID: PMCPMC6481311.

26. Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, Gliedt TP, Boehnke M, Abecasis GR, Willer CJ. LocusZoom: regional visualization of genome-wide association scan results. Bioinformatics. 2010;26(18):2336-7. Epub 07/15. doi: 10.1093/bioinformatics/btq419. PubMed PMID: 20634204.

27. Bulik-Sullivan BK, Loh P-R, Finucane HK, Ripke S, Yang J, Patterson N, Daly MJ, Price AL, Neale BM, Schizophrenia Working Group of the Psychiatric Genomics C. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nature genetics. 2015;47(3):291-5. doi: 10.1038/ng.3211.

28. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, Hemani G, Tansey K, Laurin C, Early G, Lifecourse Epidemiology Eczema C, Pourcain BS, Warrington NM, Finucane HK, Price AL, Bulik-Sullivan BK, Anttila V, Paternoster L, Gaunt TR, Evans DM, Neale BM. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2017;33(2):272-9. doi: 10.1093/bioinformatics/btw613.

29. Watanabe K, Umićević Mirkov M, de Leeuw CA, van den Heuvel MP, Posthuma D. Genetic mapping of cell type specificity for complex traits. Nature Communications. 2019;10(1):3222. doi: 10.1038/s41467-019-11181-1.

30. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: Generalized Gene-Set Analysis of GWAS Data. PLOS Computational Biology. 2015;11(4):e1004219. doi: 10.1371/journal.pcbi.1004219.

31. Carithers LJ, Ardlie K, Barcus M, Branton PA, Britton A, Buia SA, Compton CC, DeLuca DS, Peter-Demchok J, Gelfand ET, Guan P, Korzeniewski GE, Lockhart NC, Rabiner CA, Rao AK, Robinson KL, Roche NV, Sawyer SJ, Segrè AV, Shive CE, Smith AM, Sobin LH, Undale AH, Valentino KM, Vaught J, Young TR, Moore HM. A Novel Approach to High-Quality Postmortem Tissue Procurement: The GTEx Project. Biopreservation and Biobanking. 2015;13(5):311-9. doi: 10.1089/bio.2015.0032.

32. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science (New York, NY). 2020;369(6509):1318-30. Epub 2020/09/12. doi: 10.1126/science.aaz1776. PubMed PMID: 32913098 PMCID: PMCPMC7737656.

33. Ongen H, Buil A, Brown AA, Dermitzakis ET, Delaneau O. Fast and efficient QTL mapper for thousands of molecular phenotypes. Bioinformatics. 2016;32(10):1479-85. Epub 2015/12/29. doi: 10.1093/bioinformatics/btv722. PubMed PMID: 26708335 PMCID: PMCPMC4866519.

34. Stegle O, Parts L, Piipari M, Winn J, Durbin R. Using probabilistic estimation of expression residuals (PEER) to obtain increased power and interpretability of gene expression analyses. Nat Protoc. 2012;7(3):500-7. doi: 10.1038/nprot.2011.457. PubMed PMID: 22343431.

35. Gelernter J, Sun N, Polimanti R, Pietrzak R, Levey DF, Bryois J, Lu Q, Hu Y, Li B, Radhakrishnan K, Aslan M, Cheung K-H, Li Y, Rajeevan N, Sayward F, Harrington K, Chen Q, Cho K, Pyarajan S, Sullivan PF, Quaden R, Shi Y, Hunter-Zinck H, Gaziano JM, Concato J, Zhao H, Stein MB, Department of Veterans Affairs Cooperative Studies P, Million Veteran P. Genome-wide association study of post-traumatic stress disorder reexperiencing symptoms in >165,000 US veterans. Nature neuroscience. 2019;22(9):1394-401. Epub 07/29. doi: 10.1038/s41593-019-0447-7. PubMed PMID: 31358989.

36. Turley P, Walters RK, Maghzian O, Okbay A, Lee JJ, Fontana MA, Nguyen-Viet TA, Wedow R, Zacher M, Furlotte NA, Magnusson P, Oskarsson S, Johannesson M, Visscher PM, Laibson D, Cesarini D, Neale BM, Benjamin DJ. Multi-trait analysis of genome-wide association summary statistics using MTAG. Nat Genet. 2018;50(2):229-37. Epub 2018/01/03. doi: 10.1038/s41588-017-0009-4. PubMed PMID: 29292387 PMCID: PMCPMC5805593.

37. Watanabe K, Stringer S, Frei O, Umićević Mirkov M, de Leeuw C, Polderman TJC, van der Sluis S, Andreassen OA, Neale BM, Posthuma D. A global overview of pleiotropy and genetic architecture in complex traits. Nat Genet. 2019;51(9):1339-48. Epub 2019/08/21. doi: 10.1038/s41588-019-0481-0. PubMed PMID: 31427789.

38. McCullough KM, Chatzinakos C, Hartmann J, Missig G, Neve RL, Fenster RJ, Carlezon WA, Daskalakis NP, Ressler KJ. Genome-wide translational profiling of amygdala Crh-expressing neurons reveals role for CREB in fear extinction learning. Nature Communications. 2020;11(1):5180. doi: 10.1038/s41467-020-18985-6.

39. Konopka G, Bomar JM, Winden K, Coppola G, Jonsson ZO, Gao F, Peng S, Preuss TM, Wohlschlegel JA, Geschwind DH. Human-specific transcriptional regulation of CNS development genes by FOXP2. Nature. 2009;462(7270):213-7. Epub 2009/11/13. doi: 10.1038/nature08549. PubMed PMID: 19907493 PMCID: PMCPMC2778075.

40. Schieweck R, Kiebler MA. Posttranscriptional Gene Regulation of the GABA Receptor to Control Neuronal Inhibition. Frontiers in Molecular Neuroscience. 2019;12(152). doi: 10.3389/fnmol.2019.00152.

41. Sheen VL, Ganesh VS, Topcu M, Sebire G, Bodell A, Hill RS, Grant PE, Shugart YY, Imitola J, Khoury SJ, Guerrini R, Walsh CA. Mutations in ARFGEF2 implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. Nat Genet. 2004;36(1):69-76. Epub 2003/12/03. doi: 10.1038/ng1276. PubMed PMID: 14647276.

42. Saitoh Y, Kamijo A, Yamauchi J, Sakamoto T, Terada N. The membrane palmitoylated protein, MPP6, is involved in myelin formation in the mouse peripheral nervous system. Histochemistry and cell biology. 2019;151(5):385-94. Epub 2018/10/26. doi: 10.1007/s00418-018-1745-y. PubMed PMID: 30357511.

43. Li Y, Ohira M, Zhou Y, Xiong T, Luo W, Yang C, Li X, Gao Z, Zhou R, Nakamura Y, Kamijo T, Kaneko Y, Taketani T, Ueyama J, Tajiri T, Zhang H, Wang J, Yang H, Yin Y, Nakagawara A. Genomic analysis–integrated whole-exome sequencing of neuroblastomas identifies genetic mutations in axon guidance pathway. Oncotarget. 2017;8(34).

44. Perez-Ortiz AC, Peralta-Ildefonso MJ, Lira-Romero E, Moya-Albor E, Brieva J, Ramirez-Sanchez I, Clapp C, Luna-Angulo A, Rendon A, Adan-Castro E, Ramírez-Hernández G, Díaz-Lezama N, Coral-Vázquez RM, Estrada-Mena FJ. Lack of Delta-Sarcoglycan (Sgcd) Results in Retinal Degeneration. International journal of molecular sciences. 2019;20(21). Epub 2019/11/07. doi: 10.3390/ijms20215480. PubMed PMID: 31689918 PMCID: PMCPMC6862322.

45. Wang P, Zhao W, Zhao K, Zhang L, Gao C. TRIM26 Negatively Regulates Interferon-β Production and Antiviral Response through Polyubiquitination and Degradation of Nuclear IRF3. PLOS Pathogens. 2015;11(3):e1004726. doi: 10.1371/journal.ppat.1004726.

46. Miao X, Xiang Y, Mao W, Chen Y, Li Q, Fan B. TRIM27 promotes IL-6-induced proliferation and inflammation factor production by activating STAT3 signaling in HaCaT cells. American Journal of Physiology-Cell Physiology. 2019;318(2):C272-C81. doi: 10.1152/ajpcell.00314.2019.

47. Ishigaki K, Kochi Y, Suzuki A, Tsuchida Y, Tsuchiya H, Sumitomo S, Yamaguchi K, Nagafuchi Y, Nakachi S, Kato R, Sakurai K, Shoda H, Ikari K, Taniguchi A, Yamanaka H, Miya F, Tsunoda T, Okada Y, Momozawa Y, Kamatani Y, Yamada R, Kubo M, Fujio K, Yamamoto K. Polygenic burdens on cell-specific pathways underlie the risk of rheumatoid arthritis. Nature genetics. 2017;49(7):1120-5. doi: 10.1038/ng.3885.

48. Huckins LM, Chatzinakos C, Breen MS, Hartmann J, Klengel T, da Silva Almeida AC, Dobbyn A, Girdhar K, Hoffman GE, Klengel C, Logue MW, Lori A, Maihofer AX, Morrison FG, Nguyen HT, Park Y, Ruderfer D, Sloofman LG, van Rooij SJH, Baker DG, Chen C-Y, Cox N, Duncan LE, Geyer MA, Glatt SJ, Im HK, Risbrough VB, Smoller JW, Stein DJ, Yehuda R, Liberzon I, Koenen KC, Jovanovic T, Kellis M, Miller MW, Bacanu S-A, Nievergelt CM, Buxbaum JD, Sklar P, Ressler KJ, Stahl EA, Daskalakis NP. Analysis of Genetically Regulated Gene Expression Identifies a Prefrontal PTSD Gene, SNRNP35, Specific to Military Cohorts. Cell Reports. 2020;31(9):107716. doi: https://doi.org/10.1016/j.celrep.2020.107716.

49. Girgenti MJ, Wang J, Ji D, Cruz DA, Alvarez VE, Benedek D, Brady C, Davis DA, Holtzheimer PE, Keane TM, Kowell N, Logue MW, McKee A, Marx B, Mash D, Miller MW, Scott WK, Stein T, Ursano R, Wolf EJ, Stein MB, Gelernter J, Young KA, Huber BR, Williamson DE, Friedman MJ, Krystal JH, Zhao H, Duman RS, Traumatic Stress Brain Research G. Transcriptomic organization of the human brain in post-traumatic stress disorder. Nature Neuroscience. 2021;24(1):24-33. doi: 10.1038/s41593-020-00748-7.

50. Sniekers S, Stringer S, Watanabe K, Jansen PR, Coleman JRI, Krapohl E, Taskesen E, Hammerschlag AR, Okbay A, Zabaneh D, Amin N, Breen G, Cesarini D, Chabris CF, Iacono WG, Ikram MA, Johannesson M, Koellinger P, Lee JJ, Magnusson PKE, McGue M, Miller MB, Ollier WER, Payton A, Pendleton N, Plomin R, Rietveld CA, Tiemeier H, van Duijn CM, Posthuma D. Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. Nature genetics. 2017;49(7):1107-12. doi: 10.1038/ng.3869.

51. Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, Savage JE, Hammerschlag AR, Skene NG, Muñoz-Manchado AB, Agee M, Alipanahi B, Auton A, Bell RK, Bryc K, Elson SL, Fontanillas P, Furlotte NA, Hinds DA, Hromatka BS, Huber KE, Kleinman A, Litterman NK, McIntyre MH, Mountain JL, Noblin ES, Northover CAM, Pitts SJ, Sathirapongsasuti JF, Sazonova OV, Shelton JF, Shringarpure S, Tian C, Tung JY, Vacic V, Wilson CH, White T, Tiemeier H, Linnarsson S, Hjerling-Leffler J, Polderman TJC, Sullivan PF, van der Sluis S, Posthuma D, andMe Research T. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nature genetics. 2018;50(7):920-7. doi: 10.1038/s41588-018-0151-7.

52. Abdellaoui A, Sanchez-Roige S, Sealock J, Treur JL, Dennis J, Fontanillas P, Elson S, The 23andme Research T, Nivard MG, Ip HF, van der Zee M, Baselmans BML, Hottenga JJ, Willemsen G, Mosing M, Lu Y, Pedersen NL, Denys D, Amin N, M van Duijn C, Szilagyi I, Tiemeier H, Neumann A, Verweij KJH, Cacioppo S, Cacioppo

JT, Davis LK, Palmer AA, Boomsma DI. Phenome-wide investigation of health outcomes associated with genetic predisposition to loneliness. Human Molecular Genetics. 2019;28(22):3853-65. doi: 10.1093/hmg/ddz219.

53. Selzam S, Coleman JRI, Caspi A, Moffitt TE, Plomin R. A polygenic p factor for major psychiatric disorders. Translational Psychiatry. 2018;8(1):205. doi: 10.1038/s41398-018-0217-4.

54. Dahl A, Cai N, Ko A, Laakso M, Pajukanta P, Flint J, Zaitlen N. Reverse GWAS: Using genetics to identify and model phenotypic subtypes. PLOS Genetics. 2019;15(4):e1008009. doi: 10.1371/journal.pgen.1008009.

55. Hayes JP, Hayes SM, Mikedis AM. Quantitative meta-analysis of neural activity in posttraumatic stress disorder. Biology of mood & anxiety disorders. 2012;2:9. Epub 2012/06/29. doi: 10.1186/2045-5380-2-9. PubMed PMID: 22738125 PMCID: PMCPMC3430553.

56. Stevens JS, Kim YJ, Galatzer-Levy IR, Reddy R, Ely TD, Nemeroff CB, Hudak LA, Jovanovic T, Rothbaum BO, Ressler KJ. Amygdala Reactivity and Anterior Cingulate Habituation Predict Posttraumatic Stress Disorder Symptom Maintenance After Acute Civilian Trauma. Biological psychiatry. 2017;81(12):1023-9. Epub 12/23. doi: 10.1016/j.biopsych.2016.11.015. PubMed PMID: 28117048.

57. Miller DR, Hayes SM, Hayes JP, Spielberg JM, Lafleche G, Verfaellie M. Default Mode Network Subsystems are Differentially Disrupted in Posttraumatic Stress Disorder. Biological psychiatry Cognitive neuroscience and neuroimaging. 2017;2(4):363-71. Epub 2017/04/25. doi: 10.1016/j.bpsc.2016.12.006. PubMed PMID: 28435932 PMCID: PMCPMC5396184.

58. Morey RA, Dolcos F, Petty CM, Cooper DA, Hayes JP, LaBar KS, McCarthy G. The role of trauma-related distractors on neural systems for working memory and emotion processing in posttraumatic stress disorder. Journal of psychiatric research. 2009;43(8):809-17. Epub 2008/12/19. doi: 10.1016/j.jpsychires.2008.10.014. PubMed PMID: 19091328 PMCID: PMCPMC2684984.

59. Nicholson AA, Rabellino D, Densmore M, Frewen PA, Paret C, Kluetsch R, Schmahl C, Théberge J, Neufeld RW, McKinnon MC, Reiss J, Jetly R, Lanius RA. The neurobiology of emotion regulation in posttraumatic stress disorder: Amygdala downregulation via real-time fMRI neurofeedback. Human brain mapping. 2017;38(1):541-60. Epub 2016/09/21. doi: 10.1002/hbm.23402. PubMed PMID: 27647695 PMCID: PMCPMC6866912.

60. Felmingham KL, Falconer EM, Williams L, Kemp AH, Allen A, Peduto A, Bryant RA. Reduced amygdala and ventral striatal activity to happy faces in PTSD is associated with emotional numbing. PloS one. 2014;9(9):e103653. Epub 2014/09/04. doi: 10.1371/journal.pone.0103653. PubMed PMID: 25184336 PMCID: PMCPMC4153581.

61. Morey RA, Davis SL, Garrett ME, Haswell CC, Marx CE, Beckham JC, McCarthy G, Hauser MA, Ashley-Koch AE, Mid-Atlantic MW. Genome-wide association study of subcortical brain volume in PTSD cases and trauma-exposed controls. Translational Psychiatry. 2017;7(11):1265. doi: 10.1038/s41398-017-0021-6.

62. Olson EA, Kaiser RH, Pizzagalli DA, Rauch SL, Rosso IM. Anhedonia in Trauma-Exposed Individuals: Functional Connectivity and Decision-Making Correlates. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2018;3(11):959-67. doi: https://doi.org/10.1016/j.bpsc.2017.10.008.

63. Galatzer-Levy IR, Bryant RA. 636,120 Ways to Have Posttraumatic Stress Disorder. Perspectives on Psychological Science. 2013;8(6):651-62. doi: 10.1177/1745691613504115.

64. Cai N, Choi KW, Fried EI. Reviewing the genetics of heterogeneity in depression: operationalizations, manifestations and etiologies. Human Molecular Genetics. 2020;29(R1):R10-R8. doi: 10.1093/hmg/ddaa115.

65. Olff M, Langeland W, Draijer N, Gersons BP. Gender differences in posttraumatic stress disorder. Psychological bulletin. 2007;133(2):183-204. Epub 2007/03/07. doi: 10.1037/0033-2909.133.2.183. PubMed PMID: 17338596.

66. Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, Karam EG, Meron Ruscio A, Benjet C, Scott K, Atwoli L, Petukhova M, Lim CCW, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, Bunting B, Ciutan M, de Girolamo G, Degenhardt L, Gureje O, Haro JM, Huang Y, Kawakami N, Lee S, Navarro-Mateu F, Pennell BE, Piazza M, Sampson N, Ten Have M, Torres Y, Viana MC, Williams D, Xavier M, Kessler RC. Posttraumatic stress disorder in the World Mental Health Surveys. Psychological medicine. 2017;47(13):2260-74. Epub 2017/04/08. doi: 10.1017/s0033291717000708. PubMed PMID: 28385165 PMCID: PMCPMC6034513.

67. Duncan LE, Ratanatharathorn A, Aiello AE, Almli LM, Amstadter AB, Ashley-Koch AE, Baker DG, Beckham JC, Bierut LJ, Bisson J, Bradley B, Chen CY, Dalvie S, Farrer LA, Galea S, Garrett ME, Gelernter JE, Guffanti G, Hauser MA, Johnson EO, Kessler RC, Kimbrel NA, King A, Koen N, Kranzler HR, Logue MW, Maihofer AX, Martin AR, Miller MW, Morey RA, Nugent NR, Rice JP, Ripke S, Roberts AL, Saccone NL, Smoller JW, Stein DJ, Stein MB, Sumner JA, Uddin M, Ursano RJ, Wildman DE, Yehuda R, Zhao H, Daly MJ, Liberzon I, Ressler KJ, Nievergelt CM, Koenen KC. Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. Molecular Psychiatry. 2018;23(3):666-73. doi: 10.1038/mp.2017.77.

68. Benjet C, Bromet E, Karam EG, Kessler RC, McLaughlin KA, Ruscio AM, Shahly V, Stein DJ, Petukhova M, Hill E, Alonso J, Atwoli L, Bunting B, Bruffaerts R, Caldas-de-Almeida JM, de Girolamo G, Florescu S, Gureje O, Huang Y, Lepine JP, Kawakami N, Kovess-Masfety V, Medina-Mora ME, Navarro-Mateu F, Piazza M, Posada-Villa J, Scott KM, Shalev A, Slade T, ten Have M, Torres Y, Viana MC, Zarkov Z, Koenen KC. The epidemiology of traumatic event exposure worldwide: results from the World Mental

Health Survey Consortium. Psychological medicine. 2016;46(2):327-43. Epub 2015/10/30. doi: 10.1017/s0033291715001981. PubMed PMID: 26511595 PMCID: PMCPMC4869975.

69. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. Nature genetics. 2019;51(4):584-91. doi: 10.1038/s41588-019-0379-x.

70. Atkinson EG, Maihofer AX, Kanai M, Martin AR, Karczewski KJ, Santoro ML, Ulirsch JC, Kamatani Y, Okada Y, Finucane HK, Koenen KC, Nievergelt CM, Daly MJ, Neale BM. Tractor uses local ancestry to enable the inclusion of admixed individuals in GWAS and to boost power. Nature genetics. 2021. doi: 10.1038/s41588-020-00766-y.

71. Koenen KC, Stellman SD, Dohrenwend BP, Sommer JF, Jr., Stellman JM. The consistency of combat exposure reporting and course of PTSD in Vietnam War veterans. Journal of traumatic stress. 2007;20(1):3-13. Epub 2007/03/09. doi: 10.1002/jts.20191. PubMed PMID: 17345644.

72. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. Epidemiology. 2014;25(5):749-61. doi: 10.1097/EDE.0000000000000121. PubMed PMID: 25000145.

73. Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address pmhe, Cross-Disorder Group of the Psychiatric Genomics C. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. Cell. 2019;179(7):1469-82 e11. Epub 2019/12/14. doi: 10.1016/j.cell.2019.11.020. PubMed PMID: 31835028 PMCID: PMCPMC7077032.

74. Grotzinger AD, Mallard TT, Akingbuwa WA, Ip HF, Adams MJ, Lewis CM, McIntosh AM, Grove J, Dalsgaard S, Peter-Lesch K, Strom N, Meier SM, Mattheisen M, Børglum AD, Mors O, Breen G, Lee PH, Kendler KS, Smoller JW, Tucker-Drob EM, Nivard MG. Genetic Architecture of 11 Major Psychiatric Disorders at Biobehavioral, Functional Genomic, and Molecular Genetic Levels of Analysis. medRxiv. 2020:2020.09.22.20196089. doi: 10.1101/2020.09.22.20196089.

Chapter 3: Rare copy number variation in post traumatic stress disorder

3.1 Abstract

Background: Post traumatic stress disorder (PTSD) is a heritable (24%-71%) psychiatric illness. Copy number variation (CNV) is a form of rare genetic variation that has been implicated for its role in psychiatric disorders, but no large-scale investigation of CNV in PTSD has been performed. We present the largest association study between CNV burden and PTSD symptoms in a sample of 114,383 participants.

Methods: CNVs were called using two calling algorithms and intersected to a consensus set. Quality control was performed to remove strong outlier samples. CNVs were examined for association with PTSD within each cohort using linear or logistic regression analysis adjusted for population structure and CNV quality metrics, then inverse variance weighted meta-analyzed across cohorts. CNVs were examined on the level of genome-wide total span of CNVs, enrichment of CNVs within specified gene-sets, within individual genes, and implicated neurodevelopmental regions.

Results: PTSD risk was elevated in CNVs that crossed over known neurodevelopmental CNV regions (beta=0.0089, SE=0.0020, $P=9.9 \times 10^{-6}$). The genome-wide neurodevelopmental CNV burden identified explains 0.033% of the variation in PTSD symptoms. Specifically, CNVs overlapping known neurodevelopmental CNV regions, 15q11.2 and 22q11.2, were significantly associated with PTSD. No individual significant genes interrupted by CNV were identified, but 7 gene pathways related to the function of the nervous system and brain were significant (FDR $q<0.05$).

Conclusion: This study is the first to identify significant association of CNVs with PTSD. Larger sample size data, better detection methods, and annotated resources of CNV are needed to explore this relationship further.

3.2 Introduction

Post traumatic stress disorder (PTSD) has a substantial genetic component [1]. Recent large investigations of PTSD genetics have focused on common genetic variation [2, 3], but rare and structural forms of genetic variation are hypothesized to be important contributors to the development of psychiatric disorders [4]. Rare and structural variation have been little studied in the context of PTSD [5]. However, these forms of variation have been studied more thoroughly in the context of other psychiatric disorders, where many investigations have specifically focused on copy number variants (CNVs) [6]. CNV associations have been identified for attention-deficit/hyperactivity disorder (ADHD) [7], autism spectrum disorder (ASD) [8], depression [9, 10], obsessive-compulsive disorder (OCD) [11], and schizophrenia [12]. Many of the identified psychiatric associations involved neurodevelopmental disorder (NDD) implicated CNVs with high penetrance [9, 10, 13], but also the cumulative burden of CNVs across the genome and enrichment over specific pathways related to the brain and development of the nervous system [12]. Largely owing to lack of available data, there has been no major reported investigation of CNVs and PTSD. However, the recent availability of large sample size PTSD genetic data [2] and available techniques to leverage this data to identify CNVs [14], means that it is now possible to investigate the association between PTSD and CNV burden with an unprecedented level of discovery power.

We present an association study between CNVs and PTSD symptoms, conducted in a sample of 114,383 participants from the Psychiatric Genomics Consortium - PTSD [2, 15]. We detected rare (<1% population frequency) CNVs using algorithms [16-18] applied to the SNP genotyping array intensity data. Following this, we

examined the impact of CNV on PTSD on multiple scales: genome-wide CNV burden, enrichment over 46 neuropsychiatric gene-sets (15), CNV burden on individual genes, and CNV carrier status over 53 previously implicated NDD CNV regions [9]. We conclude by comparing the risk contribution from CNVs to the contribution of common variant polygenic risk scores (PRSs).

3.3 Methods

3.3.1 Participants and phenotyping

The study sample consisted of 114,383 European ancestry participants across 20 cohorts within the Psychiatric Genomics Consortium - PTSD freeze 2 data collection. Details of genotyping and phenotype measurement have been described in detail [2]. In brief, participants were assessed for PTSD using either clinical assessment, clinician administered inventory, or self-reported inventory (Supplementary Table 3.1). Participants were genotyped using Illumina arrays, with the exception that the UK Biobank (UKBB) cohort used Affymetrix arrays. For this investigation, we retained only cohorts and collections of cohorts that were genotyped and analyzable together with at least 150 unrelated samples of genetically determined European ancestry (2). All participants provided written informed consent, and studies were approved by the relevant institutional review boards and the University of California San Diego Human Research Protection Program.

3.3.2 CNV calling

Illumina genotype platform data was self-clustered in Genome-Studio 2.0 and exported as intensity data inputs for CNV callers (SNP name, chromosome, position, allele 1, allele 2, B allele frequency, log R ratio, X, and Y). Affymetrix platform genotype

data clustering methods have been described previously (9), and log R ratio and B allele frequency data were downloaded directly from the UKBB. For Illumina datasets, CNV were quality controlled according to the PGC CNV calling pipeline for Illumina data [12]. For Illumina data, CNVs were called using PennCNV [17] and iPattern [16]. For Affymetrix data, CNVs were called using PennCNV and QuantiSNP [18]. For PennCNV calling, population frequency of B allele files were generated using the data itself. Waviness correction was applied using a GC content model file generated from UCSC gc_model data (https://genome.ucsc.edu/cgi-bin/hgTables). For the Hidden Markov Model input of PennCNV, the pre-supplied files were used: hhall.hmm for Illumina data and was affygw6.hmm for the UKBB data (https://penncnv.openbioinformatics.org/en/latest/user-guide/input/#hmm-file). iPattern calls were made using the default program settings, in batches of up to 196 samples. Batches were selected such that samples within a batch were genotyped on the same plate or genotyped at approximately the same time.

3.3.3 CNV quality control

To ensure that the analysis included a reliable set of calls, CNV calls from PennCNV and iPattern were intersected and merged to produce a consensus set. CNVs called as gain by one method and loss by the other were also excluded from further analyses. Fragmented large CNVs in a locus were annealed if the gap length between them was less than 30% of the overall length of the annealed CNV. CNV quality metrics calculated by PennCNV were used to perform sample QC. Subjects were removed if their values for SD of log R ratio, B allele frequency, or waviness were >= Q3 + 3IQR, if >20% of any chromosome was copy number variant (aneuploidy), or if

they had excessive CNV count (>= Q3 + 3IQR CNVs) or KB burden (>= Q3 + 3 IQR megabases). Participants who failed standard genotype QC described in Nievergelt et al. [2] (sample missingness rates>2%, excess heterozygosity, mismatch between self-reported sex and genetically determined sex, π relatedness coefficient>0.2) were also removed. We removed CNVs for any of the following reasons: 50% overlap with centromeres, telomere, immunoglobulin or T-cell receptor loci, >50% overlap with known segmental duplications, CNV frequency > 1% (measured within the data) in cases and controls and < 10kb in CNV length or intersecting < 10 probes.

3.3.4 CNV burden calculation

CNV burden was measured and evaluated for association with PTSD in multiple ways: The cumulative burden of CNVs was calculated as the genome-wide total distance (in megabases) spanned by CNVs. For each of the 53 NDD CNV regions, NDD CNV carrier status was determined as having at least 50% of the NDD CNV region overlapped by CNV. As a sensitivity analysis, two different overlap criteria (>0% or 100% overlap) were also evaluated. For gene-level CNV burden, first gene positions (GRCh37 human genome build) were downloaded from the UCSC table browser (https://genome.ucsc.edu/cgi-bin/hgTables). Genes were filtered to protein coding genes, based on having an "NM_" accession prefix in the National Center for Biotechnology Information reference sequence database [19]. For genes with multiple isoforms, the minimum start and the maximum end positions were used. For each CNV, the CNV was mapped to all genes it overlapped by at least one base pair. The CNV burden variable was then calculated for each gene, coded 1 if the subject carried a CNV that mapped onto the gene, and 0 otherwise. For gene-set analysis, a gene-set

burden variable was calculated for each set tested, coded as the number of genes within the set overlapped by the CNVs. The gene-set analysis included 53 gene-sets, consisting of 23 gene-sets related to neurofunction or nervous system, 6 brain expression from BrainSpan consortium and 7 mouse phenotype negative control gene-sets from previous neurological disorders studies [12, 20], a set of loss-of-function intolerant genes as defined by gnomAD v2.0 [21], and 16 brain-expressed gene-sets from human neocortex scRNA data [22].

3.3.5 Statistical Analyses

Within each cohort, the association between PTSD and CNVs was tested using a regression model of PTSD as predicted by the CNV variable, 5 principal components captured population structure [2], and the log R ratio standard deviation sample quality metric from PennCNV. For the gene-set analyses, in order to follow the enrichment test model outlined by Raychaudhuri et al. [23] analyses also contained predictors for genome-wide total CNV count, genome-wide average length of CNVs, count of CNV overlapping NDD regions, and average length of NDD overlapping CNVs. Linear regression was used for cohorts with continuous PTSD symptom measures, and probit regression was used for case/control cohorts. Results across cohorts were meta-analyzed using fixed effects inverse variance weighted meta-analysis in the metafor [24] R package. For the meta-analysis, to account for the different PTSD measure scales used across cohorts, PTSD measures were scaled from 0 to 1 according to the theoretical range of scores of the assessment method (i.e. 0 = no PTSD symptoms, 1 = theoretical maximum possible PTSD symptoms), and case/control estimates were interpreted as being the observed, censored variable for a latent symptom measure variable.

Polygenic risk scores (PRSs) for PTSD were computed using PRSice2 v2.3.5 [25], where Million Veteran Program PTSD GWAS [3] summary statistics were used as the discovery dataset and the UKBB was used as the target. SNPs were filtered to common (minor allele frequency > 1%) variants and were linkage disequilibrium clumped (r-squared > 0.1, 250 KB window). The optimal PRS threshold was selected as the one with the lowest p-value in a regression model of PTSD in the UKBB. The proportion of variance in PTSD explained by PRS and CNV was the difference in model r-squared values between a baseline model that included basic covariates and an extended model with additional terms for PRS and CNV.

3.4 Results

The PTSD CNV meta-analysis included 114,383 participants of European ancestry across 20 cohorts (Supplementary Table 3.1, Table 3.1). 15 cohorts were genotyped using the Psych array (N=6,813 samples), 1 with the Psych Chip (N=756 samples), 3 with the OmniExpressExome+Custom content (N=9,432 samples), and one with the Affymetrix UK Biobank Axiom array (N=97,382). The method of PTSD assessment varied across cohorts, with most participants being assessed via PCL (N=106,353). The final dataset included 103,036 CNVs (41,473 gains and 61,563 losses), an average of 0.90 CNVs per sample (SD=1.03). 60.1% of subjects were carriers of at least one CNV (Table 3.1). Among CNV carriers, the average total span of CNV carried was 0.32 megabases (SD=0.35), and the average of within subject average CNV lengths was 0.23 megabases (SD=0.26)

3.4.1 Genome-wide CNV burden analysis

Genome-wide cumulative CNV burden was significantly associated with PTSD (beta=0.0028, SE=0.0008, P=0.0003) (Figure 3.1). We examined CNV burden stratified by type (duplication or deletion), finding that the total distance covered by deletions was significant (beta=0.0046, SE=0.0013, P=0.0004) but the total distance covered by duplications was not (beta=0.0018, SE=0.0010, P=0.065). Next, we examined CNV burden stratified by overlap with any of 53 previously implicated NDD CNV regions. The cumulative burden of CNV deletions that overlapped NDD regions was significantly associated with PTSD (beta=0.0290, SE=0.0054, $P=6.3 \times 10^{-8}$), while the duplication burden was only suggestively significant (beta=0.0053, SE=0.0023, P=0.024). The genome-wide burden of non-NDD CNV deletions was only suggestively significant (beta=0.0031, SE=0.0013, P=0.023), but significant if we considered only the CNVs overlapping genes (beta=0.0039, SE=0.0014, P=0.0065) (Supplementary Table 3.2).

3.4.2 Specific NDD CNV regions confer risk for PTSD

We investigated the association between PTSD and NDD CNV carrier status. 33 out of 53 NDD CNVs had at least 1 carrier (Supplementary Table 3.3). The most common NDD CNV was the 15q11.2 BP1-BP2 deletion (N=529 carriers, frequency = 0.0046). Two NDD CNV were significantly associated with increased PTSD symptoms, the 2q13 deletion (chr2:111,394,040-112,012,649, N=15 carriers, beta=0.1455, SE=0.0367, P=0.0001) and the 15q11.2 BP1-BP2 microdeletion (chr15:22,805,313-23,094,530, N=529 carriers, beta=0.0206, SE=0.0056, P=0.0002) (Figure 3.2). Given the limited number of carriers for 2q13, we tested the association again using robust standard errors, finding that the result was no longer significant (P=0.11). Overall results were similar under a stricter definition of carrier status (100% overlap of NDD CNV

region) (Supplementary Table 3.3). Under a loose definition of carrier status (>0% overlap of NDD CNV region), the 8p23.1 del, 15q11.2 BP1-BP2 del, 15q11.2q12 Prader-Willi/Angelman syndrome del, and 22q11.2 dup regions were significant.

3.4.3 Gene-level analysis

We examined CNV association on the level of protein coding genes. 2,880 genes harbored CNV with at least 0.01% frequency. We found that no gene was significant after multiple comparisons correction for the number of genes, in any strata (overall CNV, duplications, or deletions) (Supplementary table 4.4). However, the most significant genes among deletions were those in the 15q11.2 BP1-BP2 region and the most significant genes among duplications were in the 22q11.2 dup region.

3.4.4 Deletion burden aggregates across nervous system related gene-sets

We investigated if CNV burden association with PTSD was enriched in any of 46 different gene-sets related to the brain and nervous system. We identified 7 sets enriched in deletions. Out of these 7 gene-sets, 4 were neurofunction or nervous systems-related, two were sets of genes expressed in maturing excitatory neurons, and a set of genes highly expressed in the brain (Supplementary Table 3.5). For the genes highly expressed in the brain, we found that the enrichment is mainly from those expressed in the postnatal stage (beta=0.0023, SE=0.0010, P=0.023, FDR-q=0.10) (Supplementary Table 3.5). Many of the leading genes in these significant sets were overlapped by NDD CNVs (Supplementary table 3.6). As a sensitivity analysis, we removed subjects with CNV overlapping NDD regions (Supplementary Table 3.7). Under this analysis, gene-sets related to nervous system and neurological functions remained FDR significant, while the others fell outside of significance (FDR-q<0.1).

3.4.5 Comparisons with common variant genetics

We generated PTSD polygenic risk scores in our data using MVP PTSD GWAS as the training dataset and the UKBB as the target dataset. Common variant PRS explained 0.38% of the variation in PTSD symptoms (optimal pT=0.11, beta=0.0080, SE=0.0004, $P=5.3 \times 10^{-83}$). Adding coefficient for cumulative burden of CNV overlapping NDD CNV regions explained an additional 0.033% of the variation (beta=0.0418, SE=0.0073, $P=1.2 \times 10^{-8}$) (Supplementary Table 3.8).

3.5 Discussion

The association between the cumulative burden of CNVs and PTSD was largely driven by CNVs overlapping previously implicated NDD CNV regions. This is a quite similar finding to those of two recent studies of major depression and CNVs [9, 10]. In terms of how this burden modifies depression risk, Kendall et al. [9] suggested that some of the CNV effects are mediated by sociodemographic risk factors. As PTSD has similar risk factors [26], NDD CNVs may influence PTSD risk via the same mediated mechanisms. We propose that some of the psychiatric and neurodevelopmental consequences of CNVs may also increase PTSD risk, as they represent PTSD risk factors [27 28].

In examining the individual NDD CNVs, the most significant association we observed with PTSD was the 15q11.2 BP1-BP2 microdeletion, one of the most frequently occurring pathogenic CNVs identified in humans [29]. This CNV is associated with alterations in brain morphology and cognition [30]. There a wide variety of possible clinical manifestations, including developmental delays, intellectual disability, as well as behavioral and psychiatric problems, including ADHD, ASD and schizophrenia [31].

However, some of these associated outcomes are thought to be false positives caused by ascertainment bias [32]. Under a less strict definition of NDD carrier status (>0% overlap with NDD CNV region), the most significant association identified was with the 22q11.2 duplication region. The 22q11.2 duplication has a variety of deleterious impacts [33], but generally they are less severe than those observed in the 22q11.2 deletion [34]. Rather than any specific functional aspects of these CNVs having led to the significant associations that we observed, we suspect that their relatively high frequencies in the data made them among the most statistically powered to identify.

On a broader level, we observed enrichment of CNVs overlapping gene-sets related to the function of the brain and nervous system, such as deletions in genes expressed in maturing excitatory neurons, as well as those highly expressed in the brain during the postnatal stage. These results are fairly in line with findings from common variant analyses of PTSD and other psychiatric disorders, which tend to find enrichment of signals in brain regions and neurodevelopmental gene-sets [3, 35-37]. Thus, CNVs may ultimately influence the same genes and pathways as common variants, as was recently hypothesized in an analysis of schizophrenia [38].

Our PRS analysis suggests that CNVs represent genetic risk factors for PTSD that are not readily identified by common variant analyses. In terms of the accuracy of population risk prediction, the addition of CNVs was only a marginal improvement over PRS. However, given the rarity of CNVs, population genetic risk prediction may not be the most useful aspect [39] of determining CNV risk. Rather, CNV carriers may be a subset of individuals for whom a tailored health management strategy [39] applies. Indeed, CNV carrier status has been proposed as a tool in clinical decision making for

psychiatric disorders, albeit one that will first require expansion of the clinical knowledge base of CNVs [40]. But it is unclear how much this will apply directly to PTSD, as the CNV effect sizes we observed were relatively modest compared to the ones observed in disorders like schizophrenia [12].

3.5.1 Limitations

We focused only on rare (<1% frequency) CNVs larger than 10 kilobases in length due to the detection limits of array based CNV calling. However, small CNVs may have clinical importance [41, 42] . Future investigation of the relationship between small CNVs and PTSD will likely require sequencing data, as the dense genotyping allows for the determination of CNV at a higher resolution than SNP genotyping arrays [43]. Thus, we expect that CNV investigations will emerge as sequencing data becomes available from biobank resources [44] . We were unable to assess the impact of *de novo* CNV specifically, which would require case-parent trio data to identify. Yet, *de novo* variation is an important form of risk to investigate, as it occurs more often in cases than controls for ADHD, ASD, and schizophrenia [45]. PTSD genetic studies usually do not gather parent genotype data, implying that new data would need to be gathered in order to study this. We note that several of the cohorts investigated were from specially selected populations. The UKBB is known to be healthier than the general population of the United Kingdom [46]. As well, we analyzed several military populations, where good physical and mental health are required for enlistment. Due to carriers not having been selected for health reasons consequential to their carrier status, our study may have incorrectly estimated (or outright not detected) some effects of CNV on PTSD. Indeed, this may be why we specifically identified the 15q11.2 BP1-BP2 deletion and 22q11.2

duplications: As these CNVs have relatively milder impacts compared to some CNVs [32] [34], more seemingly unaffected carriers would exist in the investigated cohorts. We did not identify any particular genes where the presence of CNVs had a significant association with PTSD. The limited statistical power of low frequency variation [47] perhaps inhibited our ability to detect these genes. Therefore, we hypothesize that specific gene associations will emerge given greater sample sizes or analytic techniques more suited for this form of data, especially as we had positively identified specific gene-sets. We only tested for enrichment of gene sets related to the brain and nervous system, however, CNV may act on other relevant pathways; CNV are thought to have widespread phenotypic effects, such as on the immune system [48], which is also deeply implicated in PTSD development [49] .

3.5.2 Conclusions

We have performed, to our knowledge, the largest (N=114,383 participants) investigation of the influence of CNV burden on PTSD risk, and furthermore, are the first to identify significant associations. Risk was enriched in regions that crossed over known NDD regions and in pathways related to the function of the nervous system and brain. In particular, we have implicated the 15q11.2 BP1-BP2 microdeletion. Larger sample size data, better detection methods, and annotated resources of CNV are necessary to explore these relationships further.

3.6 Acknowledgements

This research has been conducted using the UK Biobank resource under application number 41209.

Chapter 3 is currently being prepared for submission for publication of the material. Co-authors include Worrawat Engchuan, Marieke Klein, Jeffrey R MacDonald, Omar Shanta, Bhooma Thiruvahindrapuram, Guillaume Huguet, Martineau Jean-louis, Zohra Saci, Sebastien Jacquemont, Stephen W Scherer, Elizabeth Ketema, , Allison E Aiello, Ananda B Amstadter, Esmina Avdibegovic, Dragan Babic, Jonathan I Bisson, Elizabeth A Bolger, Richard A Bryant, Jose Miguel Caldas-de-Almeida, Jurgen Deckert, Douglas L Delahanty, Katharina Domschke, Boadie Dunlop, Alma Dzubur-Kulenovic, Alexandra Evans, Norah C Feeny, Carol E Franz, Aarti Gautam, Aferdita Goci Uka, Rasha Hammamieh, Miro Jakovljevic, Marti Jett, Ian Jones, Milissa L Kaufman, Ronald C Kessler, Anthony P King, William S Kremen, Bruce R Lawford, Lauren A M Lebois, Catrin Lewis, Israel Liberzon, Sarah D Linnstaedt ,Bozo Lugonja, Michael J Lyons, Matig R Mavissakalian, Katie A McLaughlin, Samuel A McLean, Divya Mehta, Rebecca Mellor, Charles Phillip Morris, Seid Muhie, Holly K Orcutt, Matthew Peverill, Andrew Ratanatharathorn, Albert Rizzo, Andrea L Roberts, Alex O Rothbaum, Barbara O Rothbaum, Peter Roy-Byrne, Kenneth J Ruggiero, Julia S Seng, Christina M Sheerin, Martin H Teicher, Robert J Ursano, Joanne Voisey, Heike Weber, Sherry Winternitz, Ruoting Yang, Ross McD Young, Lori A Zoellner, Rany M Salem, Richard Shaffer, Tianying Wu, Kerry J Ressler, Murray B Stein, Karestan C Koenen, Jonathan Sebat, and Caroline M Nievergelt. The dissertation author was the primary investigator and author of this paper.

3.7 Figures

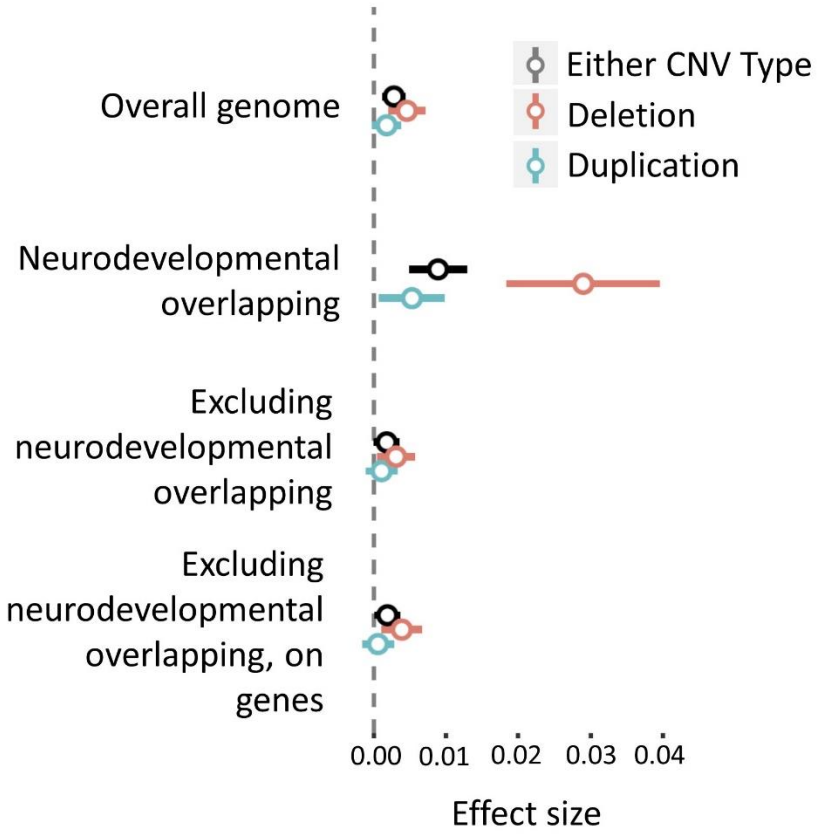

Figure 3.1. Genome-wide CNV burden association.

Footnote: The bar plot depicts regression beta coefficients as effect sizes (on the x-axis) of genome-wide CNV burden on PTSD, including overall burden, overlapping neurodevelopmental regions only, and genome-wide with neurodevelopmental regions excluded (on the y-axis). Data are shown stratified by CNV type, both CNV types (colored black), duplications only (colored red), and deletions only (colored blue). Effect sizes are shown in terms of megabases of the genome spanned by CNV.

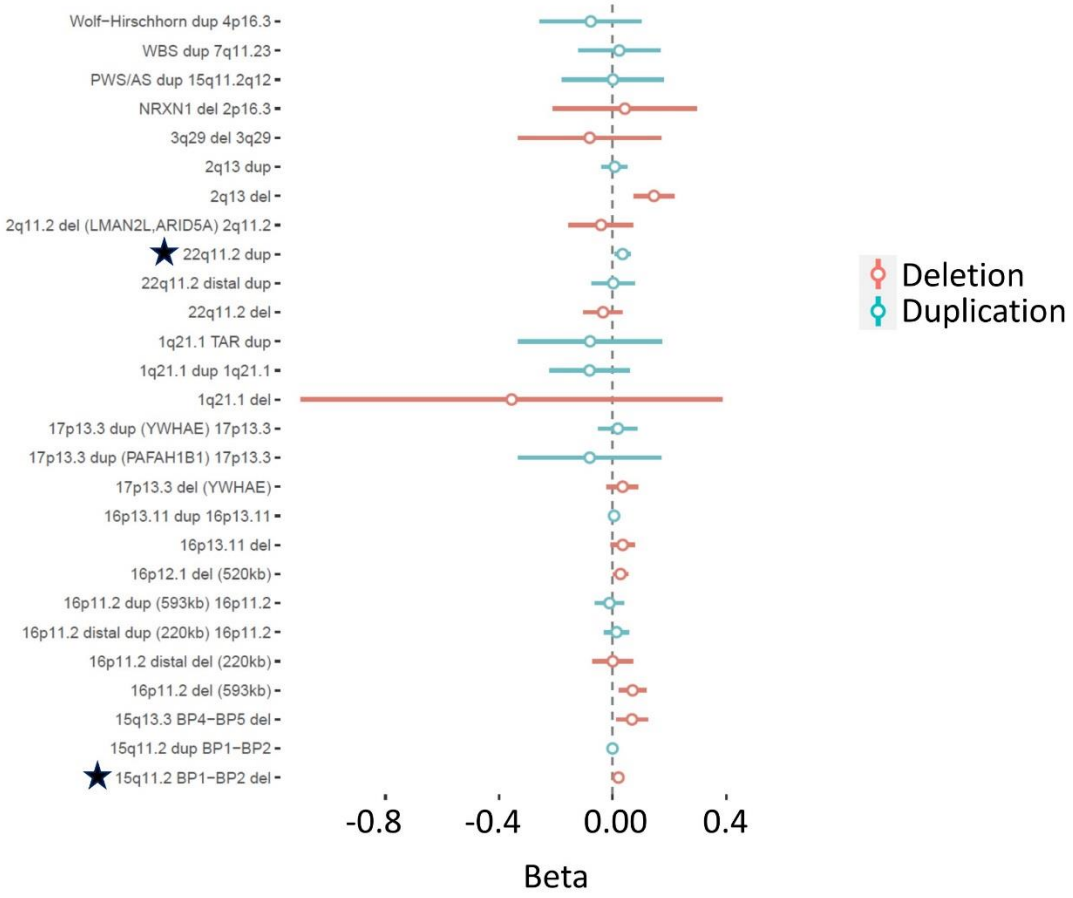

Figure 3.2. Association of individual NDD CNVs with PTSD

Footnote: The bar plot depicts regression beta coefficients as effect sizes (on the x-axis) of NDD CNVs (on the y-axis) on PTSD. Data are colored by CNV type, with deletions in blue and duplications in red. Effect sizes are shown in terms of megabases of the genome spanned by CNV. A star indicates an FDR significant CNVs.

Table 3.1. Cohorts analyzed

Number	Study	Genotyping array	N subjects	N CNVs	N Deletions	Duplication	N Carriers	CNV Span	SD	N CNV/Carrier	SD	Length	SD
52	FTCB	PsychChip	756	991	450	541	504	0.31	0.42	1.97	1.39	0.16	0.19
55	GMRF	PsychArray 1.1	192	177	80	97	105	0.40	0.56	1.69	0.96	0.21	0.19
54	GRAC	PsychArray 1.1	151	174	91	83	99	0.29	0.31	1.76	1.11	0.16	0.14
1	MRSC	OmniExpressExome8 + Custon	1374	2,927	1,399	1,528	1,147	0.26	0.32	2.55	1.74	0.10	0.12
14	NSS1	OmniExpressExome8 + Custon	3664	7,363	3,308	4,055	3,031	0.31	0.42	2.43	1.66	0.12	0.15
16	PPDS	OmniExpressExome8 + Custon	4394	9,012	4,052	4,960	3,649	0.28	0.37	2.47	1.67	0.11	0.16
21	PSY2	PsychArray 1.1	4446	6,061	2,929	3,132	2,997	0.43	0.90	2.02	1.59	0.20	0.27
37	PSY3	PsychArray 1.1	699 [a]	1,017	537	480	491	0.37	0.53	2.07	1.57	0.18	0.23
41	NCMH	PsychArray 1.1	961	1,067	442	625	598	0.43	0.67	1.78	1.08	0.23	0.31
17	PTS1	PsychArray 1.1	364 [b]	556	214	342	271	0.32	0.48	2.02	1.32	0.15	0.18
60	UKBB	ffymetrix UK Biobank Axiom arra	97382	73,691	48,061	25,630	55,872	0.36	0.57	1.32	0.56	0.27	0.39

Abbreviations: Number, study accession number in PGC-PTSD Freeze 2; N, sample size, CNV Span, mean genomic length spanned by CNV (in megabases), in CNV carriers only ; N CNV, mean number of detected CNVs , among CNV carriers only; Length, across carriers, the mean of subjects' mean CNV length (in megabases)

[a] Analyzed as a case/control study with 254 cases and 445 controls

[b] Analyzed as a case/control study with 215 cases and 149 controls

Table 3.2. FDR significant gene-sets

Set Name	Set Category	Beta	SE	Z	p	FDR
PhHs_NervSys_All	PhenoNeuro	0.0053	0.0015	3.5842	0.0003	0.016
Neurof_GoNeuronProj	Neurofunction	0.0054	0.0016	3.3300	0.0009	0.024
Neurof_UnionStringent	Neurofunction	0.0047	0.0016	2.9809	0.0029	0.033
scRNA_Expressed_ExM	scRNA brain expressed ge	0.0033	0.0011	2.9549	0.0031	0.033
scRNA_Expressed_ExM_U	scRNA brain expressed ge	0.0031	0.0010	2.9786	0.0029	0.033
BspanVH_lg2rpkm4.74	ExprBrainSpan	0.0023	0.0008	2.8762	0.0040	0.035
PhHs_NervSys_ADX	PhenoNeuro	0.0057	0.0021	2.7779	0.0055	0.042

Abbreviation: FDR, false discovery rate q value

3.9 References

1. Duncan LE, Cooper BN, Shen H. Robust Findings From 25 Years of PTSD Genetics Research. Curr Psychiatry Rep. 2018;20(12):115-. doi: 10.1007/s11920-018-0980-1. PubMed PMID: 30350223.

2. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, Levey DF, Logue MW, Polimanti R, Provost AC, Ratanatharathorn A, Stein MB, Torres K, Aiello AE, Almli LM, Amstadter AB, Andersen SB, Andreassen OA, Arbisi PA, Ashley-Koch AE, Austin SB, Avdibegovic E, Babić D, Bækvad-Hansen M, Baker DG, Beckham JC, Bierut LJ, Bisson JI, Boks MP, Bolger EA, Børglum AD, Bradley B, Brashear M, Breen G, Bryant RA, Bustamante AC, Bybjerg-Grauholm J, Calabrese JR, Caldas- de- Almeida JM, Dale AM, Daly MJ, Daskalakis NP, Deckert J, Delahanty DL, Dennis MF, Disner SG, Domschke K, Dzubur-Kulenovic A, Erbes CR, Evans A, Farrer LA, Feeny NC, Flory JD, Forbes D, Franz CE, Galea S, Garrett ME, Gelaye B, Geuze E, Gillespie C, Uka AG, Gordon SD, Guffanti G, Hammamieh R, Harnal S, Hauser MA, Heath AC, Hemmings SMJ, Hougaard DM, Jakovljevic M, Jett M, Johnson EO, Jones I, Jovanovic T, Qin X-J, Junglen AG, Karstoft K-I, Kaufman ML, Kessler RC, Khan A, Kimbrel NA, King AP, Koen N, Kranzler HR, Kremen WS, Lawford BR, Lebois LAM, Lewis CE, Linnstaedt SD, Lori A, Lugonja B, Luykx JJ, Lyons MJ, Maples-Keller J, Marmar C, Martin AR, Martin NG, Maurer D, Mavissakalian MR, McFarlane A, McGlinchey RE, McLaughlin KA, McLean SA, McLeay S, Mehta D, Milberg WP, Miller MW, Morey RA, Morris CP, Mors O, Mortensen PB, Neale BM, Nelson EC, Nordentoft M, Norman SB, O'Donnell M, Orcutt HK, Panizzon MS, Peters ES, Peterson AL, Peverill M, Pietrzak RH, Polusny MA, Rice JP, Ripke S, Risbrough VB, Roberts AL, Rothbaum AO, Rothbaum BO, Roy-Byrne P, Ruggiero K, Rung A, Rutten BPF, Saccone NL, Sanchez SE, Schijven D, Seedat S, Seligowski AV, Seng JS, Sheerin CM, Silove D, Smith AK, Smoller JW, Sponheim SR, Stein DJ, Stevens JS, Sumner JA, Teicher MH, Thompson WK, Trapido E, Uddin M, Ursano RJ, van den Heuvel LL, Van Hooff M, Vermetten E, Vinkers CH, Voisey J, Wang Y, Wang Z, Werge T, Williams MA, Williamson DE, Winternitz S, Wolf C, Wolf EJ, Wolff JD, Yehuda R, Young RM, Young KA, Zhao H, Zoellner LA, Liberzon I, Ressler KJ, Haas M, Koenen KC. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nature Communications. 2019;10(1):4558. doi: 10.1038/s41467-019-12576-w.

3. Stein MB, Levey DF, Cheng Z, Wendt FR, Harrington K, Pathak GA, Cho K, Quaden R, Radhakrishnan K, Girgenti MJ, Ho YA, Posner D, Aslan M, Duman RS, Zhao H, Polimanti R, Concato J, Gelernter J. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. Nat Genet. 2021;53(2):174-84. Epub 2021/01/30. doi: 10.1038/s41588-020-00767-x. PubMed PMID: 33510476 PMCID: PMCPMC7972521.

4. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Børglum AD, Breen G, Cichon S, Edenberg HJ, Faraone SV, Gelernter J, Mathews CA, Nievergelt CM, Smoller JW, O'Donovan MC, Psychiatric Genomics C. Psychiatric Genomics: An Update and an

Agenda. Am J Psychiatry. 2018;175(1):15-27. Epub 2017/10/03. doi: 10.1176/appi.ajp.2017.17030283. PubMed PMID: 28969442.

5. Smoller JW. The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders. Neuropsychopharmacology. 2016;41(1):297-319. Epub 2015/08/31. doi: 10.1038/npp.2015.266. PubMed PMID: 26321314.

6. Ask H, Cheesman R, Jami ES, Levey DF, Purves KL, Weber H. Genetic contributions to anxiety disorders: where we are and where we are heading. Psychological Medicine. 2021;51(13):2231-46. Epub 2021/02/09. doi: 10.1017/S0033291720005486.

7. Gudmundsson OO, Walters GB, Ingason A, Johansson S, Zayats T, Athanasiu L, Sonderby IE, Gustafsson O, Nawaz MS, Jonsson GF, Jonsson L, Knappskog P-M, Ingvarsdottir E, Davidsdottir K, Djurovic S, Knudsen GPS, Askeland RB, Haraldsdottir GS, Baldursson G, Magnusson P, Sigurdsson E, Gudbjartsson DF, Stefansson H, Andreassen OA, Haavik J, Reichborn-Kjennerud T, Stefansson K. Attention-deficit hyperactivity disorder shares copy number variant risk with schizophrenia and autism spectrum disorder. Translational Psychiatry. 2019;9(1):258. doi: 10.1038/s41398-019-0599-y.

8. Rylaarsdam L, Guemez-Gamboa A. Genetic Causes and Modifiers of Autism Spectrum Disorder. Frontiers in Cellular Neuroscience. 2019;13. doi: 10.3389/fncel.2019.00385.

9. Kendall KM, Rees E, Bracher-Smith M, Legge S, Riglin L, Zammit S, O'Donovan MC, Owen MJ, Jones I, Kirov G, Walters JTR. Association of Rare Copy Number Variants With Risk of Depression. JAMA Psychiatry. 2019;76(8):818-25. doi: 10.1001/jamapsychiatry.2019.0566.

10. Birnbaum R, Mahjani B, Loos RJF, Sharp AJ. Clinical Characterization of Copy Number Variants Associated With Neurodevelopmental Disorders in a Large-scale Multiancestry Biobank. JAMA Psychiatry. 2022. doi: 10.1001/jamapsychiatry.2021.4080.

11. Saraiva LC, Cappi C, Simpson HB, Stein DJ, Viswanath B, van den Heuvel OA, Reddy YJ, Miguel EC, Shavitt RG. Cutting-edge genetics in obsessive-compulsive disorder. Fac Rev. 2020;9:30-. doi: 10.12703/r/9-30. PubMed PMID: 33659962.

12. Marshall CR, Howrigan DP, Merico D, Thiruvahindrapuram B, Wu W, Greer DS, Antaki D, Shetty A, Holmans PA, Pinto D, Gujral M, Brandler WM, Malhotra D, Wang Z, Fajarado KVF, Maile MS, Ripke S, Agartz I, Albus M, Alexander M, Amin F, Atkins J, Bacanu SA, Belliveau RA, Bergen SE, Bertalan M, Bevilacqua E, Bigdeli TB, Black DW, Bruggeman R, Buccola NG, Buckner RL, Bulik-Sullivan B, Byerley W, Cahn W, Cai G, Cairns MJ, Campion D, Cantor RM, Carr VJ, Carrera N, Catts SV, Chambert KD, Cheng W, Cloninger CR, Cohen D, Cormican P, Craddock N, Crespo-Facorro B, Crowley JJ, Curtis D, Davidson M, Davis KL, Degenhardt F, Del Favero J, DeLisi LE, Dikeos D, Dinan T, Djurovic S, Donohoe G, Drapeau E, Duan J, Dudbridge F, Eichhammer P, Eriksson J, Escott-Price V, Essioux L, Fanous AH, Farh K-H, Farrell MS, Frank J, Franke L, Freedman R, Freimer NB, Friedman JI, Forstner AJ, Fromer M, Genovese G,

Georgieva L, Gershon ES, Giegling I, Giusti-Rodríguez P, Godard S, Goldstein JI, Gratten J, de Haan L, Hamshere ML, Hansen M, Hansen T, Haroutunian V, Hartmann AM, Henskens FA, Herms S, Hirschhorn JN, Hoffmann P, Hofman A, Huang H, Ikeda M, Joa I, Kähler AK, Kahn RS, Kalaydjieva L, Karjalainen J, Kavanagh D, Keller MC, Kelly BJ, Kennedy JL, Kim Y, Knowles JA, Konte B, Laurent C, Lee P, Lee SH, Legge SE, Lerer B, Levy DL, Liang K-Y, Lieberman J, Lönnqvist J, Loughland CM, Magnusson PKE, Maher BS, Maier W, Mallet J, Mattheisen M, Mattingsdal M, McCarley RW, McDonald C, McIntosh AM, Meier S, Meijer CJ, Melle I, Mesholam-Gately RI, Metspalu A, Michie PT, Milani L, Milanova V, Mokrab Y, Morris DW, Müller-Myhsok B, Murphy KC, Murray RM, Myin-Germeys I, Nenadic I, Nertney DA, Nestadt G, Nicodemus KK, Nisenbaum L, Nordin A, O'Callaghan E, O'Dushlaine C, Oh S-Y, Olincy A, Olsen L, O'Neill FA, Van Os J, Pantelis C, Papadimitriou GN, Parkhomenko E, Pato MT, Paunio T, Perkins DO, Pers TH, Pietiläinen O, Pimm J, Pocklington AJ, Powell J, Price A, Pulver AE, Purcell SM, Quested D, Rasmussen HB, Reichenberg A, Reimers MA, Richards AL, Roffman JL, Roussos P, Ruderfer DM, Salomaa V, Sanders AR, Savitz A, Schall U, Schulze TG, Schwab SG, Scolnick EM, Scott RJ, Seidman LJ, Shi J, Silverman JM, Smoller JW, Söderman E, Spencer CCA, Stahl EA, Strengman E, Strohmaier J, Stroup TS, Suvisaari J, Svrakic DM, Szatkiewicz JP, Thirumalai S, Tooney PA, Veijola J, Visscher PM, Waddington J, Walsh D, Webb BT, Weiser M, Wildenauer DB, Williams NM, Williams S, Witt SH, Wolen AR, Wormley BK, Wray NR, Wu JQ, Zai CC, Adolfsson R, Andreassen OA, Blackwood DHR, Bramon E, Buxbaum JD, Cichon S, Collier DA, Corvin A, Daly MJ, Darvasi A, Domenici E, Esko T, Gejman PV, Gill M, Gurling H, Hultman CM, Iwata N, Jablensky AV, Jönsson EG, Kendler KS, Kirov G, Knight J, Levinson DF, Li QS, McCarroll SA, McQuillin A, Moran JL, Mowry BJ, Nöthen MM, Ophoff RA, Owen MJ, Palotie A, Pato CN, Petryshen TL, Posthuma D, Rietschel M, Riley BP, Rujescu D, Sklar P, St Clair D, Walters JTR, Werge T, Sullivan PF, O'Donovan MC, Scherer SW, Neale BM, Sebat J, Psychosis Endophenotypes International C, Cnv, Schizophrenia Working Groups of the Psychiatric Genomics C. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nature Genetics. 2017;49(1):27-35. doi: 10.1038/ng.3725.

13. Zarrei M, Burton CL, Engchuan W, Young EJ, Higginbotham EJ, MacDonald JR, Trost B, Chan AJS, Walker S, Lamoureux S, Heung T, Mojarad BA, Kellam B, Paton T, Faheem M, Miron K, Lu C, Wang T, Samler K, Wang X, Costain G, Hoang N, Pellecchia G, Wei J, Patel RV, Thiruvahindrapuram B, Roifman M, Merico D, Goodale T, Drmic I, Speevak M, Howe JL, Yuen RKC, Buchanan JA, Vorstman JAS, Marshall CR, Wintle RF, Rosenberg DR, Hanna GL, Woodbury-Smith M, Cytrynbaum C, Zwaigenbaum L, Elsabbagh M, Flanagan J, Fernandez BA, Carter MT, Szatmari P, Roberts W, Lerch J, Liu X, Nicolson R, Georgiades S, Weksberg R, Arnold PD, Bassett AS, Crosbie J, Schachar R, Stavropoulos DJ, Anagnostou E, Scherer SW. A large data resource of genomic copy number variation across neurodevelopmental disorders. npj Genomic Medicine. 2019;4(1):26. doi: 10.1038/s41525-019-0098-3.

14. Balagué-Dobón L, Cáceres A, González JR. Fully exploiting SNP arrays: a systematic review on the tools to extract underlying genomic structure. Briefings in Bioinformatics. 2022:bbac043. doi: 10.1093/bib/bbac043.

15. Logue MW, Amstadter AB, Baker DG, Duncan L, Koenen KC, Liberzon I, Miller MW, Morey RA, Nievergelt CM, Ressler KJ, Smith AK, Smoller JW, Stein MB, Sumner JA, Uddin M. The Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup: Posttraumatic Stress Disorder Enters the Age of Large-Scale Genomic Collaboration. Neuropsychopharmacology. 2015;40(10):2287-97. Epub 2015/04/23. doi: 10.1038/npp.2015.118. PubMed PMID: 25904361.

16. Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, Almeida J, Bacchelli E, Bader GD, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bölte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Bryson SE, Carson AR, Casallo G, Casey J, Chung BHY, Cochrane L, Corsello C, Crawford EL, Crossett A, Cytrynbaum C, Dawson G, de Jonge M, Delorme R, Drmic I, Duketis E, Duque F, Estes A, Farrar P, Fernandez BA, Folstein SE, Fombonne E, Freitag CM, Gilbert J, Gillberg C, Glessner JT, Goldberg J, Green A, Green J, Guter SJ, Hakonarson H, Heron EA, Hill M, Holt R, Howe JL, Hughes G, Hus V, Igliozzi R, Kim C, Klauck SM, Kolevzon A, Korvatska O, Kustanovich V, Lajonchere CM, Lamb JA, Laskawiec M, Leboyer M, Le Couteur A, Leventhal BL, Lionel AC, Liu X-Q, Lord C, Lotspeich L, Lund SC, Maestrini E, Mahoney W, Mantoulan C, Marshall CR, McConachie H, McDougle CJ, McGrath J, McMahon WM, Merikangas A, Migita O, Minshew NJ, Mirza GK, Munson J, Nelson SF, Noakes C, Noor A, Nygren G, Oliveira G, Papanikolaou K, Parr JR, Parrini B, Paton T, Pickles A, Pilorge M, Piven J, Ponting CP, Posey DJ, Poustka A, Poustka F, Prasad A, Ragoussis J, Renshaw K, Rickaby J, Roberts W, Roeder K, Roge B, Rutter ML, Bierut LJ, Rice JP, Salt J, Sansom K, Sato D, Segurado R, Sequeira AF, Senman L, Shah N, Sheffield VC, Soorya L, Sousa I, Stein O, Sykes N, Stoppioni V, Strawbridge C, Tancredi R, Tansey K, Thiruvahindrapduram B, Thompson AP, Thomson S, Tryfon A, Tsiantis J, Van Engeland H, Vincent JB, Volkmar F, Wallace S, Wang K, Wang Z, Wassink TH, Webber C, Weksberg R, Wing K, Wittemeyer K, Wood S, Wu J, Yaspan BL, Zurawiecki D, Zwaigenbaum L, Buxbaum JD, Cantor RM, Cook EH, Coon H, Cuccaro ML, Devlin B, Ennis S, Gallagher L, Geschwind DH, Gill M, Haines JL, Hallmayer J, Miller J, Monaco AP, Nurnberger JI, Jr., Paterson AD, Pericak-Vance MA, Schellenberg GD, Szatmari P, Vicente AM, Vieland VJ, Wijsman EM, Scherer SW, Sutcliffe JS, Betancur C. Functional impact of global rare copy number variation in autism spectrum disorders. Nature. 2010;466(7304):368-72. Epub 2010/06/09. doi: 10.1038/nature09146. PubMed PMID: 20531469.

17. Wang K, Li M, Hadley D, Liu R, Glessner J, Grant SFA, Hakonarson H, Bucan M. PennCNV: an integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. Genome Res. 2007;17(11):1665-74. Epub 2007/10/05. doi: 10.1101/gr.6861907. PubMed PMID: 17921354.

18. Colella S, Yau C, Taylor JM, Mirza G, Butler H, Clouston P, Bassett AS, Seller A, Holmes CC, Ragoussis J. QuantiSNP: an Objective Bayes Hidden-Markov Model to detect and accurately map copy number variation using SNP genotyping data. Nucleic Acids Res. 2007;35(6):2013-25. doi: 10.1093/nar/gkm076.

19. O'Leary NA, Wright MW, Brister JR, Ciufo S, Haddad D, McVeigh R, Rajput B, Robbertse B, Smith-White B, Ako-Adjei D, Astashyn A, Badretdin A, Bao Y, Blinkova O,

Brover V, Chetvernin V, Choi J, Cox E, Ermolaeva O, Farrell CM, Goldfarb T, Gupta T, Haft D, Hatcher E, Hlavina W, Joardar VS, Kodali VK, Li W, Maglott D, Masterson P, McGarvey KM, Murphy MR, O'Neill K, Pujar S, Rangwala SH, Rausch D, Riddick LD, Schoch C, Shkeda A, Storz SS, Sun H, Thibaud-Nissen F, Tolstoy I, Tully RE, Vatsan AR, Wallin C, Webb D, Wu W, Landrum MJ, Kimchi A, Tatusova T, DiCuccio M, Kitts P, Murphy TD, Pruitt KD. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016;44(D1):D733-D45. Epub 2015/11/08. doi: 10.1093/nar/gkv1189. PubMed PMID: 26553804.

20. Trost B, Engchuan W, Nguyen CM, Thiruvahindrapuram B, Dolzhenko E, Backstrom I, Mirceta M, Mojarad BA, Yin Y, Dov A, Chandrakumar I, Prasolava T, Shum N, Hamdan O, Pellecchia G, Howe JL, Whitney J, Klee EW, Baheti S, Amaral DG, Anagnostou E, Elsabbagh M, Fernandez BA, Hoang N, Lewis MES, Liu X, Sjaarda C, Smith IM, Szatmari P, Zwaigenbaum L, Glazer D, Hartley D, Stewart AK, Eberle MA, Sato N, Pearson CE, Scherer SW, Yuen RKC. Genome-wide detection of tandem DNA repeats that are expanded in autism. Nature. 2020;586(7827):80-6. Epub 2020/07/28. doi: 10.1038/s41586-020-2579-z. PubMed PMID: 32717741.

21. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, Collins RL, Laricchia KM, Ganna A, Birnbaum DP, Gauthier LD, Brand H, Solomonson M, Watts NA, Rhodes D, Singer-Berk M, England EM, Seaby EG, Kosmicki JA, Walters RK, Tashman K, Farjoun Y, Banks E, Poterba T, Wang A, Seed C, Whiffin N, Chong JX, Samocha KE, Pierce-Hoffman E, Zappala Z, O'Donnell-Luria AH, Minikel EV, Weisburd B, Lek M, Ware JS, Vittal C, Armean IM, Bergelson L, Cibulskis K, Connolly KM, Covarrubias M, Donnelly S, Ferriera S, Gabriel S, Gentry J, Gupta N, Jeandet T, Kaplan D, Llanwarne C, Munshi R, Novod S, Petrillo N, Roazen D, Ruano-Rubio V, Saltzman A, Schleicher M, Soto J, Tibbetts K, Tolonen C, Wade G, Talkowski ME, Neale BM, Daly MJ, MacArthur DG. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581(7809):434-43. Epub 2020/05/29. doi: 10.1038/s41586-020-2308-7. PubMed PMID: 32461654 PMCID: PMCPMC7334197 from Takeda Pharmaceutical Company. A.H.O'D.-L. has received honoraria from ARUP and Chan Zuckerberg Initiative. E.V.M. has received research support in the form of charitable contributions from Charles River Laboratories and Ionis Pharmaceuticals, and has consulted for Deerfield Management. J.S.W. is a consultant for MyoKardia. B.M.N. is a member of the scientific advisory board at Deep Genomics and consultant for Camp4 Therapeutics, Takeda Pharmaceutical, and Biogen. M.J.D. is a founder of Maze Therapeutics. D.G.M. is a founder with equity in Goldfinch Bio, and has received research support from AbbVie, Astellas, Biogen, BioMarin, Eisai, Merck, Pfizer, and Sanofi-Genzyme. The views expressed in this article are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. M.I.M. has served on advisory panels for Pfizer, NovoNordisk, Zoe Global; has received honoraria from Merck, Pfizer, NovoNordisk and Eli Lilly; has stock options in Zoe Global and has received research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier & Takeda. As of June 2019, M.I.M. is an employee of Genentech, and holds stock in Roche. N.R. is a non-executive director of AstraZeneca.

22. Polioudakis D, de la Torre-Ubieta L, Langerman J, Elkins AG, Shi X, Stein JL, Vuong CK, Nichterwitz S, Gevorgian M, Opland CK, Lu D, Connell W, Ruzzo EK, Lowe JK, Hadzic T, Hinz FI, Sabri S, Lowry WE, Gerstein MB, Plath K, Geschwind DH. A Single-Cell Transcriptomic Atlas of Human Neocortical Development during Mid-gestation. Neuron. 2019;103(5):785-801.e8. Epub 2019/07/16. doi: 10.1016/j.neuron.2019.06.011. PubMed PMID: 31303374 PMCID: PMCPMC6831089.

23. Raychaudhuri S, Korn JM, McCarroll SA, The International Schizophrenia C, Altshuler D, Sklar P, Purcell S, Daly MJ. Accurately Assessing the Risk of Schizophrenia Conferred by Rare Copy-Number Variation Affecting Genes with Brain Function. PLOS Genetics. 2010;6(9):e1001097. doi: 10.1371/journal.pgen.1001097.

24. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. 2010;36(3):1 - 48. doi: 10.18637/jss.v036.i03.

25. Choi SW, O'Reilly PF. PRSice-2: Polygenic Risk Score software for biobank-scale data. GigaScience. 2019;8(7):giz082. doi: 10.1093/gigascience/giz082.

26. Breslau N. The Epidemiology of Trauma, PTSD, and Other Posttrauma Disorders. Trauma, Violence, & Abuse. 2009;10(3):198-210. doi: 10.1177/1524838009334448.

27. O'Hare T, Shen C, Sherrer M. High-risk behaviors and drinking-to-cope as mediators of lifetime abuse and PTSD symptoms in clients with severe mental illness. Journal of Traumatic Stress. 2010;23(2):255-63. doi: https://doi.org/10.1002/jts.20515.

28. Breslau N, Chen Q, Luo Z. The role of intelligence in posttraumatic stress disorder: does it vary by trauma severity? PLoS One. 2013;8(6):e65391-e. doi: 10.1371/journal.pone.0065391. PubMed PMID: 23762357.

29. Rafi SK, Butler MG. The 15q11.2 BP1-BP2 Microdeletion (Burnside–Butler) Syndrome: In Silico Analyses of the Four Coding Genes Reveal Functional Associations with Neurodevelopmental Disorders. Int J Mol Sci. 2020;21(9). doi: 10.3390/ijms21093296.

30. Writing Committee for the E-CNVWG. Association of Copy Number Variation of the 15q11.2 BP1-BP2 Region With Cortical and Subcortical Morphology and Cognition. JAMA Psychiatry. 2020;77(4):420-30. doi: 10.1001/jamapsychiatry.2019.3779.

31. Cox DM, Butler MG. The 15q11.2 BP1-BP2 microdeletion syndrome: a review. Int J Mol Sci. 2015;16(2):4068-82. doi: 10.3390/ijms16024068. PubMed PMID: 25689425.

32. Jønch AE, Douard E, Moreau C, Van Dijck A, Passeggeri M, Kooy F, Puechberty J, Campbell C, Sanlaville D, Lefroy H, Richetin S, Pain A, Geneviève D, Kini U, Le Caignec C, Lespinasse J, Skytte A-B, Isidor B, Zweier C, Caberg J-H, Delrue M-A, Møller RS, Bojesen A, Hjalgrim H, Brasch-Andersen C, Lemyre E, Ousager LB, Jacquemont S. Estimating the effect size of the 15Q11.2 BP1–BP2 deletion and its

contribution to neurodevelopmental symptoms: recommendations for practice. Journal of Medical Genetics. 2019;56(10):701. doi: 10.1136/jmedgenet-2018-105879.

33. Ou Z, Berg JS, Yonath H, Enciso VB, Miller DT, Picker J, Lenzi T, Keegan CE, Sutton VR, Belmont J, Chinault AC, Lupski JR, Cheung SW, Roeder E, Patel A. Microduplications of 22q11.2 are frequently inherited and are associated with variable phenotypes. Genet Med. 2008;10(4):267-77. Epub 2008/04/17. doi: 10.1097/GIM.0b013e31816b64c2. PubMed PMID: 18414210.

34. Wenger TL, Miller JS, DePolo LM, de Marchena AB, Clements CC, Emanuel BS, Zackai EH, McDonald-McGinn DM, Schultz RT. 22q11.2 duplication syndrome: elevated rate of autism spectrum disorder and need for medical screening. Molecular Autism. 2016;7(1):27. doi: 10.1186/s13229-016-0090-z.

35. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, Als TD, Bigdeli TB, Børte S, Bryois J, Charney AW, Drange OK, Gandal MJ, Hagenaars SP, Ikeda M, Kamitaki N, Kim M, Krebs K, Panagiotaropoulou G, Schilder BM, Sloofman LG, Steinberg S, Trubetskoy V, Winsvold BS, Won H-H, Abramova L, Adorjan K, Agerbo E, Al Eissa M, Albani D, Alliey-Rodriguez N, Anjorin A, Antilla V, Antoniou A, Awasthi S, Baek JH, Bækvad-Hansen M, Bass N, Bauer M, Beins EC, Bergen SE, Birner A, Bøcker Pedersen C, Bøen E, Boks MP, Bosch R, Brum M, Brumpton BM, Brunkhorst-Kanaan N, Budde M, Bybjerg-Grauholm J, Byerley W, Cairns M, Casas M, Cervantes P, Clarke T-K, Cruceanu C, Cuellar-Barboza A, Cunningham J, Curtis D, Czerski PM, Dale AM, Dalkner N, David FS, Degenhardt F, Djurovic S, Dobbyn AL, Douzenis A, Elvsåshagen T, Escott-Price V, Ferrier IN, Fiorentino A, Foroud TM, Forty L, Frank J, Frei O, Freimer NB, Frisén L, Gade K, Garnham J, Gelernter J, Giørtz Pedersen M, Gizer IR, Gordon SD, Gordon-Smith K, Greenwood TA, Grove J, Guzman-Parra J, Ha K, Haraldsson M, Hautzinger M, Heilbronner U, Hellgren D, Herms S, Hoffmann P, Holmans PA, Huckins L, Jamain S, Johnson JS, Kalman JL, Kamatani Y, Kennedy JL, Kittel-Schneider S, Knowles JA, Kogevinas M, Koromina M, Kranz TM, Kranzler HR, Kubo M, Kupka R, Kushner SA, Lavebratt C, Lawrence J, Leber M, Lee H-J, Lee PH, Levy SE, Lewis C, Liao C, Lucae S, Lundberg M, MacIntyre DJ, Magnusson SH, Maier W, Maihofer A, Malaspina D, Maratou E, Martinsson L, Mattheisen M, McCarroll SA, McGregor NW, McGuffin P, McKay JD, Medeiros H, Medland SE, Millischer V, Montgomery GW, Moran JL, Morris DW, Mühleisen TW, O'Brien N, O'Donovan C, Olde Loohuis LM, Oruc L, Papiol S, Pardiñas AF, Perry A, Pfennig A, Porichi E, Potash JB, Quested D, Raj T, Rapaport MH, DePaulo JR, Regeer EJ, Rice JP, Rivas F, Rivera M, Roth J, Roussos P, Ruderfer DM, Sánchez-Mora C, Schulte EC, Senner F, Sharp S, Shilling PD, Sigurdsson E, Sirignano L, Slaney C, Smeland OB, Smith DJ, Sobell JL, Søholm Hansen C, Soler Artigas M, Spijker AT, Stein DJ, Strauss JS, Świątkowska B, Terao C, Thorgeirsson TE, Toma C, Tooney P, Tsermpini E-E, Vawter MP, Vedder H, Walters JTR, Witt SH, Xi S, Xu W, Yang JMK, Young AH, Young H, Zandi PP, Zhou H, Zillich L, Adolfsson R, Agartz I, Alda M, Alfredsson L, Babadjanova G, Backlund L, Baune BT, Bellivier F, Bengesser S, Berrettini WH, Blackwood DHR, Boehnke M, Børglum AD, Breen G, Carr VJ, Catts S, Corvin A, Craddock N, Dannlowski U, Dikeos D, Esko T, Etain B, Ferentinos P, Frye M, Fullerton JM, Gawlik M, Gershon ES, Goes FS, Green MJ, Grigoroiu-Serbanescu M, Hauser J,

Henskens F, Hillert J, Hong KS, Hougaard DM, Hultman CM, Hveem K, Iwata N, Jablensky AV, Jones I, Jones LA, Kahn RS, Kelsoe JR, Kirov G, Landén M, Leboyer M, Lewis CM, Li QS, Lissowska J, Lochner C, Loughland C, Martin NG, Mathews CA, Mayoral F, McElroy SL, McIntosh AM, McMahon FJ, Melle I, Michie P, Milani L, Mitchell PB, Morken G, Mors O, Mortensen PB, Mowry B, Müller-Myhsok B, Myers RM, Neale BM, Nievergelt CM, Nordentoft M, Nöthen MM, O'Donovan MC, Oedegaard KJ, Olsson T, Owen MJ, Paciga SA, Pantelis C, Pato C, Pato MT, Patrinos GP, Perlis RH, Posthuma D, Ramos-Quiroga JA, Reif A, Reininghaus EZ, Ribasés M, Rietschel M, Ripke S, Rouleau GA, Saito T, Schall U, Schalling M, Schofield PR, Schulze TG, Scott LJ, Scott RJ, Serretti A, Shannon Weickert C, Smoller JW, Stefansson H, Stefansson K, Stordal E, Streit F, Sullivan PF, Psychiatry HA-I. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nature Genetics. 2021;53(6):817-29. doi: 10.1038/s41588-021-00857-4.

36. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, Baldursson G, Belliveau R, Bybjerg-Grauholm J, Bækvad-Hansen M, Cerrato F, Chambert K, Churchhouse C, Dumont A, Eriksson N, Gandal M, Goldstein JI, Grasby KL, Grove J, Gudmundsson OO, Hansen CS, Hauberg ME, Hollegaard MV, Howrigan DP, Huang H, Maller JB, Martin AR, Martin NG, Moran J, Pallesen J, Palmer DS, Pedersen CB, Pedersen MG, Poterba T, Poulsen JB, Ripke S, Robinson EB, Satterstrom FK, Stefansson H, Stevens C, Turley P, Walters GB, Won H, Wright MJ, Albayrak Ö, Anney RJL, Arranz MJ, Banaschewski TJ, Bau C, Biederman J, Buitelaar JK, Casas M, Charach A, Crosbie J, Dempfle A, Doyle AE, Ebstein RP, Elia J, Freitag C, Föcker M, Gill M, Grevet E, Hawi Z, Hebebrand J, Herpertz-Dahlmann B, Hervas A, Hinney A, Hohmann S, Holmans P, Hutz M, Ickowitz A, Johansson S, Kent L, Kittel-Schneider S, Lambregts-Rommelse N, Lehmkuhl G, Loo SK, McGough JJ, Meyer J, Mick E, Middleton F, Miranda A, Mota NR, Mulas F, Mulligan A, Nelson F, Nguyen TT, Oades RD, O'Donovan MC, Owen MJ, Palmason H, Ramos-Quiroga JA, Renner TJ, Ribasés M, Rietschel M, Rivero O, Romanos J, Romanos M, Rothenberger A, Royers H, Sánchez-Mora C, Scherag A, Schimmelmann BG, Schäfer H, Sergeant J, Sinzig J, Smalley SL, Steinhausen H-C, Thompson M, Todorov A, Vasquez AA, Walitza S, Wang Y, Warnke A, Williams N, Witt SH, Yang L, Zayats T, Zhang-James Y, Smith GD, Davies GE, Ehli EA, Evans DM, Fedko IO, Greven CU, Groen-Blokhuis MM, Guxens M, Hammerschlag AR, Hartman CA, Heinrich J, Jan Hottenga J, Hudziak J, Jugessur A, Kemp JP, Krapohl E, Murcia M, Myhre R, Nolte IM, Nyholt DR, Ormel J, Ouwens KG, Pappa I, Pennell CE, Plomin R, Ring S, Standl M, Stergiakouli E, Pourcain BS, Stoltenberg C, Sunyer J, Thiering E, Tiemeier H, Tiesler CMT, Timpson NJ, Trzaskowski M, van der Most PJ, Vilor-Tejedor N, Wang CA, Whitehouse AJO, Zhao H, Agee M, Alipanahi B, Auton A, Bell RK, Bryc K, Elson SL, Fontanillas P, Furlotte NA, Hinds DA, Hromatka BS, Huber KE, Kleinman A, Litterman NK, McIntyre MH, Mountain JL, Northover CAM, Pitts SJ, Sathirapongsasuti JF, Sazonova OV, Shelton JF, Shringarpure S, Tian C, Vacic V, Wilson CH, Andreassen OA, Asherson P, Burton CL, Boomsma DI, Cormand B, Dalsgaard S, Franke B, Gelernter J, Geschwind D, Hakonarson H, Haavik J, Kranzler HR, Kuntsi J, Langley K, Lesch K-P, Middeldorp C, Reif A, Rohde LA, Roussos P, Schachar R, Sklar P, Sonuga-Barke EJS, Sullivan PF, Thapar A, Tung JY, Waldman ID, Medland SE, Stefansson K, Nordentoft M, Hougaard DM, Werge T, Mors O, Mortensen PB, Daly MJ, Faraone SV, Børglum AD, Neale BM,

Consortium AWGotPG, Early L, Genetic Epidemiology C, andMe Research T. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nature Genetics. 2019;51(1):63-75. doi: 10.1038/s41588-018-0269-7.

37. Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, Legge SE, Bishop S, Cameron D, Hamshere ML, Han J, Hubbard L, Lynham A, Mantripragada K, Rees E, MacCabe JH, McCarroll SA, Baune BT, Breen G, Byrne EM, Dannlowski U, Eley TC, Hayward C, Martin NG, McIntosh AM, Plomin R, Porteous DJ, Wray NR, Caballero A, Geschwind DH, Huckins LM, Ruderfer DM, Santiago E, Sklar P, Stahl EA, Won H, Agerbo E, Als TD, Andreassen OA, Bækvad-Hansen M, Mortensen PB, Pedersen CB, Børglum AD, Bybjerg-Grauholm J, Djurovic S, Durmishi N, Pedersen MG, Golimbet V, Grove J, Hougaard DM, Mattheisen M, Molden E, Mors O, Nordentoft M, Pejovic-Milovancevic M, Sigurdsson E, Silagadze T, Hansen CS, Stefansson K, Stefansson H, Steinberg S, Tosato S, Werge T, Harold D, Sims R, Gerrish A, Chapman J, Escott-Price V, Abraham R, Hollingworth P, Pahwa J, Denning N, Thomas C, Taylor S, Powell J, Proitsi P, Lupton M, Lovestone S, Passmore P, Craig D, McGuinness B, Johnston J, Todd S, Maier W, Jessen F, Heun R, Schurmann B, Ramirez A, Becker T, Herold C, Lacour A, Drichel D, Nothen M, Goate A, Cruchaga C, Nowotny P, Morris JC, Mayo K, Holmans P, O'Donovan M, Owen M, Williams J, Achilla E, Agerbo E, Barr CL, Böttger TW, Breen G, Cohen D, Collier DA, Curran S, Dempster E, Dima D, Sabes-Figuera R, Flanagan RJ, Frangou S, Frank J, Gasse C, Gaughran F, Giegling I, Grove J, Hannon E, Hartmann AM, Heißerer B, Helthuis M, Horsdal HT, Ingimarsson O, Jollie K, Kennedy JL, Köhler O, Konte B, Lang M, Legge SE, Lewis C, MacCabe J, Malhotra AK, McCrone P, Meier SM, Mill J, Mors O, Mortensen PB, Nöthen MM, O'Donovan MC, Owen MJ, Pardiñas AF, Pedersen CB, Rietschel M, Rujescu D, Schwalber A, Sigurdsson E, Sørensen HJ, Spencer B, Stefansson H, Støvring H, Strohmaier J, Sullivan P, Vassos E, Verbelen M, Walters JTR, Werge T, Collier DA, Rujescu D, Kirov G, Owen MJ, O'Donovan MC, Walters JTR, Consortium G, Consortium C. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nature Genetics. 2018;50(3):381-9. doi: 10.1038/s41588-018-0059-2.

38. The Schizophrenia Working Group of the Psychiatric Genomics C, Ripke S, Walters JTR, O'Donovan MC. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. medRxiv. 2020:2020.09.12.20192922. doi: 10.1101/2020.09.12.20192922.

39. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nature Reviews Genetics. 2018;19(9):581-90. doi: 10.1038/s41576-018-0018-x.

40. Sullivan PF, Owen MJ. Increasing the Clinical Psychiatric Knowledge Base About Pathogenic Copy Number Variation. American Journal of Psychiatry. 2020;177(3):204-9. doi: 10.1176/appi.ajp.2019.19040335.

41. Coughlin CR, Scharer GH, Shaikh TH. Clinical impact of copy number variation analysis using high-resolution microarray technologies: advantages, limitations and concerns. Genome Medicine. 2012;4(10):80. doi: 10.1186/gm381.

42. Nowakowska B. Clinical interpretation of copy number variants in the human genome. J Appl Genet. 2017;58(4):449-57. Epub 2017/09/30. doi: 10.1007/s13353-017-0407-4. PubMed PMID: 28963714.

43. Zhao M, Wang Q, Wang Q, Jia P, Zhao Z. Computational tools for copy number variation (CNV) detection using next-generation sequencing data: features and perspectives. BMC Bioinformatics. 2013;14(11):S1. doi: 10.1186/1471-2105-14-S11-S1.

44. Kaiser J. 200,000 whole genomes made available for biomedical studies. Science. 2021;374(6571):1036.

45. Rees E, Kirov G. Copy number variation and neuropsychiatric illness. Current Opinion in Genetics & Development. 2021;68:57-63. doi: https://doi.org/10.1016/j.gde.2021.02.014.

46. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R, Allen NE. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017;186(9):1026-34. Epub 2017/06/24. doi: 10.1093/aje/kwx246. PubMed PMID: 28641372 PMCID: PMCPMC5860371.

47. Lee S, Abecasis GR, Boehnke M, Lin X. Rare-variant association analysis: study designs and statistical tests. Am J Hum Genet. 2014;95(1):5-23. Epub 2014/07/06. doi: 10.1016/j.ajhg.2014.06.009. PubMed PMID: 24995866 PMCID: PMCPMC4085641.

48. Li YR, Glessner JT, Coe BP, Li J, Mohebnasab M, Chang X, Connolly J, Kao C, Wei Z, Bradfield J, Kim C, Hou C, Khan M, Mentch F, Qiu H, Bakay M, Cardinale C, Lemma M, Abrams D, Bridglall-Jhingoor A, Behr M, Harrison S, Otieno G, Thomas A, Wang F, Chiavacci R, Wu L, Hadley D, Goldmuntz E, Elia J, Maris J, Grundmeier R, Devoto M, Keating B, March M, Pellagrino R, Grant SFA, Sleiman PMA, Li M, Eichler EE, Hakonarson H. Rare copy number variants in over 100,000 European ancestry subjects reveal multiple disease associations. Nature Communications. 2020;11(1):255. doi: 10.1038/s41467-019-13624-1.

49. Hori H, Kim Y. Inflammation and post-traumatic stress disorder. Psychiatry and Clinical Neurosciences. 2019;73(4):143-53. doi: https://doi.org/10.1111/pcn.12820.

Chapter 4. The effects of genetically predicted posttraumatic stress disorder on autoimmune conditions and inflammatory biomarkers

4.1 Abstract

Background: Posttraumatic stress disorder (PTSD) is associated with elevated levels of peripheral inflammatory markers and increased risk of developing disorders with an inflammatory component. Some research suggests inflammation itself may increase risk of developing PTSD after trauma. It is uncertain if these relationships are causal, as associations originate from observational studies. Mendelian randomization (MR) can be used to investigate the causal relationships using readily available genome-wide association study (GWAS) summary data.

Methods: The genetic correlations between PTSD and inflammatory biomarkers and diseases with an inflammatory component were estimated using linkage disequilibrium score regression. Genetic causality proportions were estimated using latent causal variable analysis. Bidirectional MR was performed using genome-wide significant, linkage disequilibrium independent single nucleotide polymorphisms. Inverse variance weighted, weighted median, and MR Egger estimates were generated. Sensitivity analyses for sample overlap (MRlap), heterogeneity (Cochran's Q test), and uncorrelated (MR PRESSO) and correlated horizontal pleiotropy (CAUSE) were performed.

Results: PTSD had significant genetic correlations with 11 inflammatory phenotypes. CRP had a significant shared genetic causality with PTSD (gcp = -0.3, se = 0.04, p = 1.3e-19). MR analyses indicated that genetically predicted PTSD was significantly associated with asthma, CRP, IL6, psoriasis, and white blood cell count

(FDR $q < 0.05$). MR effects were not significant in the other causal direction. Inferences were not significantly altered by sample overlap or horizontal pleiotropy. In multivariable MR analyses, the effect of PTSD on psoriasis was no longer significant when adjusted for CRP.

Conclusion: Our findings suggest that PTSD has a putative causal effect on some inflammatory phenotypes, consistent with evidence of stress- and trauma-related disorders predicting greater risk of inflammatory disorders. Previously proposed inflammatory mechanisms seem to be involved in some of these relationships.

4.2 Introduction

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric illness that develops in response to traumatic stress exposure [1]. PTSD is characterized by intrusive memories, avoidance, negative changes in thinking and mood, and changes in physical and emotional reactions[2]. Symptoms last for longer than one month and cause considerable distress and/or interference with multiple areas of life[2]. PTSD is often co-morbid with physical and psychiatric illnesses [3], many of which have an inflammatory component [4]. For example, longitudinal studies suggest that PTSD precedes the development of asthma [5] and autoimmune diseases [6, 7]. This has led to the general hypothesis that PTSD involves dysregulation of the immune system [4]. Much of the direct evidence for an inflammatory component of PTSD comes from biomarker studies that show elevated serum measures of inflammatory cytokines [8] and white blood cell counts [9] in PTSD cases. As well, evidence is provided from emerging genetic [10], epigenetic [11, 12], and transcriptomic [13] studies. The causal relationship between inflammation and PTSD is unclear and suspected to involve a complicated temporality [4]. The few longitudinal studies of the inflammatory biomarker C-reactive protein (CRP) have provided mixed evidence [14] of the temporal relationship between PTSD and inflammation.

Deeper understanding of the nature of the relationship between inflammation and PTSD may enhance treatment options for PTSD, as well as treatment options for co-morbid diseases with inflammatory components [15] [4]. Two sample Mendelian randomization (MR) [16] has been proposed as a means of evaluating the causal relationship between PTSD and inflammation [14]. This method requires genetic

predictors of PTSD and inflammatory phenotypes, which have now been identified by large genome-wide association studies (GWASes) of PTSD and these traits [10, 17 18]. Extensions of MR [19] and other methods of genetic causal inference analysis such as latent causal variable (LCV) analysis [20] continue to be developed to strengthen confidence in the validity of causal inferences made using genetic data.

In the current study, we investigated the causal relationship between PTSD and several inflammatory phenotypes by applying genetically-informed causal inference analyses to large-scale GWAS summary data. First, we examined the genetic overlap between PTSD and these phenotypes using genetic correlation analyses [21]. For traits with significant genetic correlation, we inferred genetic causality between them using LCV analyses and two sample MR. We performed several sensitivity analyses to evaluate the validity of our findings. We examined all associations for a confounding or mediating effect of a general inflammatory signal [22]

4.3 Methods

4.3.1 Data sources and harmonization

PTSD summary data came from the PGC-PTSD [10] Freeze 3 European ancestry GWAS (manuscript in preparation). For inflammatory phenotypes, we compiled a list of phenotypes with published association with PTSD, which included blood cell types, inflammatory biomarkers, autoimmune diseases, and other diseases with an inflammatory component. We searched Google Scholar and the GWAS catalog (https://www.ebi.ac.uk/gwas/) for GWASes of these phenotypes. SNP level summary statistics were downloaded where available, either via public link or request made to the

authors. To be considered for analysis, genome-wide GWAS summary data needed to contain SNP rs-id, coded and non-coded alleles, effect size, corresponding standard error, and p-value. To prevent confounding due to ancestral differences, only European ancestry GWAS summary statistics were considered. When multiple GWAS were available for the same phenotype, our analytic preference was to use the set of summary statistics from the largest sample size data available. Our analytic sample consisted of 47 phenotypes, including allergic diseases and asthma [23], 15 blood cell phenotypes[24], celiac disease [25], 16 circulating cytokines[26], CRP[27], interleukin-6 (IL-6) [28], inflammatory bowel disease [29] (including Crohn's and ulcerative colitis disease), Parkinson's disease [30], primary biliary cirrhosis[31], psoriasis [32], rheumatoid arthritis[33], systemic lupus erythematosus[34], suPAR [35], and type 1 diabetes [36] (Supplementary table 4.1).

4.3.2 Linkage disequilibrium (LD) score regression (LDSC)

SNP-based heritability of phenotypes and their genetic correlations (r_gs) with PTSD were estimated using LDSC [21] with the 1000 Genomes Phase 3 European reference panel. Significance of r_g was based on FDR adjustment for the number of correlations tested. Phenotypes with significant r_g with PTSD were carried forward for MR analyses. We omitted phenotypes with heritability z-scores < 4 from further analyses, as r_gs are not easily interpretable when the precision of the heritability estimate is this low [37].

4.3.3 LCV analysis

To broadly estimate genetic causality shared between PTSD and immune-related phenotypes, we used the LCV method [20]. This method estimates the r_g between

phenotypes, then an LCV model is fit to determine the degree to which the r_g is mediated by a latent variable with a causal effect on both phenotypes. This latent variable estimates the proportion of genetic causality shared between phenotypes (GCP), ranging from -1 to 1. Positive values reflect a causal influence of the first trait on the second, negative values reflect a causal influence of the second trait on the first. Values of -1 or 1 reflect total causal overlap, while a value of 0 indicates no shared causality.

4.3.4 MR analyses

The TwoSampleMR R package [38] was used to harmonize data and perform MR. Effect allele coding was harmonized across phenotypes using the harmonise_data function. As minor allele frequency was missing for several phenotypes, strand ambiguous SNPs were excluded. Genetic instruments were constructed using genome-wide significant SNPs. SNPs were LD clumped (r^2 <= 0.001 in 1000 Genomes Phase 3 Europeans data [39]) to insure independence. SNPs within two highly pleiotropic regions, the MHC region [20] (Chromosome 6, 28,477,797 - 33,448,354 BP) and 17q21.31 region inversion (Chromosome 17, 40,928,986 - 42,139,672 BP) were excluded, with a 3MB buffer added to ensure markers in LD were also removed.

We conducted two-sample bidirectional MR analysis using the inverse variance weighted (IVW) estimator with multiplicative random effects. MR analysis was also performed using complementary MR Egger regression [40] and weighted median [41] estimators. To account for multiple testing, false discovery rate (FDR) correction was applied within each estimator. Multiple sensitivity analyses were performed. To detect unbalanced horizontal pleiotropy (defined as direct effects of genetic instruments on the

outcome of interest with a net nonzero effect), we used the MR Egger intercept test [40]. Heterogeneity among SNP instruments was identified using the Cochran's Q test and the MR PRESSO [42] global test. The MR PRESSO outlier test was performed to identify outliers. The MR PRESSO distortion test was used to determine if the outlier-adjusted IVW estimate was significantly different from the unadjusted one. To evaluate if our associations could be explained by correlated horizontal pleiotropy (defined as genes influencing a third factor which in turn has pleiotropic effects on the exposure and outcome traits) on the investigated traits, we used the CAUSE method [19]. This method fits a set of nested models: a 'null' model where only uncorrelated horizontal pleiotropy (defined as direct effects of genes on the outcome with net zero effect) is modeled, a 'sharing' model where an additional parameter is fit to account for correlated horizontal pleiotropy, and a 'causal' model where an additional causal effect parameter is fit. The relative fits of the models are compared to determine if a causal model explains the relationship better than a model that only accounts for correlated horizontal pleiotropy. To account for potential sample overlap between PTSD and other phenotypes, we applied the MRlap [43] method. MRlap uses the LDSC genetic covariance intercept as an adjustment factor to account for sample overlap. MRlap compares the adjusted and unadjusted IVW estimates using a z-test. Multivariable MR analysis was performed using CRP as an additional exposure using the MendelianRandomization R package [44].

4.4 Results

4.4.1 r_g and genetic causality between PTSD and immune-related phenotypes

We evaluated the SNP-based heritability of 47 phenotypes. 17 phenotypes had heritability Z-scores less than 4, making them unreliable for estimating r_g and were

therefore excluded from further analyses. Of the remaining 30 phenotypes, PTSD had significant r_g with 11 (Figure 4.1), with the correlations ranging in magnitude from 0.05 (neutrophil cell count) to 0.28 (IL-6) (Supplementary Table 4.2). LCV analysis indicated that CRP was partially genetically causal for PTSD (genetic causality proportion = -0.3, SE= 0.04, $p = 1.26x10^{-19}$; rg= 0.25, se= 0.05). No other phenotype had evidence of genetic causality that reached statistical significance (Supplementary Table 4.3).

4.4.2 MR analysis

The 11 phenotypes with significant r_g with PTSD were carried forward for MR analyses. Up to 62 independent genome-wide significant SNPs were included in the genetic instrumental variable for PTSD. For the IVW based estimator, there was evidence of significant association between genetically predicted PTSD and seven inflammatory phenotypes, including asthma, CRP, IL-6, psoriasis, neutrophil count, and total white blood cell count (Table 4.1), all in the positive effect direction. With the exception of psoriasis, the IVW estimate that accounted for sample overlap between PTSD and the investigated phenotypes was significantly higher than the unadjusted estimate (Supplementary Table 4.4). For the weighted median estimator, CRP, asthma, and white blood cell count effects were FDR significant and similar to IVW effects. No result was significant under the MR Egger regression method. We performed multivariable MR using genetically predicted CRP as a surrogate variable for general inflammatory processes (Figure 4.2). The genetically predicted PTSD effect size on psoriasis was significantly weaker after this adjustment (Table 4.2). We performed MR in the other causal direction, testing for association between genetically predicted

inflammatory phenotypes and PTSD. No genetically predicted inflammatory phenotypes were significantly associated with PTSD (Supplementary Table 4.5).

4.4.3 Sensitivity analyses

Of the seven inflammatory phenotypes that were significantly associated with PTSD in the IVW MR analyses, Cochran's Q test suggested significant heterogeneity for CRP, asthma, white blood cell count, and neutrophil count, indicating pleiotropy (Table 4.1). Similarly, MR PRESSO global test for horizontal pleiotropy was significant for these phenotypes (Supplementary Table 4.6). However, following outlier removal, the outlier-corrected IVW estimates for these phenotypes were not significantly different from the original IVW estimates. The MR Egger intercept test for unbalanced horizontal pleiotropy was not significant for any phenotype tested (Table 4.1).

To determine if putative associations could potentially be accounted for by a third factor, we contrasted CAUSE estimated sharing and causal models to null models (Supplementary Table 4.7). For the effect of genetically predicted PTSD on CRP, a causal model was a better fit than a sharing model (causal effect = 0.05, 95% CI=[0.13 - 0.18], $p=8.5x10^{-8}$). For asthma, psoriasis, and white blood cell count, the causal model was only a nominally significantly better fit than the sharing model ($p < 0.05$). When we tested for causal effects in the other direction, for CRP the sharing model was a better fit than the null model ($p=0.0047$), but the causal model was not a better fit than the sharing model ($p=0.18$). No other phenotype had a significantly better fit using sharing or causal models versus the null model.

4.5 Discussion

PTSD is associated with a pro-inflammatory state and is co-morbid with inflammatory disorders [4]. The causal relationship between PTSD and inflammation is unclear, as is the causal relationship between PTSD and the development of inflammatory diseases [4]. In the current study, we performed genetic causal inference analyses of PTSD and several inflammatory biomarkers and diseases. We identified putative causal relationships between PTSD inflammatory biomarkers, CRP, IL-6, and white blood cell count (overall and neutrophils), as well as with diseases with an inflammatory component including asthma and psoriasis.

CRP is often used as a biomarker of inflammation, such that it has been used as a surrogate variable for inflammation in MR [22]. A recent MR study suggested that there is a bi-directional causal relationship between PTSD and CRP[45], further suggesting the complicated directionality of the relationship between PTSD and inflammation [4]. Our current results provided mixed evidence for both directions of causal association. Our MR analyses suggested a causal effect of PTSD on CRP, but that the causal effect of CRP on PTSD is perhaps confounded by a third factor. In contrast, the LCV analyses suggested that there is a shared genetic causality of PTSD and CRP that is driven by CRP. We however cannot rule out that the observed associations are the result of the limitations of using CRP as a biomarker for inflammation. Namely, CRP considered to be a downstream inflammatory biomarker [46 47], such that CRP may measure both upstream inflammation and pro-inflammatory effects of PTSD, thus resulting in bias from reverse causation.

Longitudinal studies suggest that PTSD increases the risk of autoimmune diseases such as psoriasis [7]. We observed a significant causal effect of genetically determined PTSD on psoriasis. Given that the association attenuated upon conditioning on CRP, our results may suggest that the inflammatory component of PTSD is what mediates increased risk of psoriasis. Thus, to understand how PTSD relates to risk of autoimmune diseases, it remains imperative to understand the relationship is between PTSD and inflammation.

Our MR results suggest a causal effect of PTSD on asthma, but that this association may be explained by an unknown confounding factor. Adjustment for CRP as a surrogate for inflammation did not attenuate the observed association. Thus, despite the inflammatory component of asthma [48], the inflammatory signals measured by CRP may not represent a mediating factor in the association between PTSD and asthma. Longitudinal cohort studies suggest that stress and social factors related to PTSD do not account for this increased risk [5, 49], leaving us to speculate on what aspect of PTSD increases asthma risk. However, we note these findings are complicated by the general heterogeneity of asthma, which has an imperfect genetic correlation between subtypes [23], and thus findings may be different if asthma sub-types were to be considered.

Adjusting for CRP provided some degree of attenuation for the effect of PTSD on IL-6 and white blood cell count. The production of CRP is stimulated by IL-6 (42), suggesting that there is a correlation between their serum measures. Further, white blood cells have a reciprocal relationship with cytokines (41), such that they may be measuring similar inflammatory signals. Indeed, we measured significant r_g of CRP with

IL-6 and white blood cell count. It is not clear however, if CRP is measuring a broad inflammatory signal, such that it is also unclear if the underlying inflammatory signal measured by these three biomarkers is truly the same. For that reason, it would be beneficial to differentiate the genetic signals contributing to different inflammatory biomarkers to help differentiate what they measure [18, 26], perhaps then leading to insights into their association with PTSD.

4.5.1 Limitations

Power to perform MR in the direction of phenotype effects on PTSD was limited due to phenotypes having relatively few genetic markers with strong effects. However, as this is a very active field of investigation, we expect that more powered GWAS summary data will be released in the future. We did not focus on disorders related to systemic inflammation [4] such as cardiovascular disease and metabolic syndrome, but these are major co-morbidities with PTSD [1]. Of the phenotypes examined, our investigation focused only on phenotypes with significant r_g with PTSD. However, some traits may have significant genetic overlap with PTSD, albeit with complicated pleiotropy that r_g cannot adequately summarize [50]. MR could still be performed if this pleiotropy were properly accounted for. Thus, a future investigation could screen on shared genetic overlap rather than r_g, then take great care in the selection of instrumental variables for MR. While outside the scope of this analysis, a detailed study of genetic overlap between PTSD and inflammatory traits, using recently developed methods [50 51], could help deliver additional mechanistic insights. It is unclear if the associations we observed are related to PTSD itself, or consequences of traumatic stress exposure, as in general stress is related to inflammation. It is also unclear if factors like socio-

economic status mediate some of these relationships, as was suggested by Polimanti et al. [45].

4.5.2 Conclusions

PTSD has a putative causal effect on inflammatory phenotypes, consistent with evidence of stress-related disorders increasing risk of conditions with an inflammatory component [5, 7]. Previously proposed inflammatory mechanisms may mediate some of these relationships. Further mechanistic investigation has to be performed to understand the role of inflammation in PTSD [14].

4.6 Acknowledgements

We acknowledge the “CHARGE Inflammation Working Group” for their contribution of summary statistics from genetic studies of C-reactive protein and Interleukin 6.

Chapter 4 is currently being prepared for submission for publication of the material. Co-authors include Andrew Ratanatharathorn, Sian M.J. Hemmings, Vasiliki Michopoulos, Renato Polimanti, Alex O. Rothbaum, Soraya Seedat, Erika J. Wolf, Elizabeth Ketema, Rany M. Salem, Jonathan Sebat, Richard A. Shaffer, Tianying Wu, Psychiatric Genomics Consortium, Kerry J. Ressler, Murray B. Stein, Karestan C. Koenen, Jennifer A. Sumner, and Caroline M. Nievergelt. The dissertation author was the primary investigator and author of this paper.

4.7 Figures

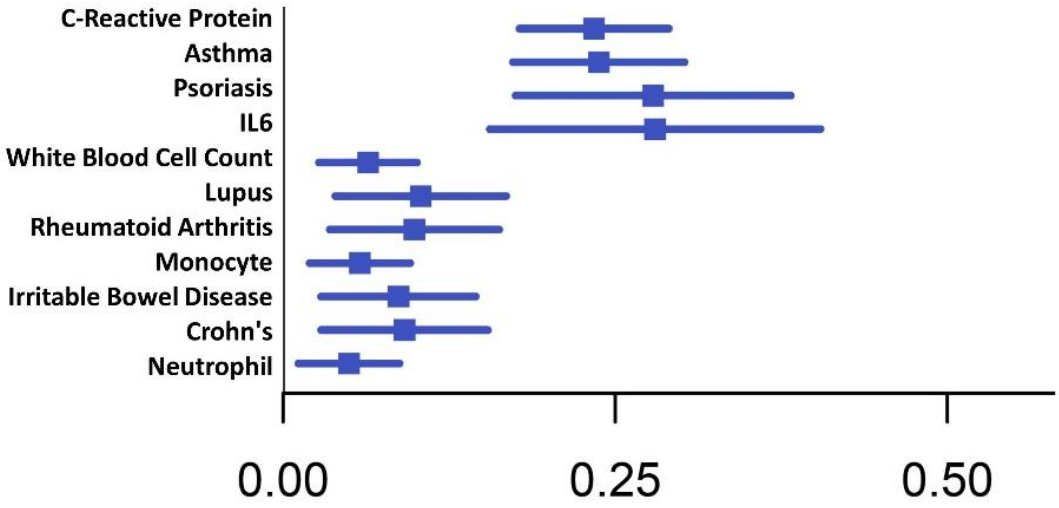

Figure 4.1. Significant genetic correlations between PTSD and autoimmune disorders and inflammatory biomarkers.

Footnote: The x-axis indicates the magnitude of genetic correlation with PTSD. The y-axis represents each trait with significant association with PTSD, indexed in the style of a barplot. Each square represents the genetic correlation of a given trait with PTSD, with the bars representing 95% confidence intervals.

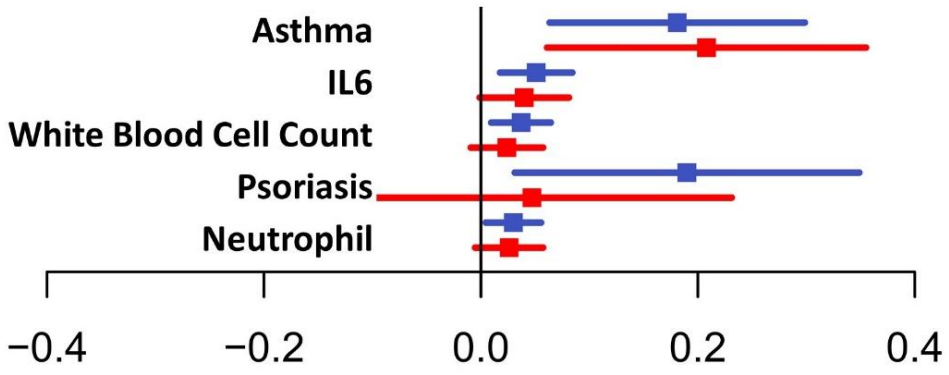

Figure 4.2. Causal effects of PTSD on autoimmune disorders and inflammatory biomarkers.

Footnote: The x-axis indicates the magnitude of association of genetically predicted PTSD with each trait. The y-axis represents each trait evaluated, indexed in the style of a barplot. Each square represents the effect size of genetically predicted PTSD on a given trait with PTSD, with the bars representing 95% confidence intervals. Blue bars are single variable IVW MR estimates, red bars are MVMR IVW estimates adjusted for CRP.

Table 4.1. Mendelian Randomization Analysis of PTSD on outcome traits

		Inverse Variance Weighted				Weighted Median				IVW Het	MR Egger			MR Egger Intercept Test		
Outcome	**N SNP**	**Beta**	**SE**	**p**	**FDR**	**Beta**	**SE**	**p**	**FDR**	**Qp**	**Beta**	**SE**	**p**	**Intercept**	**SE**	**p**
C-Reative Protein	61	0.090	0.018	4.28E-07	2.57E-06	0.071	0.015	1.38E-06	8.28E-06	1.79E-25	0.052	0.103	0.61	0.001	0.004	0.71
Asthma	59	0.181	0.060	0.0027	0.010	0.184	0.074	0.01	0.03	7.23E-03	0.441	0.343	0.20	-0.010	0.013	0.44
IL6	57	0.051	0.017	0.0032	0.010	0.035	0.024	0.15	0.23	6.68E-01	-0.041	0.108	0.71	0.004	0.004	0.40
White Blood Cell Count	56	0.037	0.014	0.0066	0.016	0.036	0.011	0.0015	0.01	9.95E-20	0.059	0.079	0.46	-0.001	0.003	0.78
Psoriasis	61	0.190	0.081	0.019	0.034	0.232	0.115	0.04	0.07	1.88E-01	-0.441	0.464	0.35	0.025	0.018	0.17
Neutrophil	56	0.030	0.013	0.02	0.034	0.025	0.012	0.03	0.07	1.39E-15	0.034	0.077	0.67	0.000	0.003	0.96
Lupus	62	0.185	0.126	0.14	0.210	0.092	0.159	0.56	0.61	6.56E-02	0.474	0.780	0.55	-0.011	0.030	0.71
IBD	62	-0.071	0.096	0.46	0.613	-0.085	0.100	0.40	0.53	8.97E-10	-0.252	0.608	0.68	0.007	0.023	0.76
Rheumatoid Arthritis	28	0.099	0.176	0.57	0.644	0.295	0.147	0.04	0.07	2.17E-08	0.110	1.024	0.92	0.000	0.040	0.99
Monocyte	56	0.007	0.013	0.59	0.644	0.008	0.011	0.49	0.59	8.05E-18	0.092	0.077	0.24	-0.003	0.003	0.27
Crohns	61	0.005	0.126	0.97	0.970	0.066	0.130	0.61	0.61	5.02E-08	-0.244	0.793	0.76	0.010	0.030	0.75

Abbreviations: IVW Het, inverse variance weighted heterogeneity test; N SNP, number of SNP instruments; FDR, false discovery rate q value; Qp, p-value for Cochran's Q test

Table 4.2. MVMR analysis of PTSD exposure and trait outcome, adjusted for CRP

	Unadjusted IVW MR			IVW MVMR adjusted for CRP							
	PTSD			PTSD			CRP			Relative reduction [a]	
Outcome	Beta	SE	p	Beta	SE	p	Beta	SE	p	p	
C-Reative Protein	0.090	0.018	4.28E-07	NA	NA	NA	NA	NA	NA	NA	NA
Asthma	0.181	0.060	0.0027	0.208	0.075	0.006	-0.176	0.445	0.692	-0.152	0.615
IL6	0.051	0.017	0.0032	0.04	0.021	0.052	0.098	0.128	0.442	0.213	-0.904
White Blood Cell Count	0.037	0.014	0.0066	0.024	0.017	0.142	0.125	0.099	0.208	0.352	-1.282
Psoriasis	0.190	0.081	0.019	0.047	0.094	0.617	1.539	0.556	0.006	0.753	-2.992
Neutrophil	0.030	0.013	0.02	0.026	0.016	0.119	0.04	0.098	0.684	0.139	-0.471

Abbreviations: IVW, inverse variance weighted;

[a] The difference of unadjusted and adjusted betas, divided by the unadjusted beta

4.9 References

1. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, Hobfoll SE, Koenen KC, Neylan TC, Hyman SE. Post-traumatic stress disorder. Nature Reviews Disease Primers. 2015;1(1):15057. doi: 10.1038/nrdp.2015.57.

2. Diagnostic and statistical manual of mental disorders : DSM-5. American Psychiatric A, American Psychiatric Association DSMTF, editors. Arlington, VA: American Psychiatric Association; 2013.

3. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Archives of general psychiatry. 1995;52(12):1048-60. Epub 1995/12/01. doi: 10.1001/archpsyc.1995.03950240066012. PubMed PMID: 7492257.

4. Hori H, Kim Y. Inflammation and post-traumatic stress disorder. Psychiatry and Clinical Neurosciences. 2019;73(4):143-53. doi: https://doi.org/10.1111/pcn.12820.

5. Hung YH, Cheng CM, Lin WC, Bai YM, Su TP, Li CT, Tsai SJ, Pan TL, Chen TJ, Chen MH. Post-traumatic stress disorder and asthma risk: A nationwide longitudinal study. Psychiatry Res. 2019;276:25-30. Epub 2019/04/17. doi: 10.1016/j.psychres.2019.04.014. PubMed PMID: 30991276.

6. Bookwalter DB, Roenfeldt KA, LeardMann CA, Kong SY, Riddle MS, Rull RP. Posttraumatic stress disorder and risk of selected autoimmune diseases among US military personnel. BMC Psychiatry. 2020;20(1):23. doi: 10.1186/s12888-020-2432-9.

7. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, Almqvist C, Fall K, Valdimarsdóttir UA. Association of Stress-Related Disorders With Subsequent Autoimmune Disease. JAMA. 2018;319(23):2388-400. doi: 10.1001/jama.2018.7028.

8. Sun Y, Qu Y, Zhu J. The Relationship Between Inflammation and Post-traumatic Stress Disorder. Frontiers in Psychiatry. 2021;12. doi: 10.3389/fpsyt.2021.707543.

9. Lindqvist D, Mellon SH, Dhabhar FS, Yehuda R, Grenon SM, Flory JD, Bierer LM, Abu-Amara D, Coy M, Makotkine I, Reus VI, Aschbacher K, Bersani FS, Marmar CR, Wolkowitz OM. Increased circulating blood cell counts in combat-related PTSD: Associations with inflammation and PTSD severity. Psychiatry Res. 2017;258:330-6. Epub 2017/09/26. doi: 10.1016/j.psychres.2017.08.052. PubMed PMID: 28942957.

10. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, Levey DF, Logue MW, Polimanti R, Provost AC, Ratanatharathorn A, Stein MB, Torres K, Aiello AE, Almli LM, Amstadter AB, Andersen SB, Andreassen OA, Arbisi PA, Ashley-Koch AE, Austin SB, Avdibegovic E, Babić D, Bækvad-Hansen M, Baker DG, Beckham JC, Bierut LJ, Bisson JI, Boks MP, Bolger EA, Børglum AD, Bradley B, Brashear M, Breen G, Bryant RA, Bustamante AC, Bybjerg-Grauholm J, Calabrese JR, Caldas- de- Almeida JM, Dale AM, Daly MJ, Daskalakis NP, Deckert J, Delahanty DL, Dennis MF, Disner SG, Domschke K, Dzubur-

Kulenovic A, Erbes CR, Evans A, Farrer LA, Feeny NC, Flory JD, Forbes D, Franz CE, Galea S, Garrett ME, Gelaye B, Geuze E, Gillespie C, Uka AG, Gordon SD, Guffanti G, Hammamieh R, Harnal S, Hauser MA, Heath AC, Hemmings SMJ, Hougaard DM, Jakovljevic M, Jett M, Johnson EO, Jones I, Jovanovic T, Qin X-J, Junglen AG, Karstoft K-I, Kaufman ML, Kessler RC, Khan A, Kimbrel NA, King AP, Koen N, Kranzler HR, Kremen WS, Lawford BR, Lebois LAM, Lewis CE, Linnstaedt SD, Lori A, Lugonja B, Luykx JJ, Lyons MJ, Maples-Keller J, Marmar C, Martin AR, Martin NG, Maurer D, Mavissakalian MR, McFarlane A, McGlinchey RE, McLaughlin KA, McLean SA, McLeay S, Mehta D, Milberg WP, Miller MW, Morey RA, Morris CP, Mors O, Mortensen PB, Neale BM, Nelson EC, Nordentoft M, Norman SB, O'Donnell M, Orcutt HK, Panizzon MS, Peters ES, Peterson AL, Peverill M, Pietrzak RH, Polusny MA, Rice JP, Ripke S, Risbrough VB, Roberts AL, Rothbaum AO, Rothbaum BO, Roy-Byrne P, Ruggiero K, Rung A, Rutten BPF, Saccone NL, Sanchez SE, Schijven D, Seedat S, Seligowski AV, Seng JS, Sheerin CM, Silove D, Smith AK, Smoller JW, Sponheim SR, Stein DJ, Stevens JS, Sumner JA, Teicher MH, Thompson WK, Trapido E, Uddin M, Ursano RJ, van den Heuvel LL, Van Hooff M, Vermetten E, Vinkers CH, Voisey J, Wang Y, Wang Z, Werge T, Williams MA, Williamson DE, Winternitz S, Wolf C, Wolf EJ, Wolff JD, Yehuda R, Young RM, Young KA, Zhao H, Zoellner LA, Liberzon I, Ressler KJ, Haas M, Koenen KC. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nature Communications. 2019;10(1):4558. doi: 10.1038/s41467-019-12576-w.

11. Uddin M, Aiello AE, Wildman DE, Koenen KC, Pawelec G, de Los Santos R, Goldmann E, Galea S. Epigenetic and immune function profiles associated with posttraumatic stress disorder. Proc Natl Acad Sci U S A. 2010;107(20):9470-5. Epub 2010/05/03. doi: 10.1073/pnas.0910794107. PubMed PMID: 20439746.

12. Katrinli S, Maihofer AX, Wani AH, Pfeiffer JR, Ketema E, Ratanatharathorn A, Baker DG, Boks MP, Geuze E, Kessler RC, Risbrough VB, Rutten BPF, Stein MB, Ursano RJ, Vermetten E, Logue MW, Nievergelt CM, Smith AK, Uddin M. Epigenome-wide meta-analysis of PTSD symptom severity in three military cohorts implicates DNA methylation changes in genes involved in immune system and oxidative stress. Molecular Psychiatry. 2022. doi: 10.1038/s41380-021-01398-2.

13. Breen MS, Maihofer AX, Glatt SJ, Tylee DS, Chandler SD, Tsuang MT, Risbrough VB, Baker DG, O'Connor DT, Nievergelt CM, Woelk CH. Gene networks specific for innate immunity define post-traumatic stress disorder. Molecular Psychiatry. 2015;20(12):1538-45. doi: 10.1038/mp.2015.9.

14. Sumner JA, Nishimi KM, Koenen KC, Roberts AL, Kubzansky LD. Posttraumatic Stress Disorder and Inflammation: Untangling Issues of Bidirectionality. Biological Psychiatry. 2020;87(10):885-97. doi: https://doi.org/10.1016/j.biopsych.2019.11.005.

15. Neigh GN, Ali FF. Co-morbidity of PTSD and immune system dysfunction: opportunities for treatment. Curr Opin Pharmacol. 2016;29:104-10. Epub 2016/07/29. doi: 10.1016/j.coph.2016.07.011. PubMed PMID: 27479489.

16. Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. Journal of the American Society of Nephrology. 2016;27(11):3253. doi: 10.1681/ASN.2016010098.

17. Stein MB, Levey DF, Cheng Z, Wendt FR, Harrington K, Pathak GA, Cho K, Quaden R, Radhakrishnan K, Girgenti MJ, Ho YA, Posner D, Aslan M, Duman RS, Zhao H, Department of Veterans Affairs Cooperative Studies P, Program VAMV, Polimanti R, Concato J, Gelernter J. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. Nat Genet. 2021;53(2):174-84. doi: 10.1038/s41588-020-00767-x. PubMed PMID: 33510476.

18. Lincoln MR, Connally N, Axisa P-P, Gasperi C, Mitrovic M, Heel Dv, Wijmenga C, Withoff S, Jonkers IH, Padyukov L, International Multiple Sclerosis Genetics C, Rich SS, Graham RR, Gaffney PM, Langefeld CD, Hafler DA, Chun S, Sunayev SR, Cotsapas C. Joint analysis reveals shared autoimmune disease associations and identifies common mechanisms. medRxiv. 2021:2021.05.13.21257044. doi: 10.1101/2021.05.13.21257044.

19. Morrison J, Knoblauch N, Marcus JH, Stephens M, He X. Mendelian randomization accounting for correlated and uncorrelated pleiotropic effects using genome-wide summary statistics. Nat Genet. 2020;52(7):740-7. Epub 2020/05/27. doi: 10.1038/s41588-020-0631-4. PubMed PMID: 32451458 PMCID: PMCPMC7343608.

20. O'Connor LJ, Price AL. Distinguishing genetic correlation from causation across 52 diseases and complex traits. Nature genetics. 2018;50(12):1728-34. Epub 2018/10/29. doi: 10.1038/s41588-018-0255-0. PubMed PMID: 30374074.

21. Bulik-Sullivan BK, Loh P-R, Finucane HK, Ripke S, Yang J, Patterson N, Daly MJ, Price AL, Neale BM, Schizophrenia Working Group of the Psychiatric Genomics C. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nature genetics. 2015;47(3):291-5. doi: 10.1038/ng.3211.

22. Perry BI, Burgess S, Jones HJ, Zammit S, Upthegrove R, Mason AM, Day FR, Langenberg C, Wareham NJ, Jones PB, Khandaker GM. The potential shared role of inflammation in insulin resistance and schizophrenia: A bidirectional two-sample mendelian randomization study. PLoS Med. 2021;18(3):e1003455. Epub 2021/03/13. doi: 10.1371/journal.pmed.1003455. PubMed PMID: 33711016 PMCID: PMCPMC7954314 following competing interests. SB is a paid statistical consultant on PLOS Medicine's statistical board. CL is an Academic Editor on PLOS Medicine's editorial board. PBJ has received honoraria for providing scientific advice to Jansen, Ricordati and Lundbeck.

23. Zhu Z, Lee PH, Chaffin MD, Chung W, Loh P-R, Lu Q, Christiani DC, Liang L. A genome-wide cross-trait analysis from UK Biobank highlights the shared genetic architecture of asthma and allergic diseases. Nature genetics. 2018;50(6):857-64. doi: 10.1038/s41588-018-0121-0.

24. Chen M-H, Raffield LM, Mousas A, Sakaue S, Huffman JE, Moscati A, Trivedi B, Jiang T, Akbari P, Vuckovic D, Bao EL, Zhong X, Manansala R, Laplante V, Chen M, Lo KS, Qian H, Lareau CA, Beaudoin M, Hunt KA, Akiyama M, Bartz TM, Ben-Shlomo Y, Beswick A, Bork-Jensen J, Bottinger EP, Brody JA, van Rooij FJA, Chitrala K, Cho K, Choquet H, Correa A, Danesh J, Di Angelantonio E, Dimou N, Ding J, Elliott P, Esko T, Evans MK, Floyd JS, Broer L, Grarup N, Guo MH, Greinacher A, Haessler J, Hansen T, Howson JMM, Huang QQ, Huang W, Jorgenson E, Kacprowski T, Kähönen M, Kamatani Y, Kanai M, Karthikeyan S, Koskeridis F, Lange LA, Lehtimäki T, Lerch MM, Linneberg A, Liu Y, Lyytikäinen L-P, Manichaikul A, Martin HC, Matsuda K, Mohlke KL, Mononen N, Murakami Y, Nadkarni GN, Nauck M, Nikus K, Ouwehand WH, Pankratz N, Pedersen O, Preuss M, Psaty BM, Raitakari OT, Roberts DJ, Rich SS, Rodriguez BAT, Rosen JD, Rotter JI, Schubert P, Spracklen CN, Surendran P, Tang H, Tardif J-C, Trembath RC, Ghanbari M, Völker U, Völzke H, Watkins NA, Zonderman AB, Wilson PWF, Li Y, Butterworth AS, Gauchat J-F, Chiang CWK, Li B, Loos RJF, Astle WJ, Evangelou E, van Heel DA, Sankaran VG, Okada Y, Soranzo N, Johnson AD, Reiner AP, Auer PL, Lettre G. Trans-ethnic and Ancestry-Specific Blood-Cell Genetics in 746,667 Individuals from 5 Global Populations. Cell. 2020;182(5):1198-213.e14. doi: https://doi.org/10.1016/j.cell.2020.06.045.

25. Dubois PCA, Trynka G, Franke L, Hunt KA, Romanos J, Curtotti A, Zhernakova A, Heap GAR, Ádány R, Aromaa A, Bardella MT, van den Berg LH, Bockett NA, de la Concha EG, Dema B, Fehrmann RSN, Fernández-Arquero M, Fiatal S, Grandone E, Green PM, Groen HJM, Gwilliam R, Houwen RHJ, Hunt SE, Kaukinen K, Kelleher D, Korponay-Szabo I, Kurppa K, MacMathuna P, Mäki M, Mazzilli MC, McCann OT, Mearin ML, Mein CA, Mirza MM, Mistry V, Mora B, Morley KI, Mulder CJ, Murray JA, Núñez C, Oosterom E, Ophoff RA, Polanco I, Peltonen L, Platteel M, Rybak A, Salomaa V, Schweizer JJ, Sperandeo MP, Tack GJ, Turner G, Veldink JH, Verbeek WHM, Weersma RK, Wolters VM, Urcelay E, Cukrowska B, Greco L, Neuhausen SL, McManus R, Barisani D, Deloukas P, Barrett JC, Saavalainen P, Wijmenga C, van Heel DA. Multiple common variants for celiac disease influencing immune gene expression. Nature genetics. 2010;42(4):295-302. doi: 10.1038/ng.543.

26. Sliz E, Kalaoja M, Ahola-Olli A, Raitakari O, Perola M, Salomaa V, Lehtimäki T, Karhu T, Viinamäki H, Salmi M, Santalahti K, Jalkanen S, Jokelainen J, Keinänen-Kiukaanniemi S, Männikkö M, Herzig K-H, Järvelin M-R, Sebert S, Kettunen J. Genome-wide association study identifies seven novel loci associating with circulating cytokines and cell adhesion molecules in Finns. Journal of Medical Genetics. 2019;56(9):607. doi: 10.1136/jmedgenet-2018-105965.

27. Sinnott-Armstrong N, Tanigawa Y, Amar D, Mars N, Benner C, Aguirre M, Venkataraman GR, Wainberg M, Ollila HM, Kiiskinen T, Havulinna AS, Pirruccello JP, Qian J, Shcherbina A, Rodriguez F, Assimes TL, Agarwala V, Tibshirani R, Hastie T, Ripatti S, Pritchard JK, Daly MJ, Rivas MA, FinnGen. Genetics of 35 blood and urine biomarkers in the UK Biobank. Nature genetics. 2021;53(2):185-94. doi: 10.1038/s41588-020-00757-z.

28. Ahluwalia TS, Prins BP, Abdollahi M, Armstrong NJ, Aslibekyan S, Bain L, Jefferis B, Baumert J, Beekman M, Ben-Shlomo Y, Bis JC, Mitchell BD, de Geus E,

Delgado GE, Marek D, Eriksson J, Kajantie E, Kanoni S, Kemp JP, Lu C, Marioni RE, McLachlan S, Milaneschi Y, Nolte IM, Petrelis AM, Porcu E, Sabater-Lleal M, Naderi E, Seppälä I, Shah T, Singhal G, Standl M, Teumer A, Thalamuthu A, Thiering E, Trompet S, Ballantyne CM, Benjamin EJ, Casas JP, Toben C, Dedoussis G, Deelen J, Durda P, Engmann J, Feitosa MF, Grallert H, Hammarstedt A, Harris SE, Homuth G, Hottenga J-J, Jalkanen S, Jamshidi Y, Jawahar MC, Jess T, Kivimaki M, Kleber ME, Lahti J, Liu Y, Marques-Vidal P, Mellström D, Mooijaart SP, Müller-Nurasyid M, Penninx B, Revez JA, Rossing P, Räikkönen K, Sattar N, Scharnagl H, Sennblad B, Silveira A, Pourcain BS, Timpson NJ, Trollor J, Group CIW, van Dongen J, Van Heemst D, Visvikis-Siest S, Vollenweider P, Völker U, Waldenberger M, Willemsen G, Zabaneh D, Morris RW, Arnett DK, Baune BT, Boomsma DI, Chang Y-PC, Deary IJ, Deloukas P, Eriksson JG, Evans DM, Ferreira MA, Gaunt T, Gudnason V, Hamsten A, Heinrich J, Hingorani A, Humphries SE, Jukema JW, Koenig W, Kumari M, Kutalik Z, Lawlor DA, Lehtimäki T, März W, Mather KA, Naitza S, Nauck M, Ohlsson C, Price JF, Raitakari O, Rice K, Sachdev PS, Slagboom E, Sørensen TIA, Spector T, Stacey D, Stathopoulou MG, Tanaka T, Wannamethee SG, Whincup P, Rotter JI, Dehghan A, Boerwinkle E, Psaty BM, Snieder H, Alizadeh BZ. Genome-wide association study of circulating interleukin 6 levels identifies novel loci. Human Molecular Genetics. 2021;30(5):393-409. doi: 10.1093/hmg/ddab023.

29. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Daryani NE, Franke L, Fuyuno Y, Hart A, Juyal RC, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JJY, Malekzadeh R, Westra H-J, Yamazaki K, Yang S-K, Barrett JC, Franke A, Alizadeh BZ, Parkes M, B K T, Daly MJ, Kubo M, Anderson CA, Weersma RK, International Multiple Sclerosis Genetics C, International IBDGC. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nature genetics. 2015;47(9):979-86. doi: 10.1038/ng.3359.

30. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, Tan M, Kia DA, Noyce AJ, Xue A, Bras J, Young E, von Coelln R, Simón-Sánchez J, Schulte C, Sharma M, Krohn L, Pihlstrøm L, Siitonen A, Iwaki H, Leonard H, Faghri F, Gibbs JR, Hernandez DG, Scholz SW, Botia JA, Martinez M, Corvol JC, Lesage S, Jankovic J, Shulman LM, Sutherland M, Tienari P, Majamaa K, Toft M, Andreassen OA, Bangale T, Brice A, Yang J, Gan-Or Z, Gasser T, Heutink P, Shulman JM, Wood NW, Hinds DA, Hardy JA, Morris HR, Gratten J, Visscher PM, Graham RR, Singleton AB. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol. 2019;18(12):1091-102. Epub 2019/11/09. doi: 10.1016/s1474-4422(19)30320-5. PubMed PMID: 31701892 PMCID: PMCPMC8422160.

31. Cordell HJ, Han Y, Mells GF, Li Y, Hirschfield GM, Greene CS, Xie G, Juran BD, Zhu D, Qian DC, Floyd JAB, Morley KI, Prati D, Lleo A, Cusi D, Schlicht EM, Lammert C, Atkinson EJ, Chan LL, de Andrade M, Balschun T, Mason AL, Myers RP, Zhang J, Milkiewicz P, Qu J, Odin JA, Luketic VA, Bacon BR, Bodenheimer Jr HC, Liakina V, Vincent C, Levy C, Gregersen PK, Almasio PL, Alvaro D, Andreone P, Andriulli A,

Barlassina C, Battezzati PM, Benedetti A, Bernuzzi F, Bianchi I, Bragazzi MC, Brunetto M, Bruno S, Casella G, Coco B, Colli A, Colombo M, Colombo S, Cursaro C, Crocè LS, Crosignani A, Donato MF, Elia G, Fabris L, Ferrari C, Floreani A, Foglieni B, Fontana R, Galli A, Lazzari R, Macaluso F, Malinverno F, Marra F, Marzioni M, Mattalia A, Montanari R, Morini L, Morisco F, Hani S M, Muratori L, Muratori P, Niro GA, Palmieri VO, Picciotto A, Podda M, Portincasa P, Ronca V, Rosina F, Rossi S, Sogno I, Spinzi G, Spreafico M, Strazzabosco M, Tarallo S, Tarocchi M, Tiribelli C, Toniutto P, Vinci M, Zuin M, Ch'ng CL, Rahman M, Yapp T, Sturgess R, Healey C, Czajkowski M, Gunasekera A, Gyawali P, Premchand P, Kapur K, Marley R, Foster G, Watson A, Dias A, Subhani J, Harvey R, McCorry R, Ramanaden D, Gasem J, Evans R, Mathialahan T, Shorrock C, Lipscomb G, Southern P, Tibble J, Gorard D, Palegwala A, Jones S, Carbone M, Dawwas M, Alexander G, Dolwani S, Prince M, Foxton M, Elphick D, Mitchison H, Gooding I, Karmo M, Saksena S, Mendall M, Patel M, Ede R, Austin A, Sayer J, Hankey L, Hovell C, Fisher N, Carter M, Koss K, Piotrowicz A, Grimley C, Neal D, Lim G, Levi S, Ala A, Broad A, Saeed A, Wood G, Brown J, Wilkinson M, Gordon H, Ramage J, Ridpath J, Ngatchu T, Grover B, Shaukat S, Shidrawi R, Abouda G, Ali F, Rees I, Salam I, Narain M, Brown A, Taylor-Robinson S, Williams S, Grellier L, Banim P, Das D, Chilton A, Heneghan M, Curtis H, Gess M, Drake I, Aldersley M, Davies M, Jones R, McNair A, Srirajaskanthan R, Pitcher M, Sen S, Bird G, Barnardo A, Kitchen P, Yoong K, Chirag O, Sivaramakrishnan N, MacFaul G, Jones D, Shah A, Evans C, Saha S, Pollock K, Bramley P, Mukhopadhya A, Fraser A, Mills P, Shallcross C, Campbell S, Bathgate A, Shepherd A, Dillon J, Rushbrook S, Przemioslo R, Macdonald C, Metcalf J, Shmueli U, Davis A, Naqvi A, Lee T, Ryder SD, Collier J, Klass H, Ninkovic M, Cramp M, Sharer N, Aspinall R, Goggin P, Ghosh D, Douds A, Hoeroldt B, Booth J, Williams E, Hussaini H, Stableforth W, Ayres R, Thorburn D, Marshall E, Burroughs A, Mann S, Lombard M, Richardson P, Patanwala I, Maltby J, Brookes M, Mathew R, Vyas S, Singhal S, Gleeson D, Misra S, Butterworth J, George K, Harding T, Douglass A, Panter S, Shearman J, Bray G, Butcher G, Forton D, McLindon J, Cowan M, Whatley G, Mandal A, Gupta H, Sanghi P, Jain S, Pereira S, Prasad G, Watts G, Wright M, Neuberger J, Gordon F, Unitt E, Grant A, Delahooke T, Higham A, Brind A, Cox M, Ramakrishnan S, King A, Collins C, Whalley S, Li A, Fraser J, Bell A, Wong VS, Singhal A, Gee I, Ang Y, Ransford R, Gotto J, Millson C, Bowles J, Thomas C, Harrison M, Galaska R, Kendall J, Whiteman J, Lawlor C, Gray C, Elliott K, Mulvaney-Jones C, Hobson L, Van Duyvenvoorde G, Loftus A, Seward K, Canadian USPBCC, Italian PBCGSG, Consortium U-P. International genome-wide meta-analysis identifies new primary biliary cirrhosis risk loci and targetable pathogenic pathways. Nature Communications. 2015;6(1):8019. doi: 10.1038/ncomms9019.

32. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, Narita A, Konuma T, Yamamoto K, Akiyama M, Ishigaki K, Suzuki A, Suzuki K, Obara W, Yamaji K, Takahashi K, Asai S, Takahashi Y, Suzuki T, Shinozaki N, Yamaguchi H, Minami S, Murayama S, Yoshimori K, Nagayama S, Obata D, Higashiyama M, Masumoto A, Koretsune Y, Ito K, Terao C, Yamauchi T, Komuro I, Kadowaki T, Tamiya G, Yamamoto M, Nakamura Y, Kubo M, Murakami Y, Yamamoto K, Kamatani Y, Palotie A, Rivas MA, Daly MJ, Matsuda K, Okada Y, FinnGen. A cross-population atlas of genetic associations for 220 human phenotypes. Nature genetics. 2021;53(10):1415-24. doi: 10.1038/s41588-021-00931-x.

33. Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, Yoshida S, Graham RR, Manoharan A, Ortmann W, Bhangale T, Denny JC, Carroll RJ, Eyler AE, Greenberg JD, Kremer JM, Pappas DA, Jiang L, Yin J, Ye L, Su D-F, Yang J, Xie G, Keystone E, Westra H-J, Esko T, Metspalu A, Zhou X, Gupta N, Mirel D, Stahl EA, Diogo D, Cui J, Liao K, Guo MH, Myouzen K, Kawaguchi T, Coenen MJH, van Riel PLCM, van de Laar MAFJ, Guchelaar H-J, Huizinga TWJ, Dieudé P, Mariette X, Louis Bridges Jr S, Zhernakova A, Toes REM, Tak PP, Miceli-Richard C, Bang S-Y, Lee H-S, Martin J, Gonzalez-Gay MA, Rodriguez-Rodriguez L, Rantapää-Dahlqvist S, Ärlestig L, Choi HK, Kamatani Y, Galan P, Lathrop M, Eyre S, Bowes J, Barton A, de Vries N, Moreland LW, Criswell LA, Karlson EW, Taniguchi A, Yamada R, Kubo M, Liu JS, Bae S-C, Worthington J, Padyukov L, Klareskog L, Gregersen PK, Raychaudhuri S, Stranger BE, De Jager PL, Franke L, Visscher PM, Brown MA, Yamanaka H, Mimori T, Takahashi A, Xu H, Behrens TW, Siminovitch KA, Momohara S, Matsuda F, Yamamoto K, Plenge RM, the Rc, the Gc. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature. 2014;506(7488):376-81. doi: 10.1038/nature12873.

34. Langefeld CD, Ainsworth HC, Graham DSC, Kelly JA, Comeau ME, Marion MC, Howard TD, Ramos PS, Croker JA, Morris DL, Sandling JK, Almlöf JC, Acevedo-Vásquez EM, Alarcón GS, Babini AM, Baca V, Bengtsson AA, Berbotto GA, Bijl M, Brown EE, Brunner HI, Cardiel MH, Catoggio L, Cervera R, Cucho-Venegas JM, Dahlqvist SR, D'Alfonso S, Da Silva BM, de la Rúa Figueroa I, Doria A, Edberg JC, Endreffy E, Esquivel-Valerio JA, Fortin PR, Freedman BI, Frostegård J, García MA, de la Torre IG, Gilkeson GS, Gladman DD, Gunnarsson I, Guthridge JM, Huggins JL, James JA, Kallenberg CGM, Kamen DL, Karp DR, Kaufman KM, Kottyan LC, Kovács L, Laustrup H, Lauwerys BR, Li Q-Z, Maradiaga-Ceceña MA, Martín J, McCune JM, McWilliams DR, Merrill JT, Miranda P, Moctezuma JF, Nath SK, Niewold TB, Orozco L, Ortego-Centeno N, Petri M, Pineau CA, Pons-Estel BA, Pope J, Raj P, Ramsey-Goldman R, Reveille JD, Russell LP, Sabio JM, Aguilar-Salinas CA, Scherbarth HR, Scorza R, Seldin MF, Sjöwall C, Svenungsson E, Thompson SD, Toloza SMA, Truedsson L, Tusié-Luna T, Vasconcelos C, Vilá LM, Wallace DJ, Weisman MH, Wither JE, Bhangale T, Oksenberg JR, Rioux JD, Gregersen PK, Syvänen A-C, Rönnblom L, Criswell LA, Jacob CO, Sivils KL, Tsao BP, Schanberg LE, Behrens TW, Silverman ED, Alarcón-Riquelme ME, Kimberly RP, Harley JB, Wakeland EK, Graham RR, Gaffney PM, Vyse TJ. Transancestral mapping and genetic load in systemic lupus erythematosus. Nature Communications. 2017;8(1):16021. doi: 10.1038/ncomms16021.

35. Dowsett J, Ferkingstad E, Rasmussen LJH, Thørner LW, Magnússon MK, Sugden K, Thorleifsson G, Frigge M, Burgdorf KS, Ostrowski SR, Sørensen E, Erikstrup C, Pedersen OB, Hansen TF, Banasik K, Brunak S, Andersen S, Jemec G, Jennum P, Nielsen RK, Nyegaard M, Paarup HM, Petersen M, Werge T, Gudbjartsson D, Stefansson K, Þorsteinsdóttir U, Tragante V, Lund SH, Stefansdottir L, Gunnarson B, Poulton R, Arseneault L, Caspi A, Moffitt TE, Gudbjartsson D, Eugen-Olsen J, Stefánsson H, Stefánsson K, Ullum H, Consortium DG, Denmark, Iceland. Eleven genomic loci affect plasma levels of chronic inflammation marker soluble urokinase-type plasminogen activator receptor. Communications Biology. 2021;4(1):655. doi: 10.1038/s42003-021-02144-8.

36. Chiou J, Geusz RJ, Okino M-L, Han JY, Miller M, Melton R, Beebe E, Benaglio P, Huang S, Korgaonkar K, Heller S, Kleger A, Preissl S, Gorkin DU, Sander M, Gaulton KJ. Interpreting type 1 diabetes risk with genetics and single-cell epigenomics. Nature. 2021;594(7863):398-402. doi: 10.1038/s41586-021-03552-w.

37. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh P-R, ReproGen C, Psychiatric Genomics C, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control C, Duncan L, Perry JRB, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM. An atlas of genetic correlations across human diseases and traits. Nature genetics. 2015;47(11):1236-41. Epub 2015/09/28. doi: 10.1038/ng.3406. PubMed PMID: 26414676.

38. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC. The MR-Base platform supports systematic causal inference across the human phenome. eLife. 2018;7:e34408. doi: 10.7554/eLife.34408.

39. Clarke L, Zheng-Bradley X, Smith R, Kulesha E, Xiao C, Toneva I, Vaughan B, Preuss D, Leinonen R, Shumway M, Sherry S, Flicek P, The Genomes Project C. The 1000 Genomes Project: data management and community access. Nature Methods. 2012;9(5):459-62. doi: 10.1038/nmeth.1974.

40. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol. 2017;32(5):377-89. Epub 2017/05/21. doi: 10.1007/s10654-017-0255-x. PubMed PMID: 28527048 PMCID: PMCPMC5506233.

41. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol. 2016;40(4):304-14. Epub 2016/04/07. doi: 10.1002/gepi.21965. PubMed PMID: 27061298.

42. Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nature genetics. 2018;50(5):693-8. doi: 10.1038/s41588-018-0099-7.

43. Mounier N, Kutalik Z. Bias correction for inverse variance weighting Mendelian randomization. bioRxiv. 2021:2021.03.26.437168. doi: 10.1101/2021.03.26.437168.

44. Yavorska OO, Burgess S. MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. Int J Epidemiol. 2017;46(6):1734-9. Epub 2017/04/12. doi: 10.1093/ije/dyx034. PubMed PMID: 28398548 PMCID: PMCPMC5510723.

45. Muniz Carvalho C, Wendt FR, Maihofer AX, Stein DJ, Stein MB, Sumner JA, Hemmings SMJ, Nievergelt CM, Koenen KC, Gelernter J, Belangero SI, Polimanti R.

Dissecting the genetic association of C-reactive protein with PTSD, traumatic events, and social support. Neuropsychopharmacology. 2020. doi: 10.1038/s41386-020-0655-6.

46. Ridker PM. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. Circ Res. 2016;118(1):145-56. doi: 10.1161/CIRCRESAHA.115.306656. PubMed PMID: 26837745.

47. Jialal I, Devaraj S, Venugopal SK. C-Reactive Protein: Risk Marker or Mediator in Atherothrombosis? Hypertension. 2004;44(1):6-11. doi: 10.1161/01.HYP.0000130484.20501.df.

48. Lambrecht BN, Hammad H. The immunology of asthma. Nature Immunology. 2015;16(1):45-56. doi: 10.1038/ni.3049.

49. Allgire E, McAlees JW, Lewkowich IP, Sah R. Asthma and posttraumatic stress disorder (PTSD): Emerging links, potential models and mechanisms. Brain, Behavior, and Immunity. 2021;97:275-85. doi: https://doi.org/10.1016/j.bbi.2021.06.001.

50. Frei O, Holland D, Smeland OB, Shadrin AA, Fan CC, Maeland S, O'Connell KS, Wang Y, Djurovic S, Thompson WK, Andreassen OA, Dale AM. Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. Nature Communications. 2019;10(1):2417. doi: 10.1038/s41467-019-10310-0.

51. Werme J, van der Sluis S, Posthuma D, de Leeuw CA. LAVA: An integrated framework for local genetic correlation analysis. bioRxiv. 2021:2020.12.31.424652. doi: 10.1101/2020.12.31.424652.

Chapter 5. Discussion

Post traumatic stress disorder (PTSD) has severe psychological, physical, interpersonal, and societal costs [1-4]. The lifetime prevalence of PTSD in the United States is 5-10% [5], albeit is highly conditional on trauma exposure [6]. The burden of PTSD on the individual and on society makes the continued development of increasingly effectual treatments for PTSD very important. Deeper research into the biological basis of PTSD may aid these efforts [7]. Furthermore, understanding how PTSD relates biologically to the development of other diseases, such as autoimmune conditions, also opens new potential avenues for treatment [8]. The substantial heritability of PTSD implies that genetics are an important biological risk factor [3], one that is methodologically feasible to investigate [9].

This dissertation aimed to extend analyses performed by the Psychiatric Genomics Consortium (PGC)-PTSD by leveraging additional phenotype data on PTSD symptoms and trauma exposure, and information on copy number variant (CNV) data available from the GWAS arrays, to identify additional genetic risk factors contributing to PTSD, then to use this genetic variation to evaluate a potential causal relationship between PTSD and co-morbid autoimmune conditions using a Mendelian Randomization (MR) approach. Specifically, in chapter 2, we explored the common genetic variation association with PTSD, leveraging continuous PTSD symptom scores and lifetime trauma exposure (LTE) to gain additional insights. We identified novel replicable risk loci, with widespread pleiotropic associations to other psychiatric disorders, co-morbid conditions, and traits. We also identified novel loci related to LTE. There was a high genetic overlap of PTSD and LTE, albeit with some key differences

identified: negative affect traits like neuroticism and irritability were more strongly correlated with PTSD than LTE, whereas risk-taking behavior showed higher correlation with LTE than PTSD. Our results indicate a significant amount of genetic effects on PTSD are potentially mediated by trauma exposure. We found that incorporating trauma exposure data as an additional outcome in a multivariate analysis enhanced PTSD GWAS discovery power, having identified additional replicable loci.

Next, in chapter 3, we expanded the scope of genetic investigation of PTSD into rare genetic variation, performing the first large scale investigation of rare CNVs and PTSD. We found that the genome-wide burden of CNVs was positively associated with PTSD. This burden was largely concentrated in previously implicated neurodevelopmental CNV regions. Results specifically identify increased risk in CNVs overlapping the 22q11.2 duplication and 15q11.2 BP1-BP2 microdeletion regions. Outside of neurodevelopmental CNVs, association was found for several gene sets related to the function and development of the central nervous system, including small cell RNAs. In conclusion, we found that CNV burden predicted a significant fraction of the variation in PTSD symptoms, albeit one that is relatively small compared to common variant based polygenic risk scores (PRSs) generated from recent GWAS [10].

Last, in chapter 4, we used Mendelian Randomization (MR) to investigate a potential causal association between PTSD and autoimmune conditions. We found a significant association between genetically instrumented PTSD and asthma, psoriasis, C-Reactive Protein (CRP), interleukin-6, neutrophil count, and total white blood cell count. The causal association with psoriasis could be explained by a general inflammatory signal, as measured by using CRP as proxy for inflammation. The

associations for inflammatory biomarkers, interleukin-6 and white blood cell count, seemed to be related to this signal as well. We observed that the previously reported effect of genetically instrumented CRP on PTSD [11] may have been confounded by an unknown factor.

Our results suggest that future genetic studies of PTSD will benefit from the integration of trauma exposure information. Importantly, trauma exposure history is oftentimes gathered alongside PTSD status, meaning that the most important step of integration, the measurement of the phenotype, is already performed and available for researchers. We chose multivariate analyses as our means of integration, which we considered ideal for the shortcomings of our data. However, more sophisticated models integrating PTSD and trauma could be explored, in particular causal mediation analysis [12]. Causal mediation analysis allows for simultaneous investigation of mediation and gene by environment interactions (GxEs), which are thought to be an essential yet under-investigated aspect of PTSD genetics [13]. The suggestion to incorporate trauma exposure equally applies to rare variant associations. In light of identifying neurodevelopmental CNVs as being associated with PTSD, it may be particularly relevant to explore their association as mediated by childhood trauma or other factors associated with early development that are risk factors for PTSD.

While CNV primarily have been investigated in the context of autism and schizophrenia [14, 15], there is building evidence that they are relevant to other psychiatric disorders [16-18]. We identified CNV risk associations with PTSD, but their effects were relatively modest compared to CNV effects on autism and schizophrenia. For example, schizophrenia has multiple highly penetrant variants [19], such as the 22q11.2 deletion

variant, for which 25% of carriers develop schizophrenia [20]. It may be that differences in the genetic architectures of PTSD and schizophrenia seen in common variation [21] are also at least somewhat reflected in rare variation. Nevertheless, the identification of these rare variants is important, as it may still help pinpoint genes wherein mutational disruption considerably influences risk [22], suggesting them as targets for follow up [23]. Overall, our CNV findings are fairly similar to those of major depressive disorder [18], which also follows what is observed in GWAS [21]. It has been hypothesized that studying psychiatric disorders together will greatly enhance understanding of the similarities and differences of these conditions [24], where efforts are now underway to perform such cross-disorder analysis with rare CNVs [25].

The study of the causal association between PTSD and autoimmune conditions has potential applications to the diagnoses of these disorders and to the treatment of PTSD itself [8]. Our results support the notion that PTSD precedes autoimmune disease, strengthening the evidence of longitudinal studies that suggest early treatment of PTSD relates to reduces risk of developing an autoimmune disease [26]. Our results also support the notion that the relationship between PTSD and some autoimmune conditions, like psoriasis, is related to a common inflammatory factor(s) [27]. Thus, this is an important target for future investigation for both PTSD and autoimmune diseases, with further upstream in the inflammatory cascade being an obvious place to start investigation [28].

There are several limitations to the analyses contained in this dissertation, which should be addressed in future works. First, we focused on European ancestry populations, but genetic investigation of non-European populations is necessary in

addressing health disparities [29]. This is particularly relevant in the context of PTSD, as risk of PTSD is differential across ancestries [30]. In general, genetic variation in non-European populations is relatively less investigated than in European ancestry populations, due to data availability and other factors [31]. The current efforts to gather non-European ancestry samples in the PGC and PGC-PTSD in particular [21] will provide much-needed data to expand analyses to other ancestries. Ancestry deconvolution methods that we have developed [32] will facilitate the analysis of admixed individuals in these data. In addition to gene discovery and fine-mapping, availability of non-European data will serve as a resource to develop and calibrate PRS estimation in non-European populations [33].

Second, I have performed multivariate modeling of LTE and PTSD, rather than attempt to implement the proposed causal mediation analysis method. There were two major factors for this, the first being the limitations of the data: Trauma exposure is typically assessed retrospective to PTSD via self report. Recall bias has been observed in the forms of both over and under reporting of trauma exposure [34]. There is evidence to suggest that PTSD systematically influences recall bias of trauma exposure [35], which violates a required assumption of the mediation model. In contrast, there is no such required assumption for the multivariate model where LTE is treated as an additional outcome. Any causal mediation analysis should therefore consider a thorough sensitivity analysis, possibly calibrated on empirical data from prospective assessments. The second limitation was computational: causal mediation analysis takes significant computational resources to perform, for example being orders of magnitude slower to compute than a basic linear regression. Thus currently, it is feasible to examine a small

number of loci, such as the leading variants from GWAS. However, the true value of these analyses would come in the form of post-GWAS analyses of the whole genome, such as for tissue expression overrepresentation [36] or genetic correlations [37]. Rather than increasing computing capacity, it may be better to optimize methods. One avenue may involve the assumption of infinitesimal genetic effects, which has been used successfully to speed up GWAS computations in other contexts [38].

Third, the analysis of rare genetic variations focused only on large CNVs. Genotype arrays are limited to reliably calling only relatively large (>10,000 bases) CNVs, yet there is increasing evidence that very small CNVs are clinically relevant [39]. As well, the currently available CNV calling algorithms tend to produce somewhat different call sets, and analyses are limited to consensus calls to insure validity. CNVs called from sequence data may be more accurate due to the denser set of probes and allow for calling smaller CNVs than traditional arrays are capable of [40]. Additionally, outside of CNVs, large investigations of other forms of rare variation have yet to be conducted for PTSD. These deficits are now at the point of feasibility to address, given whole-genome sequencing data is becoming more affordable and is becoming available from large biobank resources [41]. As well, the emergence of large sequenced reference panels and other technical developments means that rare variation can, to some degree, also be imputed [42] [43].

Fourth, in investigating the association of autoimmune disorders and PTSD, we cannot rule out bidirectional associations, due to a lack of statistical power for many autoimmune traits (i.e. too few genetic instruments). We expect more adequately powered GWAS of autoimmune traits will be released in the near future, and that

putative associations will become clearer as this happens. Additionally, we did not capture all autoimmune disorders, so many putative associations outright remain to be investigated using MR. Joint analyses of autoimmune disorders were not considered, but recent evidence suggests that there is a substantial degree of sharing of risk alleles between disorders [44]. To study autoimmune disorders in this joint way may more easily identify the shared and unshared causal factors between these disorders and PTSD.

Last, we investigated PTSD as a homogeneous disorder, yet there may be important genetic differences that relate to different forms of PTSD, such as current and lifetime PTSD [45], externalizing and internalizing subtypes [46], symptom clusters [10], and the longitudinal course of PTSD symptomology [47]. Investigating these different aspects may increase power [48]. Genetic data can be used to indicate or provide biological validation [49] for putative subtypes [50, 51]. Knowledge of subtypes may ultimately enhance treatment via a precision medicine approach [52]. Nevertheless, my results provide additional insight into PTSD genetics that may provide targets for future investigations [53].

Recent evidence suggests that a substantial amount of the total genetic liability of some complex traits can be explained by rare variation [54]. My CNV analysis demonstrated, to a small degree, that there is a rare variant contribution to PTSD. It has been hypothesized that there is a convergence of common and rare variation [55], in that they ultimately may affect the same genes. Thus, examining rare variation in tandem with common variation will add to a more complete picture of the genetic architecture of PTSD.

GxE have long been thought to be highly relevant to PTSD [56]. The causal mediation analysis method we have proposed allows for the investigation of GxE, where traditional GxE analysis would suffer estimate bias due to mediation effects not being modeled. As this method provides more or less a traditional estimates of GxE effects, then like traditional estimation of GxE it requires large sample sizes to detect interactions [57]. Genome-wide methods are being developed that allow for the direct estimation of heritability under GxE [58], which would at least allow for an overall quantification of the contribution of GxE to PTSD risk.

Ultimately, one primary goal of enhancing the biological understanding of PTSD is to enhance clinical treatment options. One means of achieving this may be from PRS [59]. However, PRS derived from recent GWAS [10] explain < 1% of the variation in PTSD symptoms. The theoretical upper limit of trait variance explained by a PRS derived from a GWAS of single nucleotide polymorphisms (SNPs) is the total SNP based heritability [60], which in this dissertation was estimated as only approximately 5%. Thus, in using traditional methods of calculating and evaluating PRS [61] using SNP array data, even individuals at the extreme end of estimated polygenic risk are not at substantially higher risk for developing PTSD relative to the average person. Therefore, the individual utility of a PRS (i.e. for precision medicine) might require both common and rare variation be integrated together, to provide a genetic model that explains a large enough proportion of variation in PTSD to allow for meaningful individual risk prediction. However, PRS is a current focus of intense research, and future utility to individuals may extend well beyond simple additive risk prediction. For example, PRS could be partitioned based on biological annotations, to identify individual-specific relevant risk pathways and

treatments [62, 63]. In addition, rare variation such as CNV may have a direct clinical relevance, as it may in the future guide the course of treatment in carriers of highly pathogenic alleles [64].

In conclusion, my findings contribute to the genetics of PTSD, identifying some novel risk loci, for the first time significantly implicating rare CNVs with PTSD risk, and further supporting the notion that PTSD has a causal relationship with autoimmune disorders. From these findings and their limitations, I provide several suggestions for future analyses: causal mediation analysis of PTSD and trauma to explore mediation and GxE, quantification of PTSD heritability from GxE with trauma exposure, genetically driven investigation into PTSD subtypes, cross-disorder comparisons with other psychiatric disorders (particularly major depression), examination of a wider spectrum of genetic variation, deeper investigation of the genetic components that are shared jointly between autoimmune disorders and with PTSD, and investigation into non-European ancestries. While at present my results have limited translational aspects, it is my hope that as more is understood about the genetic basis for PTSD and improved methods are developed to leverage these findings, that genetic findings can be made clinically actionable.

5.1 References

1. Pacella ML, Hruska B, Delahanty DL. The physical health consequences of PTSD and PTSD symptoms: A meta-analytic review. Journal of Anxiety Disorders. 2013;27(1):33-46. doi: https://doi.org/10.1016/j.janxdis.2012.08.004.

2. Hori H, Kim Y. Inflammation and post-traumatic stress disorder. Psychiatry and Clinical Neurosciences. 2019;73(4):143-53. doi: https://doi.org/10.1111/pcn.12820.

3. Brunello N, Davidson JRT, Deahl M, Kessler RC, Mendlewicz J, Racagni G, Shalev AY, Zohar J. Posttraumatic Stress Disorder: Diagnosis and Epidemiology, Comorbidity and Social Consequences, Biology and Treatment. Neuropsychobiology. 2001;43(3):150-62. doi: 10.1159/000054884.

4. Sareen J. Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. Can J Psychiatry. 2014;59(9):460-7. doi: 10.1177/070674371405900902. PubMed PMID: 25565692.

5. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, Hobfoll SE, Koenen KC, Neylan TC, Hyman SE. Post-traumatic stress disorder. Nature Reviews Disease Primers. 2015;1(1):15057. doi: 10.1038/nrdp.2015.57.

6. Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, Degenhardt L, de Girolamo G, Dinolova RV, Ferry F, Florescu S, Gureje O, Haro JM, Huang Y, Karam EG, Kawakami N, Lee S, Lepine J-P, Levinson D, Navarro-Mateu F, Pennell B-E, Piazza M, Posada-Villa J, Scott KM, Stein DJ, Ten Have M, Torres Y, Viana MC, Petukhova MV, Sampson NA, Zaslavsky AM, Koenen KC. Trauma and PTSD in the WHO World Mental Health Surveys. Eur J Psychotraumatol. 2017;8(sup5):1353383-. doi: 10.1080/20008198.2017.1353383. PubMed PMID: 29075426.

7. Kelmendi B, Adams TG, Yarnell S, Southwick S, Abdallah CG, Krystal JH. PTSD: from neurobiology to pharmacological treatments. Eur J Psychotraumatol. 2016;7(1):31858. doi: 10.3402/ejpt.v7.31858.

8. Neigh GN, Ali FF. Co-morbidity of PTSD and immune system dysfunction: opportunities for treatment. Curr Opin Pharmacol. 2016;29:104-10. Epub 2016/07/29. doi: 10.1016/j.coph.2016.07.011. PubMed PMID: 27479489.

9. Logue MW, Amstadter AB, Baker DG, Duncan L, Koenen KC, Liberzon I, Miller MW, Morey RA, Nievergelt CM, Ressler KJ, Smith AK, Smoller JW, Stein MB, Sumner JA, Uddin M. The Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup: Posttraumatic Stress Disorder Enters the Age of Large-Scale Genomic Collaboration. Neuropsychopharmacology. 2015;40(10):2287-97. Epub 2015/04/23. doi: 10.1038/npp.2015.118. PubMed PMID: 25904361.

10. Stein MB, Levey DF, Cheng Z, Wendt FR, Harrington K, Pathak GA, Cho K, Quaden R, Radhakrishnan K, Girgenti MJ, Ho YA, Posner D, Aslan M, Duman RS, Zhao H, Department of Veterans Affairs Cooperative Studies P, Program VAMV,

Polimanti R, Concato J, Gelernter J. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. Nat Genet. 2021;53(2):174-84. doi: 10.1038/s41588-020-00767-x. PubMed PMID: 33510476.

11. Muniz Carvalho C, Wendt FR, Maihofer AX, Stein DJ, Stein MB, Sumner JA, Hemmings SMJ, Nievergelt CM, Koenen KC, Gelernter J, Belangero SI, Polimanti R. Dissecting the genetic association of C-reactive protein with PTSD, traumatic events, and social support. Neuropsychopharmacology. 2020. doi: 10.1038/s41386-020-0655-6.

12. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. Epidemiology. 2014;25(5):749-61. doi: 10.1097/EDE.0000000000000121. PubMed PMID: 25000145.

13. Koenen KC, Amstadter AB, Nugent NR. Gene-environment interaction in posttraumatic stress disorder: an update. Journal of traumatic stress. 2009;22(5):416-26. Epub 2009/09/09. doi: 10.1002/jts.20435. PubMed PMID: 19743189.

14. Merikangas AK, Corvin AP, Gallagher L. Copy-number variants in neurodevelopmental disorders: promises and challenges. Trends in Genetics. 2009;25(12):536-44. doi: https://doi.org/10.1016/j.tig.2009.10.006.

15. Kirov G, Kendall K, Rees E, Escott-Price V, Hewitt J, Thomas R, O'Donovan M, Owen M, Walters J. The Uk Biobank: A Resource For Cnv Analysis. European Neuropsychopharmacology. 2017;27:S491. doi: https://doi.org/10.1016/j.euroneuro.2016.09.584.

16. Zarrei M, Burton CL, Engchuan W, Young EJ, Higginbotham EJ, MacDonald JR, Trost B, Chan AJS, Walker S, Lamoureux S, Heung T, Mojarad BA, Kellam B, Paton T, Faheem M, Miron K, Lu C, Wang T, Samler K, Wang X, Costain G, Hoang N, Pellecchia G, Wei J, Patel RV, Thiruvahindrapuram B, Roifman M, Merico D, Goodale T, Drmic I, Speevak M, Howe JL, Yuen RKC, Buchanan JA, Vorstman JAS, Marshall CR, Wintle RF, Rosenberg DR, Hanna GL, Woodbury-Smith M, Cytrynbaum C, Zwaigenbaum L, Elsabbagh M, Flanagan J, Fernandez BA, Carter MT, Szatmari P, Roberts W, Lerch J, Liu X, Nicolson R, Georgiades S, Weksberg R, Arnold PD, Bassett AS, Crosbie J, Schachar R, Stavropoulos DJ, Anagnostou E, Scherer SW. A large data resource of genomic copy number variation across neurodevelopmental disorders. npj Genomic Medicine. 2019;4(1):26. doi: 10.1038/s41525-019-0098-3.

17. Martin J, Tammimies K, Karlsson R, Lu Y, Larsson H, Lichtenstein P, Magnusson PKE. Copy number variation and neuropsychiatric problems in females and males in the general population. Am J Med Genet B Neuropsychiatr Genet. 2019;180(6):341-50. Epub 2018/10/11. doi: 10.1002/ajmg.b.32685. PubMed PMID: 30307693.

18. Kendall KM, Rees E, Bracher-Smith M, Legge S, Riglin L, Zammit S, O'Donovan MC, Owen MJ, Jones I, Kirov G, Walters JTR. Association of Rare Copy Number Variants With Risk of Depression. JAMA Psychiatry. 2019;76(8):818-25. doi: 10.1001/jamapsychiatry.2019.0566.

19. Marshall CR, Howrigan DP, Merico D, Thiruvahindrapuram B, Wu W, Greer DS, Antaki D, Shetty A, Holmans PA, Pinto D, Gujral M, Brandler WM, Malhotra D, Wang Z, Fajarado KVF, Maile MS, Ripke S, Agartz I, Albus M, Alexander M, Amin F, Atkins J, Bacanu SA, Belliveau RA, Bergen SE, Bertalan M, Bevilacqua E, Bigdeli TB, Black DW, Bruggeman R, Buccola NG, Buckner RL, Bulik-Sullivan B, Byerley W, Cahn W, Cai G, Cairns MJ, Campion D, Cantor RM, Carr VJ, Carrera N, Catts SV, Chambert KD, Cheng W, Cloninger CR, Cohen D, Cormican P, Craddock N, Crespo-Facorro B, Crowley JJ, Curtis D, Davidson M, Davis KL, Degenhardt F, Del Favero J, DeLisi LE, Dikeos D, Dinan T, Djurovic S, Donohoe G, Drapeau E, Duan J, Dudbridge F, Eichhammer P, Eriksson J, Escott-Price V, Essioux L, Fanous AH, Farh K-H, Farrell MS, Frank J, Franke L, Freedman R, Freimer NB, Friedman JI, Forstner AJ, Fromer M, Genovese G, Georgieva L, Gershon ES, Giegling I, Giusti-Rodríguez P, Godard S, Goldstein JI, Gratten J, de Haan L, Hamshere ML, Hansen M, Hansen T, Haroutunian V, Hartmann AM, Henskens FA, Herms S, Hirschhorn JN, Hoffmann P, Hofman A, Huang H, Ikeda M, Joa I, Kähler AK, Kahn RS, Kalaydjieva L, Karjalainen J, Kavanagh D, Keller MC, Kelly BJ, Kennedy JL, Kim Y, Knowles JA, Konte B, Laurent C, Lee P, Lee SH, Legge SE, Lerer B, Levy DL, Liang K-Y, Lieberman J, Lönnqvist J, Loughland CM, Magnusson PKE, Maher BS, Maier W, Mallet J, Mattheisen M, Mattingsdal M, McCarley RW, McDonald C, McIntosh AM, Meier S, Meijer CJ, Melle I, Mesholam-Gately RI, Metspalu A, Michie PT, Milani L, Milanova V, Mokrab Y, Morris DW, Müller-Myhsok B, Murphy KC, Murray RM, Myin-Germeys I, Nenadic I, Nertney DA, Nestadt G, Nicodemus KK, Nisenbaum L, Nordin A, O'Callaghan E, O'Dushlaine C, Oh S-Y, Olincy A, Olsen L, O'Neill FA, Van Os J, Pantelis C, Papadimitriou GN, Parkhomenko E, Pato MT, Paunio T, Perkins DO, Pers TH, Pietiläinen O, Pimm J, Pocklington AJ, Powell J, Price A, Pulver AE, Purcell SM, Quested D, Rasmussen HB, Reichenberg A, Reimers MA, Richards AL, Roffman JL, Roussos P, Ruderfer DM, Salomaa V, Sanders AR, Savitz A, Schall U, Schulze TG, Schwab SG, Scolnick EM, Scott RJ, Seidman LJ, Shi J, Silverman JM, Smoller JW, Söderman E, Spencer CCA, Stahl EA, Strengman E, Strohmaier J, Stroup TS, Suvisaari J, Svrakic DM, Szatkiewicz JP, Thirumalai S, Tooney PA, Veijola J, Visscher PM, Waddington J, Walsh D, Webb BT, Weiser M, Wildenauer DB, Williams NM, Williams S, Witt SH, Wolen AR, Wormley BK, Wray NR, Wu JQ, Zai CC, Adolfsson R, Andreassen OA, Blackwood DHR, Bramon E, Buxbaum JD, Cichon S, Collier DA, Corvin A, Daly MJ, Darvasi A, Domenici E, Esko T, Gejman PV, Gill M, Gurling H, Hultman CM, Iwata N, Jablensky AV, Jönsson EG, Kendler KS, Kirov G, Knight J, Levinson DF, Li QS, McCarroll SA, McQuillin A, Moran JL, Mowry BJ, Nöthen MM, Ophoff RA, Owen MJ, Palotie A, Pato CN, Petryshen TL, Posthuma D, Rietschel M, Riley BP, Rujescu D, Sklar P, St Clair D, Walters JTR, Werge T, Sullivan PF, O'Donovan MC, Scherer SW, Neale BM, Sebat J, Psychosis Endophenotypes International C, Cnv, Schizophrenia Working Groups of the Psychiatric Genomics C. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nature genetics. 2017;49(1):27-35. doi: 10.1038/ng.3725.

20. Van L, Boot E, Bassett AS. Update on the 22q11.2 deletion syndrome and its relevance to schizophrenia. Curr Opin Psychiatry. 2017;30(3).

21. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, Levey DF, Logue MW, Polimanti R,

Provost AC, Ratanatharathorn A, Stein MB, Torres K, Aiello AE, Almli LM, Amstadter AB, Andersen SB, Andreassen OA, Arbisi PA, Ashley-Koch AE, Austin SB, Avdibegovic E, Babić D, Bækvad-Hansen M, Baker DG, Beckham JC, Bierut LJ, Bisson JI, Boks MP, Bolger EA, Børglum AD, Bradley B, Brashear M, Breen G, Bryant RA, Bustamante AC, Bybjerg-Grauholm J, Calabrese JR, Caldas- de- Almeida JM, Dale AM, Daly MJ, Daskalakis NP, Deckert J, Delahanty DL, Dennis MF, Disner SG, Domschke K, Dzubur-Kulenovic A, Erbes CR, Evans A, Farrer LA, Feeny NC, Flory JD, Forbes D, Franz CE, Galea S, Garrett ME, Gelaye B, Geuze E, Gillespie C, Uka AG, Gordon SD, Guffanti G, Hammamieh R, Harnal S, Hauser MA, Heath AC, Hemmings SMJ, Hougaard DM, Jakovljevic M, Jett M, Johnson EO, Jones I, Jovanovic T, Qin X-J, Junglen AG, Karstoft K-I, Kaufman ML, Kessler RC, Khan A, Kimbrel NA, King AP, Koen N, Kranzler HR, Kremen WS, Lawford BR, Lebois LAM, Lewis CE, Linnstaedt SD, Lori A, Lugonja B, Luykx JJ, Lyons MJ, Maples-Keller J, Marmar C, Martin AR, Martin NG, Maurer D, Mavissakalian MR, McFarlane A, McGlinchey RE, McLaughlin KA, McLean SA, McLeay S, Mehta D, Milberg WP, Miller MW, Morey RA, Morris CP, Mors O, Mortensen PB, Neale BM, Nelson EC, Nordentoft M, Norman SB, O'Donnell M, Orcutt HK, Panizzon MS, Peters ES, Peterson AL, Peverill M, Pietrzak RH, Polusny MA, Rice JP, Ripke S, Risbrough VB, Roberts AL, Rothbaum AO, Rothbaum BO, Roy-Byrne P, Ruggiero K, Rung A, Rutten BPF, Saccone NL, Sanchez SE, Schijven D, Seedat S, Seligowski AV, Seng JS, Sheerin CM, Silove D, Smith AK, Smoller JW, Sponheim SR, Stein DJ, Stevens JS, Sumner JA, Teicher MH, Thompson WK, Trapido E, Uddin M, Ursano RJ, van den Heuvel LL, Van Hooff M, Vermetten E, Vinkers CH, Voisey J, Wang Y, Wang Z, Werge T, Williams MA, Williamson DE, Winternitz S, Wolf C, Wolf EJ, Wolff JD, Yehuda R, Young RM, Young KA, Zhao H, Zoellner LA, Liberzon I, Ressler KJ, Haas M, Koenen KC. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nature Communications. 2019;10(1):4558. doi: 10.1038/s41467-019-12576-w.

22. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Børglum AD, Breen G, Cichon S, Edenberg HJ, Faraone SV, Gelernter J, Mathews CA, Nievergelt CM, Smoller JW, O'Donovan MC, Psychiatric Genomics C. Psychiatric Genomics: An Update and an Agenda. Am J Psychiatry. 2018;175(1):15-27. Epub 10/03. doi: 10.1176/appi.ajp.2017.17030283. PubMed PMID: 28969442.

23. Wray NR, Wijmenga C, Sullivan PF, Yang J, Visscher PM. Common Disease Is More Complex Than Implied by the Core Gene Omnigenic Model. Cell. 2018;173(7):1573-80. Epub 2018/06/16. doi: 10.1016/j.cell.2018.05.051. PubMed PMID: 29906445.

24. Grotzinger AD, Mallard TT, Akingbuwa WA, Ip HF, Adams MJ, Lewis CM, McIntosh AM, Grove J, Dalsgaard S, Peter-Lesch K, Strom N, Meier SM, Mattheisen M, Børglum AD, Mors O, Breen G, Lee PH, Kendler KS, Smoller JW, Tucker-Drob EM, Nivard MG. Genetic Architecture of 11 Major Psychiatric Disorders at Biobehavioral, Functional Genomic, and Molecular Genetic Levels of Analysis. medRxiv. 2020:2020.09.22.20196089. doi: 10.1101/2020.09.22.20196089.

25. Klein M, Shanta O, Hong O, MacDonald J, Thiruvahindrapuram B, de Pins A, Charney A, Letovsky SS, Humphrey J, Douard E, Saci Z, Jacquemont S, Scherer S,

Sebat J. Analysis of Genomic Copy Number Variation Across Psychiatric Disorders. Biological Psychiatry. 2021;89(9, Supplement):S106-S7. doi: https://doi.org/10.1016/j.biopsych.2021.02.274.

26. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, Almqvist C, Fall K, Valdimarsdóttir UA. Association of Stress-Related Disorders With Subsequent Autoimmune Disease. JAMA. 2018;319(23):2388-400. doi: 10.1001/jama.2018.7028.

27. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann N Y Acad Sci. 2004;1032:141-53. Epub 2005/01/29. doi: 10.1196/annals.1314.011. PubMed PMID: 15677401.

28. Ridker PM. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. Circ Res. 2016;118(1):145-56. doi: 10.1161/CIRCRESAHA.115.306656. PubMed PMID: 26837745.

29. Peterson RE, Kuchenbaecker K, Walters RK, Chen C-Y, Popejoy AB, Periyasamy S, Lam M, Iyegbe C, Strawbridge RJ, Brick L, Carey CE, Martin AR, Meyers JL, Su J, Chen J, Edwards AC, Kalungi A, Koen N, Majara L, Schwarz E, Smoller JW, Stahl EA, Sullivan PF, Vassos E, Mowry B, Prieto ML, Cuellar-Barboza A, Bigdeli TB, Edenberg HJ, Huang H, Duncan LE. Genome-wide Association Studies in Ancestrally Diverse Populations: Opportunities, Methods, Pitfalls, and Recommendations. Cell. 2019;179(3):589-603. doi: https://doi.org/10.1016/j.cell.2019.08.051.

30. Roberts AL, Gilman SE, Breslau J, Breslau N, Koenen KC. Race/ethnic differences in exposure to traumatic events, development of post-traumatic stress disorder, and treatment-seeking for post-traumatic stress disorder in the United States. Psychological medicine. 2011;41(1):71-83. Epub 2010/03/29. doi: 10.1017/S0033291710000401. PubMed PMID: 20346193.

31. Loos RJF. 15 years of genome-wide association studies and no signs of slowing down. Nature Communications. 2020;11(1):5900. doi: 10.1038/s41467-020-19653-5.

32. Atkinson EG, Maihofer AX, Kanai M, Martin AR, Karczewski KJ, Santoro ML, Ulirsch JC, Kamatani Y, Okada Y, Finucane HK, Koenen KC, Nievergelt CM, Daly MJ, Neale BM. Tractor uses local ancestry to enable the inclusion of admixed individuals in GWAS and to boost power. Nature genetics. 2021. doi: 10.1038/s41588-020-00766-y.

33. Ruan Y, Lin Y-F, Feng Y-CA, Chen C-Y, Lam M, Guo Z, Stanley Global Asia I, He L, Sawa A, Martin AR, Qin S, Huang H, Ge T. Improving Polygenic Prediction in Ancestrally Diverse Populations. medRxiv. 2021:2020.12.27.20248738. doi: 10.1101/2020.12.27.20248738.

34. Lalande KM, Bonanno GA. Retrospective memory bias for the frequency of potentially traumatic events: A prospective study. Psychological Trauma: Theory, Research, Practice, and Policy. 2011;3(2):165-70. doi: 10.1037/a0020847.

35. Roemer L, Litz BT, Orsillo SM, Ehlich PJ, Friedman MJ. Increases in retrospective accounts of war-zone exposure over time: The role of PTSD symptom severity. Journal of traumatic stress. 1998;11(3):597-605. doi: https://doi.org/10.1023/A:1024469116047.

36. de Leeuw CA, Stringer S, Dekkers IA, Heskes T, Posthuma D. Conditional and interaction gene-set analysis reveals novel functional pathways for blood pressure. Nature Communications. 2018;9(1):3768. doi: 10.1038/s41467-018-06022-6.

37. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, Hemani G, Tansey K, Laurin C, Early G, Lifecourse Epidemiology Eczema C, Pourcain BS, Warrington NM, Finucane HK, Price AL, Bulik-Sullivan BK, Anttila V, Paternoster L, Gaunt TR, Evans DM, Neale BM. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2017;33(2):272-9. doi: 10.1093/bioinformatics/btw613.

38. Loh P-R, Kichaev G, Gazal S, Schoech AP, Price AL. Mixed-model association for biobank-scale datasets. Nature genetics. 2018;50(7):906-8. doi: 10.1038/s41588-018-0144-6. PubMed PMID: 29892013.

39. Pollex RL, Hegele RA. Copy Number Variation in the Human Genome and Its Implications for Cardiovascular Disease. Circulation. 2007;115(24):3130-8. doi: 10.1161/CIRCULATIONAHA.106.677591.

40. Gordeeva V, Sharova E, Babalyan K, Sultanov R, Govorun VM, Arapidi G. Benchmarking germline CNV calling tools from exome sequencing data. Scientific Reports. 2021;11(1):14416. doi: 10.1038/s41598-021-93878-2.

41. Backman JD, Li AH, Marcketta A, Sun D, Mbatchou J, Kessler MD, Benner C, Liu D, Locke AE, Balasubramanian S, Yadav A, Banerjee N, Gillies CE, Damask A, Liu S, Bai X, Hawes A, Maxwell E, Gurski L, Watanabe K, Kosmicki JA, Rajagopal V, Mighty J, Jones M, Mitnaul L, Stahl E, Coppola G, Jorgenson E, Habegger L, Salerno WJ, Shuldiner AR, Lotta LA, Overton JD, Cantor MN, Reid JG, Yancopoulos G, Kang HM, Marchini J, Baras A, Abecasis GR, Ferreira MAR, Regeneron Genetics C, DiscovEhr. Exome sequencing and analysis of 454,787 UK Biobank participants. Nature. 2021;599(7886):628-34. doi: 10.1038/s41586-021-04103-z.

42. Mitt M, Kals M, Pärn K, Gabriel SB, Lander ES, Palotie A, Ripatti S, Morris AP, Metspalu A, Esko T, Mägi R, Palta P. Improved imputation accuracy of rare and low-frequency variants using population-specific high-coverage WGS-based imputation reference panel. European Journal of Human Genetics. 2017;25(7):869-76. doi: 10.1038/ejhg.2017.51.

43. Saini S, Mitra I, Mousavi N, Fotsing SF, Gymrek M. A reference haplotype panel for genome-wide imputation of short tandem repeats. Nature Communications. 2018;9(1):4397. doi: 10.1038/s41467-018-06694-0.

44. Lincoln MR, Connally N, Axisa P-P, Gasperi C, Mitrovic M, Heel Dv, Wijmenga C, Withoff S, Jonkers IH, Padyukov L, International Multiple Sclerosis Genetics C, Rich SS, Graham RR, Gaffney PM, Langefeld CD, Hafler DA, Chun S, Sunayev SR, Cotsapas C. Joint analysis reveals shared autoimmune disease associations and identifies common mechanisms. medRxiv. 2021:2021.05.13.21257044. doi: 10.1101/2021.05.13.21257044.

45. Sarapas C, Cai G, Bierer LM, Golier JA, Galea S, Ising M, Rein T, Schmeidler J, Müller-Myhsok B, Uhr M, Holsboer F, Buxbaum JD, Yehuda R. Genetic markers for PTSD risk and resilience among survivors of the World Trade Center attacks. Disease Markers. 2011;30:101-10. doi: 10.3233/DMA-2011-0764.

46. Miller MW, Greif JL, Smith AA. Multidimensional Personality Questionnaire profiles of veterans with traumatic combat exposure: Externalizing and internalizing subtypes. Psychological Assessment. 2003;15(2):205-15. doi: 10.1037/1040-3590.15.2.205.

47. Armenta RF, Walter KH, Geronimo-Hara TR, Porter B, Stander VA, LeardMann CA, Millennium Cohort Study T. Longitudinal trajectories of comorbid PTSD and depression symptoms among U.S. service members and veterans. BMC psychiatry. 2019;19(1):396-. doi: 10.1186/s12888-019-2375-1. PubMed PMID: 31836015.

48. Cai N, Choi KW, Fried EI. Reviewing the genetics of heterogeneity in depression: operationalizations, manifestations and etiologies. Human Molecular Genetics. 2020;29(R1):R10-R8. doi: 10.1093/hmg/ddaa115.

49. Dahl A, Cai N, Ko A, Laakso M, Pajukanta P, Flint J, Zaitlen N. Reverse GWAS: Using genetics to identify and model phenotypic subtypes. PLOS Genetics. 2019;15(4):e1008009. doi: 10.1371/journal.pgen.1008009.

50. Hansen M, Ross J, Armour C. Evidence of the dissociative PTSD subtype: A systematic literature review of latent class and profile analytic studies of PTSD. J Affect Disord. 2017;213:59-69. Epub 2017/02/14. doi: 10.1016/j.jad.2017.02.004. PubMed PMID: 28192736.

51. Dalenberg CJ, Glaser D, Alhassoon OM. STATISTICAL SUPPORT FOR SUBTYPES IN POSTTRAUMATIC STRESS DISORDER: THE HOW AND WHY OF SUBTYPE ANALYSIS. Depression and Anxiety. 2012;29(8):671-8. doi: https://doi.org/10.1002/da.21926.

52. Siegel C, Laska E. Identifying subtypes of PTSD to promote precision medicine. Neuropsychopharmacology. 2022;47(1):379-80. doi: 10.1038/s41386-021-01102-6.

53. Smeland OB, Frei O, Shadrin A, O'Connell K, Fan CC, Bahrami S, Holland D, Djurovic S, Thompson WK, Dale AM, Andreassen OA. Discovery of shared genomic loci using the conditional false discovery rate approach. Hum Genet. 2020;139(1):85-94. Epub 2019/09/15. doi: 10.1007/s00439-019-02060-2. PubMed PMID: 31520123.

54. Wainschtein P, Jain D, Zheng Z, Group TAW, Consortium NT-OfPM, Cupples LA, Shadyab AH, McKnight B, Shoemaker BM, Mitchell BD, Psaty BM, Kooperberg C, Liu C-T, Albert CM, Roden D, Chasman DI, Darbar D, Lloyd-Jones DM, Arnett DK, Regan EA, Boerwinkle E, Rotter JI, O'Connell JR, Yanek LR, de Andrade M, Allison MA, McDonald M-LN, Chung MK, Fornage M, Chami N, Smith NL, Ellinor PT, Vasan RS, Mathias RA, Loos RJF, Rich SS, Lubitz SA, Heckbert SR, Redline S, Guo X, Chen Y-DI, Laurie CA, Hernandez RD, McGarvey ST, Goddard ME, Laurie CC, North KE, Lange LA, Weir BS, Yengo L, Yang J, Visscher PM. Recovery of trait heritability from whole genome sequence data. bioRxiv. 2021:588020. doi: 10.1101/588020.

55. Momozawa Y, Mizukami K. Unique roles of rare variants in the genetics of complex diseases in humans. J Hum Genet. 2021;66(1):11-23. Epub 2020/09/20. doi: 10.1038/s10038-020-00845-2. PubMed PMID: 32948841 PMCID: PMCPMC7728599.

56. Duncan LE, Cooper BN, Shen H. Robust Findings From 25 Years of PTSD Genetics Research. Curr Psychiatry Rep. 2018;20(12):115-. doi: 10.1007/s11920-018-0980-1. PubMed PMID: 30350223.

57. Werme J, van der Sluis S, Posthuma D, de Leeuw CA. Genome-wide gene-environment interactions in neuroticism: an exploratory study across 25 environments. Translational Psychiatry. 2021;11(1):180. doi: 10.1038/s41398-021-01288-9.

58. Dahl A, Nguyen K, Cai N, Gandal MJ, Flint J, Zaitlen N. A Robust Method Uncovers Significant Context-Specific Heritability in Diverse Complex Traits. The American Journal of Human Genetics. 2020;106(1):71-91. doi: https://doi.org/10.1016/j.ajhg.2019.11.015.

59. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nature Reviews Genetics. 2018;19(9):581-90. doi: 10.1038/s41576-018-0018-x.

60. Wray NR, Kemper KE, Hayes BJ, Goddard ME, Visscher PM. Complex Trait Prediction from Genome Data: Contrasting EBV in Livestock to PRS in Humans: Genomic Prediction. Genetics. 2019;211(4):1131-41. Epub 2019/04/11. doi: 10.1534/genetics.119.301859. PubMed PMID: 30967442 PMCID: PMCPMC6456317.

61. Pain O, Gillett AC, Austin JC, Folkersen L, Lewis CM. A tool for translating polygenic scores onto the absolute scale using summary statistics. European Journal of Human Genetics. 2022. doi: 10.1038/s41431-021-01028-z.

62. Shing Wan Choi JG-G. The power of pathway-based polygenic risk scores. Research Square. 2021. doi: https://doi.org/10.21203/rs.3.rs-643696/v1.

63. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. Genome Medicine. 2020;12(1):44. doi: 10.1186/s13073-020-00742-5.

64. Sullivan PF, Owen MJ. Increasing the Clinical Psychiatric Knowledge Base About Pathogenic Copy Number Variation. American Journal of Psychiatry. 2020;177(3):204-9. doi: 10.1176/appi.ajp.2019.19040335.