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Genome-wide association study identifies novel locus for neuroticism and shows polygenic association with Major Depressive Disorder

A full list of authors and affiliations appears at the end of the article.

Abstract

Importance—Neuroticism is a personality trait that is briefly defined by emotional instability. It is a robust genetic risk factor for Major Depressive Disorder (MDD) and other psychiatric disorders. Hence, neuroticism is an important phenotype for psychiatric genetics. The Genetics of Personality Consortium (GPC) has created a resource for genome-wide association analyses of personality traits in over 63,000 participants (including MDD cases).

Objective—To identify genetic variants associated with neuroticism by performing a meta-analysis of genome-wide association (GWA) results based on 1000Genomes imputation, to evaluate if common genetic variants as assessed by Single Nucleotide Polymorphisms (SNPs) explain variation in neuroticism by estimating SNP-based heritability, and to examine whether SNPs that predict neuroticism also predict MDD.

Setting—30 cohorts with genome-wide genotype, personality and MDD data from the GPC.

Participants—The study included 63,661 participants from 29 discovery cohorts and 9,786 participants from a replication cohort. Participants came from Europe, the United States or Australia.

Main outcome measure(s)—Neuroticism scores harmonized across all cohorts by Item Response Theory (IRT) analysis, and clinically assessed MDD case-control status.

Results—A genome-wide significant SNP was found in the *MAGI1* gene (rs35855737; $P=9.26 \times 10^{-9}$ in the discovery meta-analysis, and $P=2.38 \times 10^{-8}$ in the meta-analysis of all 30 cohorts).

†To whom correspondence should be addressed: Marleen H.M. de Moor, Department of Clinical Child and Family Studies, Faculty of Psychology and Education, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT, Amsterdam, The Netherlands. Telephone: +31 20 598 8618, m.h.m.de.moor@vu.nl.

#Shared first authorship

Authors' contributions

Writing group: MHMdeM, SMvdB, KJHV, RFK, ML, AAV, LKM, JD, TE, DIB

Analytic group: MHMdeM, SMvdB, KJHV, ML, AAV, LKM, JDe, TE, NA, SG, NKH, ABH, JH, BK, JL, ML, MM, TT, ATeu, AV, JW, IOF, NT, DME, TL, IS, EP, GRA, JM, JDi, RK, YQ

Study design and project management: LF, LPR, JGE, AAP, GWM, MJW, PAFM, DP, AMin, AP, DR, MC, IG, CH, IR, AMet, JK, IJD, KR, JFW, LKJ, JMH, HJG, BWJHP, CMvD, DME, NLP, PTC, ATer, MMG, NGM, DIB, RFK, AAV, GDS, TL, OTR, PKEM, KH, JMS, DS, GRA, HC, RJR

Sample and phenotype data collection: BWJHP, AMet, AR, JA, IG, AMH, PAFM, ACH, NGM, MJW, KA, MN, LJB, JGE, LF, PTC, ATer, GDS, MGK, HdW, AAP, AKH, WSS, RS, DR, Amin, MJ, LPR, LKJ, OTR, PKEM, EV, KH, AM, FB, OP, LZ

Data preparation: MHMdeM, SMvdB, JW, KGO, JJH, SEM, NKH, YM, TE, AR, GD, ML, RG, AA, JD, EW, BK, GD, BEE, COS, GH, KJHV, SDG, DEA, TBB, JPK, NJT, BP, CM, MJ, AL, ARS, ATer, DCL, HT

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Common genetic variants explain 15% of the variance in neuroticism. Polygenic scores based on the meta-analysis of neuroticism in 27 of the discovery cohorts significantly predicted neuroticism in 2 independent cohorts. Importantly, polygenic scores also predicted MDD in these cohorts.

Conclusions and relevance—This study identifies a novel locus for neuroticism. The variant is located in a known gene that has been associated with bipolar disorder and schizophrenia in previous studies. In addition, the study shows that neuroticism is influenced by many genetic variants of small effect that are either common or tagged by common variants. These genetic variants also influence MDD. Future studies should confirm the role of the *MAGI1* locus for neuroticism, and further investigate the association of *MAGI1* and the polygenic association to a range of other psychiatric disorders that are phenotypically correlated with neuroticism.

Dimensions of personality have been linked with the liability to suffer from psychiatric illness.[1] Perhaps the strongest link between personality and psychiatric illness is the association of neuroticism with Major Depressive Disorder (MDD)[2–5]. Neuroticism is also associated with other psychiatric disorders that entail emotional dysregulation, including personality, substance use and anxiety disorders.[2,6–8] Furthermore, neuroticism is associated with neurological diseases such as migraine and Alzheimer's disease.[9,10] Hence, neuroticism is a psychological risk factor of profound public health significance.[11]

Neuroticism refers to the tendency to experience diverse and relatively more intense negative emotions. Neuroticism and similar traits such as harm avoidance and negative emotionality share an affective underpinning[12] and are found in all main theories of personality.[13–24] Twin studies of neuroticism, harm avoidance or negative emotionality generally find that between 40 and 60% of the trait variance is explained by genomic variation,[3,25–28] without large age or sex by genotype effects, modest assortative mating and large genetic and phenotypic stability across the lifespan.[28–31] These findings and the fact that neuroticism is strongly related to MDD[7,32–35] make neuroticism an important phenotype for psychiatric genetic studies.

Genome-Wide Association (GWA) studies require large sample sizes to have sufficient statistical power, which is often achieved by aggregating results in multiple cohorts in a meta-analysis. This however requires a measurement scale that is comparable across cohorts. We recently showed for neuroticism and extraversion how different personality instruments could be linked through Item Response Theory (IRT) analysis in order to assess the same underlying constructs.[36] Personality item data were harmonized in >160,000 participants from the Genetics of Personality Consortium (GPC). A meta-analysis of data from >29,000 twin pairs from six of the participating cohorts showed that the heritability of the harmonized neuroticism scores was 48%.[36] This estimate was based on twin correlations that ranged between 0.39 and 0.53 for monozygotic twin pairs, and between 0.11 and 0.26 for dizygotic twin pairs across cohorts and genders. The opposite-sex twin correlations were not significantly lower than the same-sex dizygotic twin correlations, illustrating that the same genetic factors influence neuroticism in men and women.

Gene finding studies for MDD and neuroticism-like personality traits have had limited success to date. There have been two meta-analytic GWA studies for personality traits, including neuroticism and harm-avoidance. The sample sizes were small by current

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standards (N=11,590,[37] and 17,375[38]) and single nucleotide polymorphisms (SNPs) were imputed using HAPMAP as a reference. The largest GWA[39–41] studies for MDD are those from the Psychiatric Genomics Consortium (PGC), with 9,240 MDD cases and 9,519 controls in the discovery phase of the study, and 6,783 MDD cases and 50,695 controls in the replication phase, and imputation based on HAPMAP. These studies did not detect genome-wide significant SNPs.[42]

To assess if gene-finding efforts are likely to have success, techniques have been developed that test whether common variants that are tagged by genome-wide SNP arrays contribute to variation in the phenotype.[43] Two of such studies for neuroticism found effects of common SNPs, explaining about 6% of the phenotypic variance, and another study for MDD found that common SNPs explain 28–32% of the phenotypic variance.[44–46] In young children, genome-wide SNPs explained 13% to 43% of the variance in internalizing problems.[47]

Here we report results of the largest GWA study for neuroticism so far, conducted in 63,661 participants from 29 cohorts. Imputation was performed against the 1000Genomes (1000G) reference panel. The aims of the study were: (1) to identify genetic variants for neuroticism by performing a meta-analysis of GWA results, (2) to estimate SNP-based heritability in the two largest cohorts to establish that the sets of SNPs contain information to detect genetic variants, and (3) to test whether these variants predict MDD status in a large cohort of clinically assessed MDD cases and screened controls.

Materials and methods

Cohorts

The meta-analysis included 29 discovery cohorts, with 21 cohorts from Europe, 6 from the Unites States and 2 from Australia. All participants were of European descent. The total sample size was 63,661 for the GWA meta-analysis. The Generation Scotland cohort (N=9,786) was included for replication of GWA top results. For detailed information on each cohort see the eMaterials and methods.

Phenotyping

After harmonizing all item data on neuroticism from multiple instruments, comparable neuroticism scores were obtained for all cohorts.[36] These scores were estimated for all participants after conducting IRT analysis on the available item data for neuroticism from the NEO Personality Inventory, Eysenck Personality Questionnaire, and the International Personality Item Pool inventory, all item data for harm avoidance from the Cloninger's Tridimensional Personality Questionnaire, and all item data for negative emotionality from the Multidimensional Personality Questionnaire (see eMaterials and methods). For the Generation Scotland cohort phenotypes were summed scores on the neuroticism scale of the EPQ Revised Short Form.

Genotyping and imputation

An overview of SNP genotyping, quality control (QC), and imputation is given in eTable 2. QC of genotype data was performed in each study independently, using comparable but

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study specific criteria. Basic QC steps included checks for European ancestry, sex inconsistencies, Mendelian errors, and high genome-wide homozygosity. Checks for relatedness were carried out in those samples that aimed to include unrelated individuals only. Genotype data were further checked based on Hardy–Weinberg Equilibrium (HWE), minor allele frequencies (MAF), SNP and sample call rates. Genotype data were imputed using the 1000G phase 1 version 3 (build 37, hg19) reference panel with standard software packages such as IMPUTE, MACH or Minimac (see eTable 2).

Statistical analyses

GWA analysis in each cohort—GWA analyses were conducted in each cohort using linear regression (additive model, with sex and age as covariates) with the aim to identify single common genetic variants that influence neuroticism in both men and women of different ages. Depending on the characteristics of the cohort, additional covariates such as PCs were added. Different software packages were used to run the association analysis (see eTable 2). Uncertainty of the imputed genotypes was taken into account. In those cohorts that included related individuals, the dependency among participants was accounted for. Locations of SNPs are reported on build 37 (hg19).

Meta-analysis of GWA results across cohorts—A meta-analysis of the GWA results of the discovery cohorts was conducted using the weighted inverse variance method in METAL (http://www.sph.umich.edu/csg/abecasis/metal/index.html). This is a fixed effects model in which effect sizes (beta's) are weighted by the inverse of their variance and then summed over cohorts. This model is appropriate if phenotypes are on a similar scale, which was the case for the harmonized neuroticism scores. Poorly imputed SNPs (r^2<0.30 or proper_info<0.40) and SNPs with low MAF (MAF < √(5/N, which corresponds to less than 5 estimated individuals in the least frequent genotype group, under the assumption of HWE) were excluded, resulting in a total number of 1.1M to 6.6M SNPs across cohorts. The number of unique SNPs available for meta-analysis was 7,480,565. For 530,951 SNPs association results were available in one cohort only and were discarded, leading to a final 6,949,614 SNPs for which results are reported. Genomic control inflation factors (lambda) and Manhattan and quantile–quantile plots per cohort are provided in eTable 3 and eFigures 1 and 2. SNPs with a *P*-value of 5×10^{-8} or smaller were considered genome-wide significant. In the Generation Scotland cohort, all SNPs with a *P*-value smaller than 1×10^{-5} were tested for replication. For these SNPs, a meta-analysis of all 30 cohorts was conducted. Because in the Generation Scotland cohort, sum scores were available for neuroticism, this meta-analysis was based on combining *P*-values, taking into account the direction of effect and weighting by sample size, rather than combining effect sizes.

Meta-analysis results at the SNP level were used as the input to compute *P*-values at the gene level. These analyses were performed with VEGAS2.[48,49] A gene with a *P*-value of 1×10^{-6} or lower is considered genome-wide significant in gene-wide analyses.

Variance explained by common SNPs—In two large cohorts included in the meta-analysis, the Netherlands Twin Register (NTR, N = 3,599 unrelated individuals) cohort and the QIMR Berghofer Medical Research Institute (QIMR, N= 3,369) adult cohort, Genomic-

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relatedness-matrix Restricted Maximum Likelihood (GREML) analysis in the GCTA software was applied to estimate the proportion of variance in neuroticism that can be explained by common SNPs.[43,50] GCTA analysis was based on best guess genotypes obtained in PLINK using a threshold of a maximum genotype probability >0.70, and additionally filtering on r-squared >0.80. Next, in estimating the GRM matrix in the GCTA software, SNPs with MAF <0.05 were excluded. The additive genetic relationship matrix (GRM) for all individuals in the data sets estimated based on SNPs was used to estimate the proportion of phenotypic variance due to additive genetic variance. Sex, age and population-specific principal components (PCs) were included as covariates.

Polygenic risk score analysis—Polygenic risk scores (PGS) analyses were conducted to test the predictive power of the meta-analysis results for neuroticism itself and for MDD. PGS were computed in NTR and Netherlands Study of Depression and Anxiety (NESDA[51]) and were based on the meta-analysis results excluding the NTR and NESDA cohorts, further referred to as the discovery set. PGS were calculated for all individuals of the NTR and NESDA target set by taking a set of most significant SNPs from the analysis in the discovery set and by multiplying the individual's genotypic score (0, 1 or 2 for genotyped SNPs, or any value in between 0 and 2 for imputed SNPs) by the effect size of a particular SNP (unstandardized regression coefficient based on the meta-analysis), and summing this over SNPs. PGS were calculated for six different *P*-value thresholds ($P<1 \times 10^{-5}$, $P<1 \times 10^{-4}$, $P<1 \times 10^{-3}$, $P<0.01$, $P<0.05$ and $P<0.5$). Next, linear/logistic regression was conducted to predict neuroticism from the PGS in 8,648 NTR participants and MDD status in 1,859 unrelated MDD cases and 2,391 unrelated controls from NTR and NESDA. MDD case-control status was defined as a lifetime DSM-IV diagnosis using the Composite International Diagnostic Interview (CIDI). Age, sex and nine PCs were included as covariates. See for more details eMaterials and methods.

Results

Meta-analysis of GWA results for neuroticism

Meta-analysis of GWA results across the 29 cohorts revealed one genome-wide significant SNP (rs35855737; $P=9.26 \times 10^{-9}$). The SNP is located in an intron of the *MAGI1* gene (Figure 1). The pooled regression effect was −0.04 with the minor allele C coded as the effect allele (Figure 2). Imputation quality was very high (r-squared or proper_info>0.94) in all cohorts, except in ERF ($r^2=0.63$). MAF of the SNP ranged from 0.13 to 0.22 across cohorts with imputation quality >0.94 and showed a mean of 0.18 (SD=0.02), which corresponds to the MAF for this SNP in the 1000G reference set. MAF in the ERF cohort was 0.07. Eleven other SNPs in the *MAGI1* gene showed suggestive genome-wide significance ($P<1 \times 10^{-5}$); all SNPs were intronic; one SNP was in very high LD with rs35855737 (rs1404544; $r^2>0.80$; $P=8{,}59 \times 10^{-6}$) and three SNPs were in high LD with rs35855737 (rs1524970, rs1880522 and rs6799284; $r^2>0.60$, $3.64 \times 10^{-6} < P < 8.54 \times 10^{-7}$). The Manhattan and quantile-quantile plots are given in Figures 3 and 4. A list with all 127

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suggestively genome-wide significant SNPs is provided in eTable 4[1]. The lowest p-value for the gene-based tests did not reach genome-wide significance ($P<1 \times 10^{-6}$).

Results of the follow-up analysis for all SNPs with P-value $< 1 \times 10^{-5}$ in the Generation Scotland cohort are displayed in eTable 4. Rs35855737 is not significantly associated with neuroticism in the Generation Scotland cohort, but the direction of the effect is the same (beta=−0.02 for effect allele C; P-value=0.32). A meta-analysis of the results from all 30 cohorts shows that rs35855737 remains genome-wide significant (beta=−0.04; P-value=2.38 $\times 10^{-8}$).

Variance in neuroticism explained by common SNPs

In the NTR cohort, 14.7% of the variance in neuroticism was explained by all SNPs (P=0.02; 95% Confidence Interval (CI) 0.002–0.29). In the QIMR cohort, 15.7% of the variance was explained by SNPs (P=0.18; 95% CI 0–0.47).

Polygenic risk score analysis for Neuroticism and MDD

The results of the polygenic risk score analyses are presented in Figure 5. In the NTR, polygenic risk scores are significantly ($P<0.05$) associated with neuroticism when polygenic scores are based on SNP sets with P-value thresholds of 1×10^{-3} and lower. The most significant result was found for the SNP set with a P-value threshold of 0.05, with an explained variance of 0.66% and a P-value of 1.09×10^{-12}. In the combined NTR/NESDA cohort, polygenic risk scores are significantly ($P<0.05$) associated with MDD for SNP sets with P-value thresholds of 0.01 and 0.05, with higher neuroticism predicting larger risk for MDD. The most significant result was found for the SNP set with a P-value threshold of 0.05, with an explained variance of 1.05% and a P-value of 4.02×10^{-9}.

Discussion

This study evaluated in 63,661 individuals if common genetic variants explain variation in neuroticism by performing a meta-analysis of GWA results for neuroticism and by estimating SNP-based heritability. In addition, it was examined whether genetic variants that predict neuroticism also predict MDD.

The meta-analysis of GWA results for neuroticism showed a genome-wide significant SNP in an intron of the *MAGI1* gene. The *MAGI1* gene is expressed in neuronal tissue, in particular the hippocampus, and is found at the synaptic plasma membrane.[52] In addition, it has been shown that MAGI1 acts as a scaffolding protein in the neurite growth factor (NGF) receptor-mediated signaling pathway.[53] Interestingly, the *MAGI1* gene has previously been implicated in bipolar disorder, schizophrenia and episodicity in MDD[54–56], disorders that in part share their genetic etiology.[57] A genome-wide linkage scan for early onset bipolar disorder type 1 revealed genome-wide significant linkage in the 3p14 region where *MAGI1* is located.[56] A copy number variation study found evidence for deletions in *MAGI1* to be associated with bipolar disorder and duplications to be associated with schizophrenia.[54]

[1]Full results of the meta-analysis can be downloaded from http://www.tweelingenregister.org/GPC.

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Further, a genome-wide association study found suggestive association ($P=5.1 \times 10^{-7}$) of a SNP in *MAGI1* with episodicity in MDD, a feature of MDD that shows increased risk to shifting to bipolar disorder.[55]

It was further estimated that SNP-based genetic similarity across individuals accounted for approximately 15% of the variance in neuroticism. This estimate is larger than in earlier reports using the same technique (about 6% explained)[44,46]. Heritability estimates from twin studies are usually larger and range between 40 and 55%.[36]

Polygenic risk scores based on the GWA meta-analysis significantly predicted MDD status in a large independent target set consisting of MDD cases and screened controls. The polygenic scores for neuroticism reassuringly also predicted neuroticism in MDD controls of this same independent set. MDD and neuroticism were explained about equally well by neuroticism polygenic scores (up to 1.05% explained variance). These findings are consistent with previous reports that studied the prediction of MDD and bipolar disorder based on polygenic scores derived from Big Five neuroticism GWA results.[58,59]

This study demonstrates that increasing the number of subjects and SNPs in a meta-analysis is successful in identifying a novel locus for neuroticism. Yet, the effect size of the identified SNP is very small (regression coefficient of −0.04 for the harmonized score with a variance of around 1). Together with our findings of a SNP-based heritability of around 15% and an increase in explained variance in the polygenic risk score analysis when polygenic scores are based on larger sets of SNPs, this suggests that neuroticism is highly polygenic.

Our results further indicate that the heritability of neuroticism likely consists not only of common SNPs with small additive effects. Common SNPs with non-additive effects, rare SNPs and indels may also influence neuroticism, possibly in interaction (epistasis). As a consequence, to further our understanding of the genetic and molecular basis of neuroticism (and associated psychiatric disorders) different routes need to be taken in future studies. One route would be to increase the number of subjects and SNPs to further identify more common variants of additive effect, which has shown to be successful for schizophrenia.[60] Also, the study of variants other than common variants of additive effect could be pursued. Alternative routes could include pathway analyses and genetic studies that are informed by results from the animal literature on basic emotions such as fear, sadness and anger.[61–64]

The current study more than tripled the sample size compared to the previous published meta-analysis on personality[38], providing a substantial increase in power to detect variants. The power to detect variants that explain 0.23% of the variance (corresponding to the effect size for the most significant SNP in the previous meta-analysis[38]) increased from 84% to 100%. In addition, with a sample size of 63,661 individuals there is 80% power to detect variants that explain at least 0.063% of the variance in neuroticism, compared to 1.6% power given the 17,375 subjects that were included in the previous meta-analysis.[38] The large increase in sample size was possible because an IRT approach enabled harmonization of personality data obtained from different personality questionnaires, which may serve as an example for gene-finding studies for other psychological, cognitive and psychiatric traits

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where harmonization is required to increase sample size (e.g. symptoms of depression or ADHD measured by different questionnaires).

The results for neuroticism were predictive for MDD. Future analyses may focus on whether the *MAGI1* locus and polygenic variance for neuroticism is also associated with psychiatric disorders that are phenotypically associated with neuroticism, such as Borderline personality disorder, bipolar disorder, schizophrenia, ADHD and substance use disorders. This could be achieved by combining data from with GPC with those available within the PGC[65] and the Social Science Genetic Association Consortium[66]. Novel methodologies will be needed to test whether neuroticism represents a causal risk factor for MDD and other disorders, whether reverse causality is also present, or whether the genetic association between neuroticism and psychiatric disorders reflects an underlying common liability.[57,67–69] It is expected that such studies will increase our understanding of the role that emotional instability plays in the occurrence and course of psychiatric disorders and other important health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Marleen H.M. de Moor, PhD[1,2,3,#,†], Stéphanie M. van den Berg, PhD[4,#], Karin J.H. Verweij, PhD[5,6], Robert F. Krueger, PhD[7], Michelle Luciano, PhD[8,9], Alejandro Arias Vasquez, PhD[10,11,12,13], Lindsay K. Matteson, PhD[7], Jaime Derringer, PhD[14], Tõnu Esko, PhD[15], Najaf Amin, PhD[16], Scott D. Gordon, PhD[5], Narelle K. Hansell, PhD[5], Amy B. Hart, PhD[17], Ilkka Seppälä, PhD[18], Jennifer E. Huffman, PhD[19], Bettina Konte, PhD[20], Jari Lahti, PhD[21,22], Minyoung Lee, PhD[23], Mike Miller, PhD[7], Teresa Nutile, PhD[24], Toshiko Tanaka, PhD[25], Alexander Teumer, PhD[26], Alexander Viktorin, PhD[27], Juho Wedenoja, MD, PhD[28], Goncalo R. Abecasis, PhD[29], Daniel E. Adkins, PhD[30], Arpana Agrawal, PhD[31], Jüri Allik, PhD[32,33], Katja Appel, PhD[34], Timothy B. Bigdeli, PhD[23], Fabio Busonero, PhD[35], Harry Campbell, PhD[36], Paul T. Costa, PhD[37], George Davey Smith, PhD[38], Gail Davies, PhD[8,9], Harriet de Wit, PhD[39], Jun Ding, PhD[68], Barbara E. Engelhardt, PhD[40], Johan G. Eriksson, PhD[22,41,42,43,44], Iryna O. Fedko, MSci[1], Luigi Ferrucci, PhD[25], Barbara Franke, PhD[10,11,12], Ina Giegling, PhD[20], Richard Grucza, PhD[31], Annette M. Hartmann, PhD[20], Andrew C. Heath, PhD[31], Kati Heinonen, PhD[21], Anjali K. Henders, PhD[5], Georg Homuth, PhD[45], Jouke-Jan Hottenga, PhD[1], Joost Janzing, PhD[11], Markus Jokela, PhD[21], Robert Karlsson, PhD[27], John P. Kemp, PhD[38,46], Matthew G. Kirkpatrick, PhD[39], Antti Latvala, PhD[41,28], Terho Lehtimäki, PhD[18], David C. Liewald, PhD[8,9], Pamela A.F. Madden, PhD[31], Chiara Magri, PhD[47], Patrik K.E. Magnusson, PhD[27], Jonathan Marten, MSci[19], Andrea Maschio, PhD[35], Sarah E. Medland, PhD[5], Evelin Mihailov, PhD[15,48], Yuri Milaneschi, PhD[49], Grant W. Montgomery, PhD[5], Matthias Nauck, PhD[50], Klaasjan G. Ouwens, MSci[1], Aarno Palotie, PhD[51,52], Erik Pettersson, PhD[27], Ozren Polasek, PhD[53], Yong Qian, Msc[68], Laura Pulkki-Råback, PhD[21], Olli T. Raitakari, PhD[54,55], Anu Realo, PhD[32],

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Richard J. Rose, PhD[56], Daniela Ruggiero, PhD[24], Carsten O. Schmidt, PhD[27], Wendy S. Slutske, PhD[57], Rossella Sorice, PhD[24], John M. Starr, PhD[9,58,59], Beate St Pourcain, PhD[38,60,61], Angelina R. Sutin, PhD[25,62], Nicholas J. Timpson, PhD[38], Holly Trochet, PhD[19], Sita Vermeulen, PhD[12,63], Eero Vuoksimaa, PhD[28], Elisabeth Widen, PhD[52], Jasper Wouda, MSci[1,4], Margaret J. Wright, PhD[5], Lina Zgaga, PhD[36,64], Generation Scotland, PhD[65], David Porteous, PhD[66], Alessandra Minelli, PhD[47], Abraham A. Palmer, PhD[17,39], Dan Rujescu, PhD[20], Marina Ciullo, PhD[24], Caroline Hayward, PhD[19], Igor Rudan, PhD[36], Andres Metspalu, PhD[15,33], Jaakko Kaprio, PhD[41,28,52], Ian J. Deary, PhD[8,9], Katri Räikkönen, PhD[21], James F. Wilson, PhD[36], Liisa Keltikangas-Järvinen, PhD[21], Laura J. Bierut, PhD[31], John M. Hettema, PhD[23], Hans J. Grabe, PhD[34,67], Cornelia M. van Duijn, PhD[16], David M. Evans, PhD[38,46], David Schlessinger, PhD[68], Nancy L. Pedersen, PhD[24], Antonio Terracciano, PhD[22,62], Matt McGue, PhD[7,69], Brenda W.J.H. Penninx, PhD[49], Nicholas G. Martin, PhD[5], and Dorret I. Boomsma, PhD[1]

Affiliations

[1]Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands [2]Department of Clinical Child and Family Studies, VU University Amsterdam, Amsterdam, The Netherlands [3]Department of Methods, VU University Amsterdam, Amsterdam, The Netherlands [4]Department of Research Methodology, Measurement and Data-Analysis, University of Twente, Enschede, The Netherlands [5]QIMR Berghofer Medical Research Institute, Herston, Brisbane, Australia [6]Department of Developmental Psychology and EMGO Institute for Health and Care Research, VU University Amsterdam, Amsterdam, The Netherlands [7]Department of Psychology, University of Minnesota, Minneapolis, USA [8]Department of Psychology, University of Edinburgh, Edinburgh, UK [9]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK [10]Donders Institute for Cognitive Neuroscience, Radboud University Nijmegen, Nijmegen, The Netherlands [11]Department of Psychiatry, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands [12]Department of Human Genetics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands [13]Department of Cognitive Neuroscience, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands [14]Department of Psychology, University of Illinois at Urbana-Champaign, Champaign IL, USA [15]Estonian Genome Center, University of Tartu, Tartu, Estonia [16]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands [17]Department of Human Genetics, University of Chicago, Chicago, IL, USA [18]Department of Clinical Chemistry, Fimlab Laboratories and School of Medicine, University of Tampere, Finland [19]MRC Human Genetics, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, Scotland, UK [20]Department of Psychiatry, University of Halle, Halle, Germany [21]Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland [22]Folkhälsan Research Center, Helsinki, Finland [23]Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA [24]Institute of Genetics and Biophysics “A. Buzzati-Traverso” – CNR, Naples, Italy [25]National

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Institute on Aging, NIH, Baltimore, MD, USA [26]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany [27]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden [28]Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland [29]Center for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan, USA [30]Pharmacotherapy & Outcomes Science, Virginia Commonwealth University, Richmond, Virginia, USA [31]Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA [32]Department of Psychology, University of Tartu, Tartu, Estonia [33]Estonian Academy of Sciences, Tallinn, Estonia [34]Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany [35]Istituto di Ricerca Genetica e Biomedica (IRGB), CNR, Monserrato, Italy [36]Centre for Population Health Sciences, Medical School, University of Edinburgh, Edinburgh, UK [37]Behavioral Medicine Research Center, Duke University School of Medicine, Durham NC, USA [38]Medical Research Council Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Bristol, UK [39]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, USA [40]Department of Biostatistics and Bioinformatics, Duke University, Durham NC, USA [41]National Institute for Health and Welfare (THL), Helsinki, Finland [42]Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland [43]Unit of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland [44]Vasa Central Hospital, Vasa, Finland [45]Interfaculty Institute for Genetics and Functional Genomics, University of Greifswald, Germany [46]University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Australia [47]Department of Molecular and Translational Medicine, University of Brescia, Italy [48]Department of Biotechnology, University of Tartu, Tartu, Estonia [49]Department of Psychiatry, EMGO+ Institute, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands [50]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany [51]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK [52]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, University of Helsinki, Finland [53]Department of Public Health, Faculty of Medicine, University of Split, Faculty of Medicine, University of Split, Split, Croatia [54]Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland [55]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland [56]Department of Psychological & Brain Sciences, Indiana University, Bloomington, IN, USA [57]Department of Psychological Sciences and Missouri Alcoholism Research Center, University of Missouri, Columbia, Missouri, USA [58]Alzheimer Scotland Dementia Research Centre, University of Edinburgh [59]Geriatric Medicine Royal Victoria Hospital, Edinburgh, UK [60]School of Oral and Dental Sciences, University of Bristol, Bristol, UK [61]School of Experimental Psychology, University of Bristol, Bristol, UK [62]College of Medicine, Florida State University, Tallahassee, FL, USA [63]Department for Health Evidence, Radboud University Medical Center,

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Nijmegen, The Netherlands [64]Department of Public Health and Primary Care, Trinity College Dublin, Dublin, Ireland [65]Generation Scotland, A Collaboration between the University Medical Schools and NHS, Aberdeen, Dundee, Edinburgh and Glasgow, UK [66]Medical Genetics Section, The University of Edinburgh, Centre for Genomics and Experimental Medicine, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK [67]Department of Psychiatry and Psychotherapy, HELIOS Hospital Stralsund, Stralsund, Germany [68]Laboratory of Genetics, National Institute on Aging, National Institutes of Health, Baltimore MD USA [69]Institute of Public Health, University of Southern Denmark, Odense, Denmark

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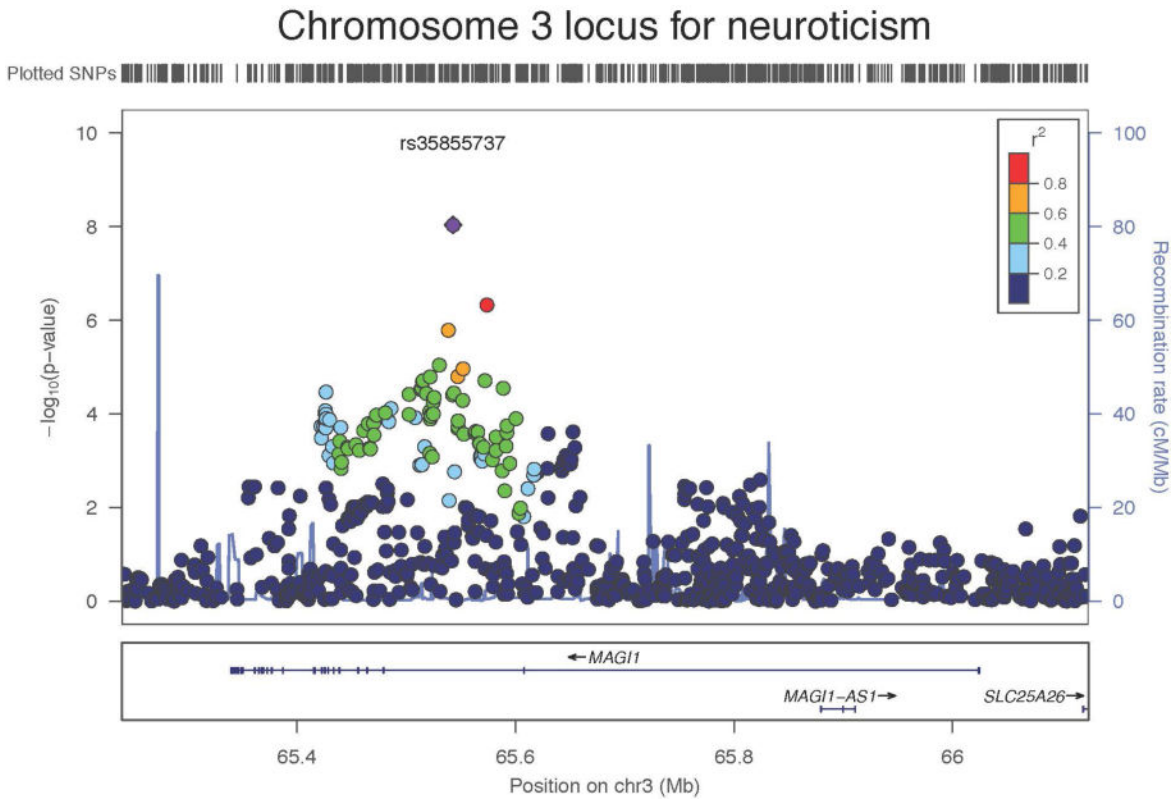

Figure 1.

Region plot for genome-wide significant SNP rs35855737 in the *MAGI1* gene on chromosome 3 for neuroticism

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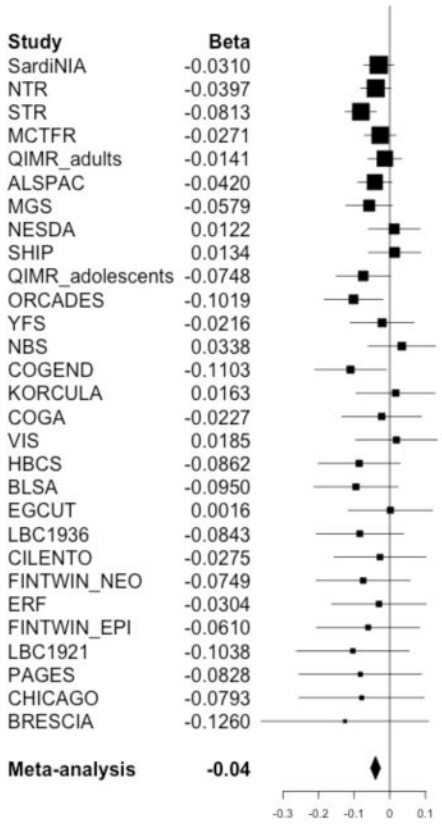

Figure 2.

Forest plot for genome-wide significant SNP rs35855737 in the *MAGI1* gene on chromosome 3 for neuroticism

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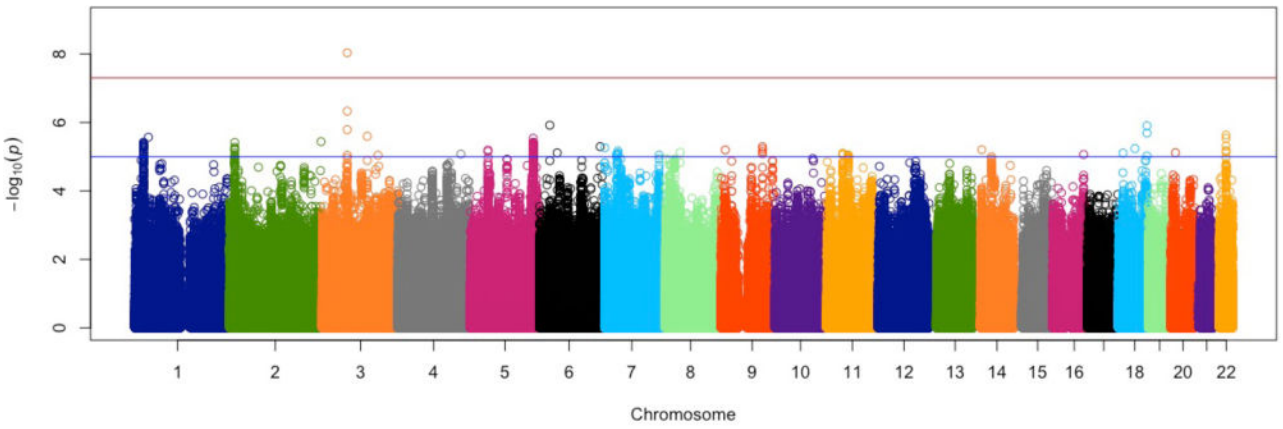

Figure 3.
Manhattan plot for meta-analysis results for neuroticism in 29 discovery cohorts

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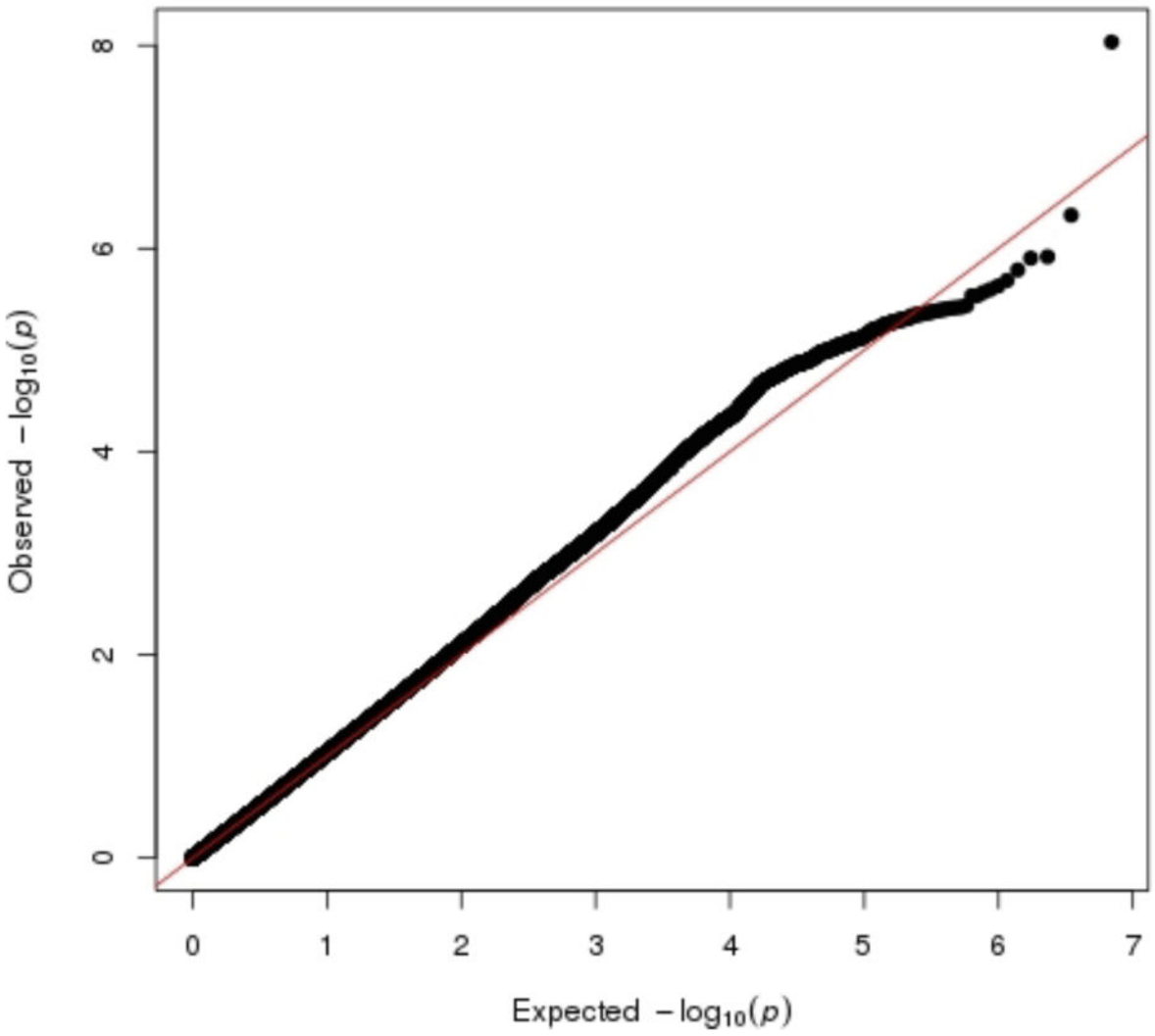

Figure 4.
Quantile-quantile plots for meta-analysis results for neuroticism in 29 discovery cohorts

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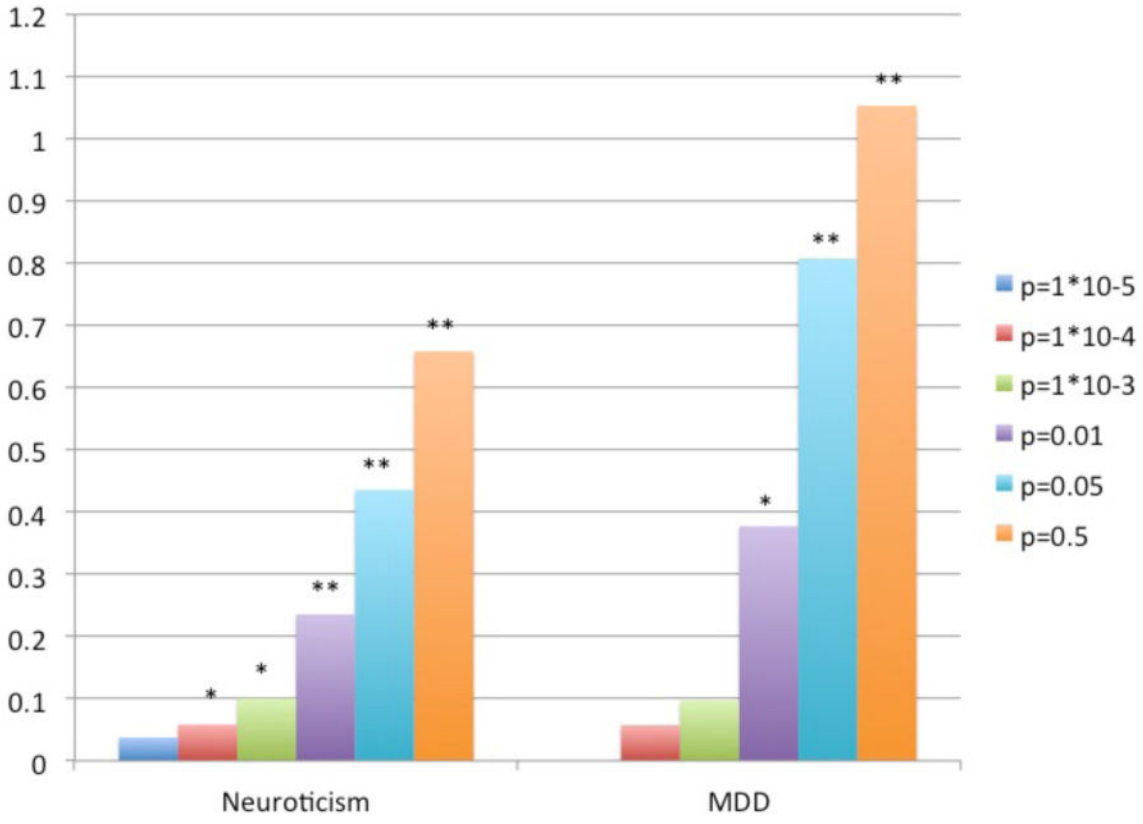

Figure 5.

Results of polygenic risk score analyses predicting MDD and neuroticism based on neuroticism polygenic risk scores

Note: Prediction of neuroticism and MDD in NTR/NESDA cohorts based on neuroticism polygenic risk scores from meta-analysis results omitting NTR/NESDA cohorts significant with *P<0.05 or ** P<0.001. Different colored bars refer to different *P*-value thresholds used to calculate the polygenic risk scores.