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Gene expression imputation across multiple tissue types provides insight into the genetic architecture of frontotemporal dementia and its clinical subtypes:

A transcriptome-wide analysis on frontotemporal dementia

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Abstract

Background: The etiology of frontotemporal dementia (FTD) is poorly understood. To identify genes with predicted expression levels associated with FTD, we integrated summary statistics with external reference gene expression data, using a transcriptome-wide association studies (TWAS) approach.

Methods: FUSION software was used to leverage FTD summary statistics (all FTD n=2,340 cases, n=7,252 controls; behavioral variant FTD (bvFTD) n=1,337 cases/2,754 controls; semantic dementia n=308 cases/616 controls; progressive non-fluent aphasia n=269 cases/538 controls, FTD with motor neuron disease n=200 cases/400 controls) from the International FTD-Genomics

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Consortium with 53 expression quantitative loci (eQTL) tissue type panels (n=12,205; five consortia). Significance was assessed using a 5% false discovery rate threshold.

Results: We identified 73 significant gene-tissue associations for FTD, representing 44 unique genes in 34 tissue types. Most significant findings were derived from dorsolateral prefrontal cortex (DLPFC) splicing data (n=19 genes, 26%). The 17q21.31 inversion locus contained 23 significant associations, representing six unique genes. Other top hits included *SEC22B*, a gene involved in vesicle trafficking, *TRGV5* and *ZNF302*. A single gene finding was observed for bvFTD (i.e., *RAB38*). For other clinical subtypes no significant associations were observed.

Discussion: We identified novel candidate genes (e.g., *SEC22B*) and previously reported risk regions (e.g., 17q.21.31) for FTD. Most significant associations were observed in DLPFC splicing data, despite the modest sample size of this reference panel. This suggests that our findings are specific to FTD and are likely to be biologically relevant highlights of genes at different FTD risk loci that are contributing to the disease pathology.

Keywords

frontotemporal dementia; transcriptome-wide association study; expression quantitative trait loci (eQTL); dorsolateral prefrontal cortex; *SEC22B* ; 17q21.31 inversion region

Introduction

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder, characterized by frontal and/or temporal patterns of atrophy. Clinically, FTD patients present with the behavioral variant of FTD (bvFTD) or language variants, such as semantic dementia (SD) and progressive non-fluent aphasia (PNFA) (1). In 10% of all cases, FTD co-occurs with motor neuron diseases (FTD-MND) (2).

Where FTD is mostly sporadic (80%), approximately 20% of all FTD cases are familial, with the most common Mendelian mutations including the hexanucleotide repeat expansion at the *C9ORF72* locus on chromosome 9, and mutations in microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*) genes in and near the chromosome 17q21 inversion locus (3–7). Genome-wide association studies (GWAS) in FTD have also identified genetic risk variants, each having small associations with disease risk (8–11). The number of known FTD disease susceptibility loci remains small due to limited power for discovery in the relatively small sample sizes of the GWAS studies thus far with n_{cases}<5,000. At this time, it is poorly understood how genetic risk variants for FTD exert effects on etiology, while such knowledge is essential for understanding disease pathology and the development of therapeutic interventions.

Genetic risk variants identified in GWAS are often located in noncoding regions with and without regulatory motifs, outside the protein encoding sequences (12). These risk variants are likely to predispose individuals to disease susceptibility by modulating mRNA expression levels, through local (*cis*) or distal (*trans*) expression quantitative trait loci (eQTL) (13). The FTD risk variant rs302652 nearby *RAB38* is a local eQTL, decreasing *RAB38* gene expression in monocytes (11) and potentially influencing bvFTD disease risk by modulating *RAB38* gene expression levels in specific brain areas. However, the joint

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effects of genetic risk loci for FTD on (differential) gene expression across multiple tissue types is unclear.

Transcriptome-wide association studies (TWAS) have emerged as a way to identify associations between traits and gene expression. The most common TWAS methods include PrediXcan, summary data–based Mendelian randomization (SMR) and FUSION (14–16). TWAS leverage the combined effects of multiple SNPs, either on individual-level (PrediXcan, SMR) or summary-level (s-PrediXcan, FUSION), on gene expression, thereby increasing power to find novel associations over a traditional GWAS when gene expression mediates risk (14–16). Imputation of the genetic control of gene expression is now widely used to decipher how GWAS identified alleles may contribute to disease risk and to identify specific candidate genes through which this effect is regulated. In this study, we performed a multi-tissue TWAS on sporadic FTD and its clinical subtypes, to identify genes whose changes in expression plays a role in FTD and to identify tissue types relevant to FTD. As a secondary aim of the study, we performed a TWAS-based enrichment analysis and explored whether FTD shows overlap in differential expression with neuropsychiatric disorders that show clinical overlap with FTD.

Methods and materials

GWAS summary statistics

GWAS summary statistics from the International Frontotemporal Dementia Genomics Consortium (IFGC) (https://ifgcsite.wordpress.com/) on frontotemporal dementia (FTD; n=2,154 cases/4,308 controls) and FTD clinical subtypes, behavioral variant FTD (bvFTD; n=1,377 cases/2,754 controls), semantic dementia (SD; n=306 cases/616 controls), progressive non-fluent dementia (PNFA; n=269 cases/ 538 controls) and FTD with motor neuron disease (FTD-MND; n=200 cases/400 controls), were used (Table S1). Written informed consent was obtained from all participants according to the Declaration of Helsinki. For all study sites, the study was approved by the Medical Ethics Committee.

Preprocessing and quality check procedures have been described previously (11). Single nucleotide polymorphisms (SNPs) were converted from chr:bp to rsID coordinates using Phase 3 1000 Genomes Project data (17). Summary statistics were quality checked and converted to LD-score format using the munge_stats.py utility from LDSC, leaving 1,068,995 SNPs for final analysis for all phenotypes (18) (Supplemental methods).

Expression quantitative trait loci (eQTL) reference panels

Local (*cis)* eQTL datasets from five different cohorts (n=12,205) on 53 tissue types were downloaded from the FUSION website (http://gusevlab.org/projects/fusion) (Table 1). The five cohorts included the CommonMind Consortium (CMC, n=452) (19), Netherlands Twin Registry (NTR, n=1,247) (20), The Cardiovascular Risk in Young Finns Study (YFS, n=1,264) (21), Metabolic Syndrome in Men Study (METSIM, n=562) (22) and the Genotype Tissue Expression project (GTEx) v7 (https://gtexportal.org/home/datasets, n=752). Local eQTLs were calculated by leveraging gene expression with genetic variation data (i.e., SNPs within ±1 Mb of the transcriptional start site (TSS) of the gene). More

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detailed information on genotyping and gene expression analyses for these datasets have been described previously: CMC (23), NTR, YFS, METSIM (15) and GTEx (24).

Local eQTL datasets from tissue types less relevant to FTD (e.g., blood) were included in this study, as local eQTLs are highly conserved across tissues (25) and eQTL datasets with non-brain tissues consist of substantially larger sample sizes, thereby maximizing power to detect significant associations between local gene expression and FTD GWAS SNPs.

FUMA

To examine the proportion of noncoding variants amongst FTD-risk SNPs, we annotated SNPs from the IFGC GWAS on FTD using Functional Mapping and Annotation (FUMA, https://fuma.ctglab.nl/)(26). The most significant ($p<5\times10^{-6}$) SNPs and SNPs in linkage disequilibrium (LD, $r2\geq0.6$) with these were used for further inspection, using 1000 Genomes Project data (17). Lead SNPs were defined as being independent from each other at $r2>0.1$. LD blocks of independent SNPs were merged into a genomic locus if they were closely located to each other (i.e., less than 250kb).

Lead and correlated SNPs were annotated for potential regulatory functions (RegulomeDB, RDB) (27), 15-core chromatin state predicted by ChromHMM (28), functional consequences on gene functions annotated by ANNOVAR (29) and deleteriousness score (Combined Annotation Dependent Depletion, CADD) (30). To test for enrichment of functional consequences of lead and correlated SNPs (as estimated with ANNOVAR) we performed a Fisher's exact test, using a 5% false discovery rate (FDR) significance threshold (see https://fuma.ctglab.nl/tutorial#annov). The enrichment value was calculated as the proportion of SNPs with an annotation divided by the proportion of SNPs with an annotation relative to all available SNPs in Phase 3 1000 Genomes Project data (17).

Statistical analysis

TWAS analysis—To identify genes whose local-regulated expression is associated with FTD and its clinical subtypes (i.e., bvFTD, SD, PNFA and FTD-MND), we performed TWAS analyses using FUSION software (http://gusevlab.org/projects/fusion/) with default settings (15). FUSION estimates the genetic correlation between local gene expression and FTD, by integrating GWAS summary statistics with external gene expression reference panel data while accounting for LD structure among SNPs (using Phase 3 1000 Genomes Project data (17)). To account for LD structure, we used 1000 Genomes (all ancestries) data as LD reference panel.

To study whether GWAS SNPs colocalized with eQTLs, we performed a Bayesian colocalization analysis for all associations with $p_{TWAS\ uncorrected}<0.05$ using the COLOC package in R (https://cran.r-project.org/web/packages/coloc/) (31) implemented in FUSION. A joint analysis was performed to identify which genes are conditionally independent.

TWAS results are presented including the major histocompatibility (MHC) locus, as the FTD GWAS included genome-wide significant loci within the MHC region (11). Results on gene-tissue associations per phenotype (i.e., FTD, bvFTD, SD, PNFA and FTD-MND) were corrected for multiple comparisons using a 5% FDR significance threshold. Significant

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TWAS loci were identified as novel if the strongest FTD associated SNP was not nominal significant (P>0.05) in the IFGC GWAS (11) within ±1 Mb of the TSS of the gene's region.

MESC analysis—In order to estimate the proportion of disease heritability mediated by local gene expression, we performed a Mediated Expression Score Regression (MESC) analysis per tissue type, hereby excluding SNPs located on the MHC locus (https://github.com/douglasyao/mesc) (32). Here, we define h^2_{med} as heritability mediated by local gene expression, h^2_g as disease heritability and h^2_{med}/h^2_g as the proportion of heritability mediated by local gene expression. First, for each gene, local heritability scores were estimated while accounting for LD structure. Genes were partitioned into bins according to their local heritability, as this has shown to provide unbiased h^2_{med}/h^2_g estimates. Second, we estimated h^2_{med}/h^2_g from expression scores estimated in the previous step and GWAS summary statistics on FTD. As MESC produces biased estimates for eQTL reference panels with small sample sizes, only eQTL datasets with sample size n>300 (n=17) were included.

Enrichment analysis—Competitive enrichment analysis on FTD TWAS results was performed using TWAS-based gene set enrichment analysis (TWAS-GSEA) (https://github.com/opain/TWAS-GSEA) (33). TWAS-GSEA is an adapted method of GWAS-based enrichment analysis implemented in software MAGMA (34). In brief, this method examines whether TWAS results are enriched for specific pathways while accounting for LD structure. Per phenotype, TWAS-GSEA was performed simultaneously for all 53 eQTL datasets. The file used as eQTL reference panel for the TWAS-GSEA analysis included unique gene identifiers only; if genes were present in multiple local eQTL datasets, the gene with the best prediction of expression (as estimated by cross-validated R^2, MODELCV.R2) was used in the GSEA. Gene identifiers in TWAS result files were converted to Entrez ID format using the biomaRt package in R, resulting in 15,004 (14,813 non-MHC) unique Entrez IDs for FTD and all clinical FTD subtypes. TWAS results were tested for enrichment across 6,778 Gene Ontology (GO) biological processes gene sets. Per phenotype, results were corrected for the number of gene sets using a 5% FDR significance threshold.

Data availability

The GWAS summary statistics on FTD can be acquired via the International FTD-Genomics Consortium (IFGC) (https://ifgcsite.wordpress.com/data-access/). Local expression quantitative trait loci (eQTL) reference weights can be downloaded from the FUSION website (http://gusevlab.org/projects/fusion).

Results

Most risk variants for FTD are located in noncoding regions

For FTD, FUMA annotated 3,103 SNPs from thirteen independent lead SNPs located in ten genomic risk loci. These SNPs showed enrichment for intronic (50.2%, $P_{enrichment}=2.98\times10^{-120}$), intronic non-coding RNA (24.3%, $P_{enrichment}=3.15\times10^{-124}$), intergenic (19.3%, $P_{enrichment}=0$) and 5'UTR regions (0.75%, $P_{enrichment}=1.61\times10^{-6}$), whereas only 1.4% of all SNPs were located in exonic regions ($P_{enrichment}=0.32$) (Table S2). Most SNPs (93.1%) were located in open chromatin regions (range minimum chromatin

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state across 127 tissue/cell types=1–7) and 11.4% SNPs had potential regulatory elements, as indicated by a RDB score below 2 (Figure S1).

Predicted gene expression levels show 73 associations with FTD

Predicted gene expression levels in 53 tissue types (range of genes per tissue type=1,505–9,229) were tested for association with FTD. We identified 73 significant gene-tissue associations for FTD, representing 44 (40 non-MHC) unique genes in 34 tissue types (Table 1, Table S3, Figure 1, Figure 2). In total, 39.7% (29/73) of these transcriptome-wide significant associations had supporting evidence from colocalization analyses (Table S4). The strongest genic FTD TWAS associations included *ARL17B* on chromosome 17 (brain cerebellar hemisphere $P_{FDR}=9.02\times10^{-22}$), *ZNF302* on chromosome 19 (DLPFC splicing data $P_{FDR}=5.80\times10^{-8}$), *LRRC37A* (lung $P_{FDR}=1.58\times10^{-5}$), *SEC22B* on chromosome 1 (thyroid $P_{FDR}=2.28\times10^{-3}$) and *TRGV5P* on chromosome 17 (cells transformed fibroblasts $P_{FDR}= 2.39\times10^{-3}$) (Table 2). Of all transcriptome-wide significant genes with supporting colocalization evidence, only the association of *SEC22B* with FTD was novel, showing no evidence for association in the FTD GWAS (minimal P within ±1Mb of the gene's region=6.14×10^{-2}) (11) (Table S5).

One region of interest is 17q21.31 on chromosome 17, which contained 23 significant associations, representing six unique genes (i.e., *ARL17B, KANSL1-AS1, LRRC37A, MAPT, MAPT-AS1* and *NSFP1*). This locus is an inversion polymorphism that has been associated previously with neurodegenerative tauopathies, but also with psychiatric disorders, such as autism spectrum disorders (33, 35). Gene expression of most gene-tissue pairs were highly correlated, except for *KANSL1-AS1*, *MAPT* and *MAPT-AS1* (Figure S2). For the majority of significant associations in 17q21.31 (n=16, 69.6%), colocalization analysis provided evidence for a shared causal genetic variant between gene expression and FTD (Table S4).

Another region was 7p14.1, for which predicted gene expression of *TRGV5* and its pseudogene *TRGV5P* achieved transcriptome-wide significance in four different tissue types. Colocalization analyses suggested that FTD and 7p14.1 gene expression share a single causal association (Table S4).

Most TWAS associations were detected in dorsolateral prefrontal cortex splicing data

The brain-derived reference panels contributed the most to the significant associations between gene expression and FTD (43.8%, 32 gene-tissue associations), with the majority derived from the dorsolateral prefrontal cortex (DLPFC) splicing data (19 splicing variants, 13 unique, all outside MHC). A previous study has shown that a larger sample size and increased number of measured genes of the eQTL reference panel correlates to a higher number of significant hits (36). Despite the modest sample size ($n_{sample}=452$) and number of measured genes ($n_{genes\ unique}=3,221$, $n_{genes\ total}=7,514$), the DLPFC splicing data accounted for 26% of all transcriptome-wide hits, thereby exceeding the number of significant hits compared to eQTL tissue types with larger sample sizes (e.g., 0% for YFS whole blood, $n_{sample}=1,264$) and more measured genes (e.g., 3% for thyroid,

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$n_{genes,\ unique}$=9,225, $n_{genes\ total}$=9,229) (Figure S3, Figure S4). Accordingly, FTD TWAS results showed significant enrichment for DLPFC splicing data ($P=7.31\times10^{-3}$) (Table S6).

MESC analysis showed that a substantial proportion of FTD heritability was mediated by the local component of gene expression levels (mean h^2_{med}=35(4.7)%). The tibial nerve had the highest heritability mediated by local gene expression levels (h^2_{med}=59.5(2.2)%), potentially reflecting a genetic component underlying the comorbidity underlying FTD and motor neuron diseases. For DLPFC splicing data the h^2_{med} was 43.8(8.5)%, whereas for the eQTL panel with the largest sample size (YFS whole blood data) this was 12.6(7.4)%. A full overview of local mediated heritability is presented in Figure S5 (see SNP heritability estimates in Table S1).

Predicted gene expression levels on clinical subtypes separately show association with bvFTD only

Predicted gene expression levels in 53 tissue types (range of genes per tissue type=1,505–9,229) were tested for association with bvFTD, SD, PNFA and FTD-MND. Gene expression of *RAB38* on chromosome 11 was significantly associated with bvFTD risk in 8 out of 25 tissue panels (colon sigmoid $P_{FDR}=4.02\times10^{-4}$, range significant gene-tissue associations $P_{FDR}=4.02\times10^{-4}$–$4.37\times10^{-2}$) (Figure 3, Figure S6, Table S7). Colocalization supported model 4 with a range posterior probability PP4 of 0.64–1.0 (range PP3=0.003–0.04) (Table S8). The former GWAS on bvFTD showed nominal evidence for the association of *RAB38* with FTD (rs302668 odd ratio(OR)=0.81(0.71–0.91); $p_{GWAS}=2.44\times10^{-7}$) (11). For SD, PNFA and FTD-MND, no significant transcriptome-wide associations were observed (Figure S7, S8, S9, Table S9–S14).

Implicated genes highlight involvement of amino acid transport in FTD pathogenesis

Full competitive results for the enrichment analysis on FTD and its clinical subtypes are presented in Table S15–S24. TWAS results for FTD were significantly enriched for ‘Sulfur amino acid transport’ (with MHC $P_{FDR}=0.04$, without MHC $P_{FDR}=0.03$) (Figure S11, S12). For all other gene sets and traits, no gene sets were significant after FDR correction.

No genetic correlation between gene expression FTD and Alzheimer’s disease, amyotrophic lateral sclerosis, and primary psychiatric disorders

Given the similarities between FTD and several neuropsychiatric disorders, we explored the genetic correlation between the predicted gene expression for FTD and Alzheimer’s disease and amyotrophic lateral sclerosis,s schizophrenia, autism spectrum disorder and major depressive disorder, using RHOGE (37) (see Supplementary method section). No significant correlations were observed after FDR correction (Table S25–S26, Figure S13).

Discussion

In this study, we aimed to better understand the genetic etiology of sporadic FTD by identifying genes whose expression plays a role in FTD, using a TWAS approach with increased power of detecting loci compared to a traditional GWAS. We identified 73 significant gene-tissue associations for FTD, representing 44 unique genes in 34 tissue

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types. The 17q.21.31 inversion region was replicated as risk region for FTD. *SEC22B* was identified as likely novel risk gene for FTD. Interestingly, most associations were derived from splicing data of the dorsolateral prefrontal cortex (DLPFC), a brain region that is almost universally involved in FTD, thereby providing some biological validation to the multi-tissue TWAS approach in FTD. Moreover, these findings highlight the importance of splicing events for disease risk (38). Our results indicate that a large proportion of FTD risk loci modulate gene expression levels, and we highlight these genes as potential candidates for functional follow-up studies.

The majority of FTD risk variants were located in noncoding regions, demonstrating that these variants likely have regulatory functions. Forty-four genes were identified as differentially expressed in FTD. We replicated the 17q21.31 locus as risk factor for FTD. This region contained 23 significant associations from six different genes, including *ARL17B, KANSL1-AS1, LRRC37A, NSFP1, MAPT-AS1* and *MAPT*. Mutations in the latter gene, *MAPT*, are identified as one of the most common Mendelian mutations implicated in familial FTD (6). The 17q21.31 region contains a common inversion polymorphism and has been associated with several neurodegenerative disorders (e.g., progressive supranuclear palsy, corticobasal degeneration, Alzheimer's disease and FTD), but also with psychiatric disorders such as autism spectrum disorder (33, 35, 39–42). Previous research has shown that different haplotypes of the 17q21.31 inversion affects expression of 17q21.31 genes in blood and different brain regions (43). Here, we highlight the role of differential gene expression of 17q21.31 genes across several tissue types in the pathogenesis of FTD.

Another implicated gene was *SEC22B* on chromosome 1, which showed evidence for differential gene expression in FTD without achieving genome-wide significance in the corresponding FTD GWAS (P>0.05 within ± 1Mb of *SEC22B*). *SEC22B* codes for a protein that plays an important role in vesicle trafficking between the Golgi apparatus and the endoplasmic reticulum, autophagy and membrane fusion. The latter is essential for the development of the nervous system including axonal and dendritic growth (44). Little is known about the precise role of *SEC22B* in neurodegeneration, but differential expression of this gene in the brain has been associated with normal aging and Alzheimer's disease (45, 46).

We found increased *C4A* gene expression to be significantly associated with FTD. The *C4* gene has two functionally different isoforms (i.e., C4A and C4B, both can vary in structure and copy number) and is located on the major histocompatibility (MHC) locus, a locus strongly associated with immune-related processes. Structural variation in *C4A/B* has been associated with schizophrenia, probably affecting synaptic pruning (47, 48). The potential role of *C4* (structure) in the etiology of FTD has not been fully understood yet. Human postmortem and mice model studies on FTD demonstrate an association between upregulated *C4A* gene expression and aggregation of transactive response (TAR) DNA binding protein, 43 kDa (TDP), one of the most common pathological subtypes underlying FTD (49, 50). Although this would suggest a specific relationship between upregulated *C4A* gene expression and FTD pathology, increased *C4A* gene expression has also been observed in Alzheimer's disease (AD) and schizophrenia (51).

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We explored the genetic correlation between predicted gene expression for FTD and primary psychiatric disorders, AD and amyotrophic lateral sclerosis (ALS). Although FTD and psychiatric disorders overlap with respect to symptoms and affected neuroanatomical regions, we found no indications for an overlapping expression profile (52, 53). We further did not observe a significant overlap of predicted gene expression for FTD with both AD and ALS. Although previous studies have reported a shared genetic architecture between FTD and ALS (54), our results suggest that the known clinical association between FTD and ALS (in about 10% of all cases) may not be driven by an overlap in gene expression. Altogether this suggests that, at least part of, the FTD TWAS signal is specific for FTD rather than generic to neuropsychiatric disorders.

Proteins differentially expressed in FTD showed enrichment for the transport of sulfur amino acids (e.g., methionine and cysteine), a process essential for the synthesis of antioxidants. For example, transport of L-cystine (i.e., oxidized form of cysteine) is needed for the production of antioxidant glutathione in the brain (55). Sulfur amino acids are sensitive to oxidative modifications by reactive oxygen-containing species (ROS). A balance between the production of ROS and antioxidants protects cells against invaders. However, an imbalance leads to increased oxidative stress, which is particularly damaging to cells in high demand of oxygen, such as neuronal cells (56). Increased oxidative stress has been associated with aging, and has been observed in several disorders, including FTD (56–58).

Despite the modest sample size of the DLPFC CMC reference panel, the DLPFC contributed to significant more transcriptome-wide findings compared to other tissue types, thereby highlighting the topology-specific neurodegenerative nature of FTD. MESC analysis, an approach to examine the genome-wide distribution of heritability, showed that the tibial nerve had the largest proportion of heritability mediated by local gene expression, which may reflect the comorbidity of FTD with motor neuron diseases. However, motor neuron disorders typically present with the degeneration of both upper and lower motor neurons (UMN, LMN), while most, but not all, studies indicate that sensory neurons are spared (59, 60). While tibial nerve degeneration has been observed in motor neuron disorders, this nerve contains both motor and sensory axons, and Schwann cells, making it possibly less specific as tissue of interest for motor neuron disorders (61). Therefore, current MESC results should be validated using reference weights of LMN and UMN tissue types.

We also observed various associations outside the brain, potentially highlighting the importance of other organ systems in FTD. In line with this, other organ systems, such as the gastrointestinal and musculoskeletal system, have been associated with FTD (62, 63). On the other hand, we included local eQTL data from many tissue types - also those that are seemingly less disease-relevant - to increase power and to include as many genes in this exploratory study. As a result we may not have detected the true mechanism of disease due to a shared cross-tissue regulatory architecture of eQTLs between the tissue types related and non-related to FTD (25, 64). This is illustrated by our finding on bvFTD, for which we only identified differential regulatory gene expression of *RAB38* in tissue types outside the brain. As *RAB38* is expressed throughout the brain (https://gtexportal.org/home/gene/RAB38) but not available in the brain tissue panels we used, we hypothesize that differential expression of *RAB38* in the brain contributes to bvFTD disease risk too. To gain

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a deeper understanding of molecular mechanisms underlying FTD, future TWAS studies should increase the sample sizes of eQTL reference panels of disease-relevant tissue types and refine tissue-specific information with, for instance, cell-type specific features.

This study is a starting point for bridging the gap between genetic variation and disease pathogenesis involving specific genes in FTD. Nevertheless, several limitations should be taken into account. First, where TWAS increases power over a traditional GWAS study, the small sample size (n=2,154 cases/4,308 controls) of the current FTD GWAS study still reduces the power to find novel transcriptome-wide associations. As such, future TWAS studies on FTD should be performed using FTD GWAS summary statistics with a larger sample size, as this would increase the power to detect true associations, but also the robustness of results on tissue enrichment and genetic correlations. A second major limitation is that this study does not address the pathological heterogeneity in FTD. The most common pathological subtypes of FTD include abnormal aggregation of tau (FTLD-tau) and FTLD-TDP (65). As we performed a TWAS on the clinical entity of FTD, this study provides only insights into generic mechanisms underlying FTD but not into specific mechanisms underlying pathological subtypes. Additional studies in postmortem verified FTD cases are required to gain more insight into distinct mechanisms underlying pathological subtypes of FTD. Moreover, our results should be replicated using independent *cis* eQTL datasets to exclude the possibility that presented findings reflect false-positive findings. Finally, it should be noted that TWAS or colocalization analysis cannot be used for causal inference (64). It is therefore essential that our efforts will be extended to functional validation, to further understand the relationship between FTD and genes reported in this study.

Results presented in this study could be used as a point of reference in future genetic association studies on FTD. We provide evidence for the contribution of many genes, with both tissue-shared as tissue-specific effects, to the pathogenesis of FTD, including potential novel (i.e., *SEC22B*) and previously reported FTD risk loci (e.g., 17q21.31 inversion region, *C4A*). Most associations were detected in DLPFC splicing data, but tissues outside the brain may be involved in FTD as well. However, functional validation is needed as TWAS is sensitive to detecting associations not relevant for disease if the disease-relevant tissue is not well-represented across reference panels. Identifying which biological processes are genetically influenced by FTD is important for understanding the disease etiology, and eventually for the development of treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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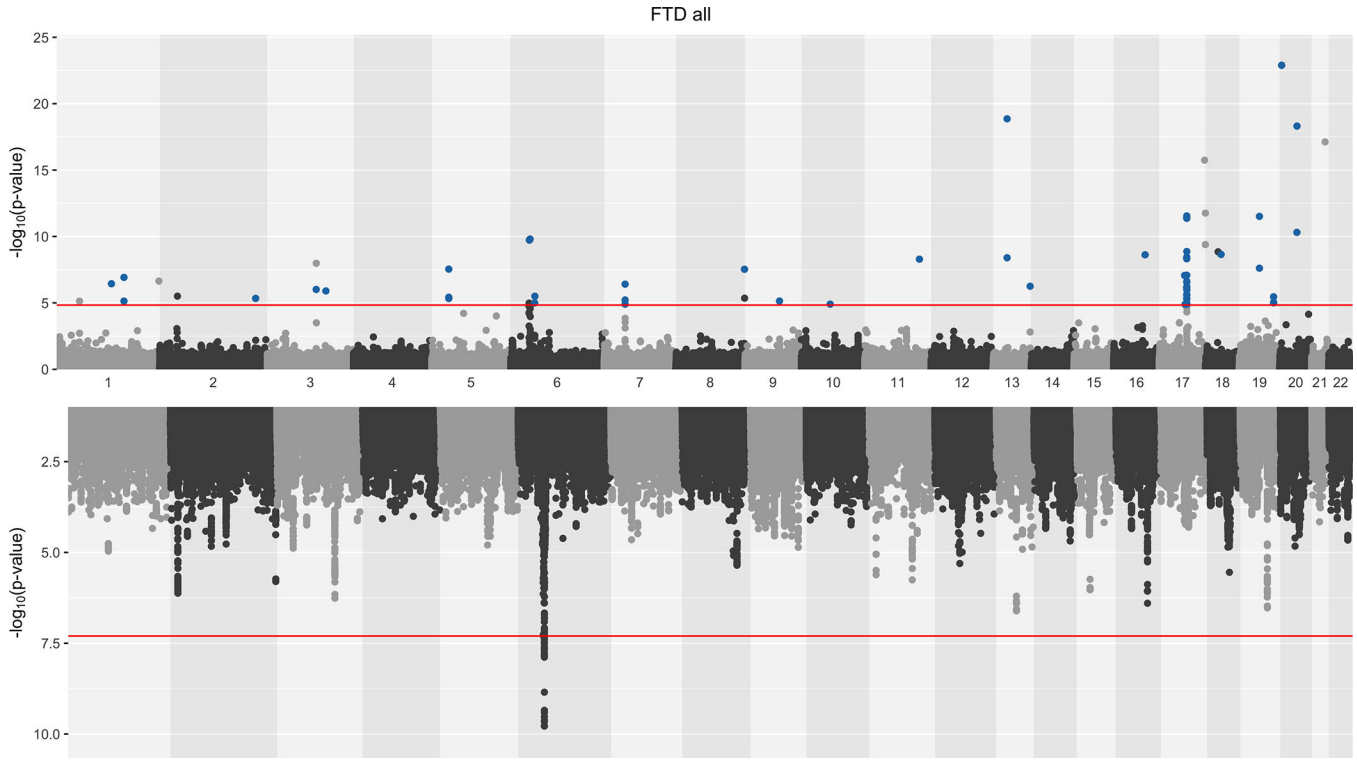

Figure 1. Miami plot on FTD TWAS (top) and GWAS (bottom). 44 unique genes were associated with FTD across 34 tissue types.

Each point depicts a distinct gene-tissue association. TWAS hits with supporting evidence from colocalization analysis are highlighted blue. The red line depicts the significance threshold; P_{FDR}<0.05 for TWAS and P<5e-8 for GWAS.

FTD; frontotemporal dementia, TWAS; transcriptome-wide association study, GWAS: genome-wide association study.

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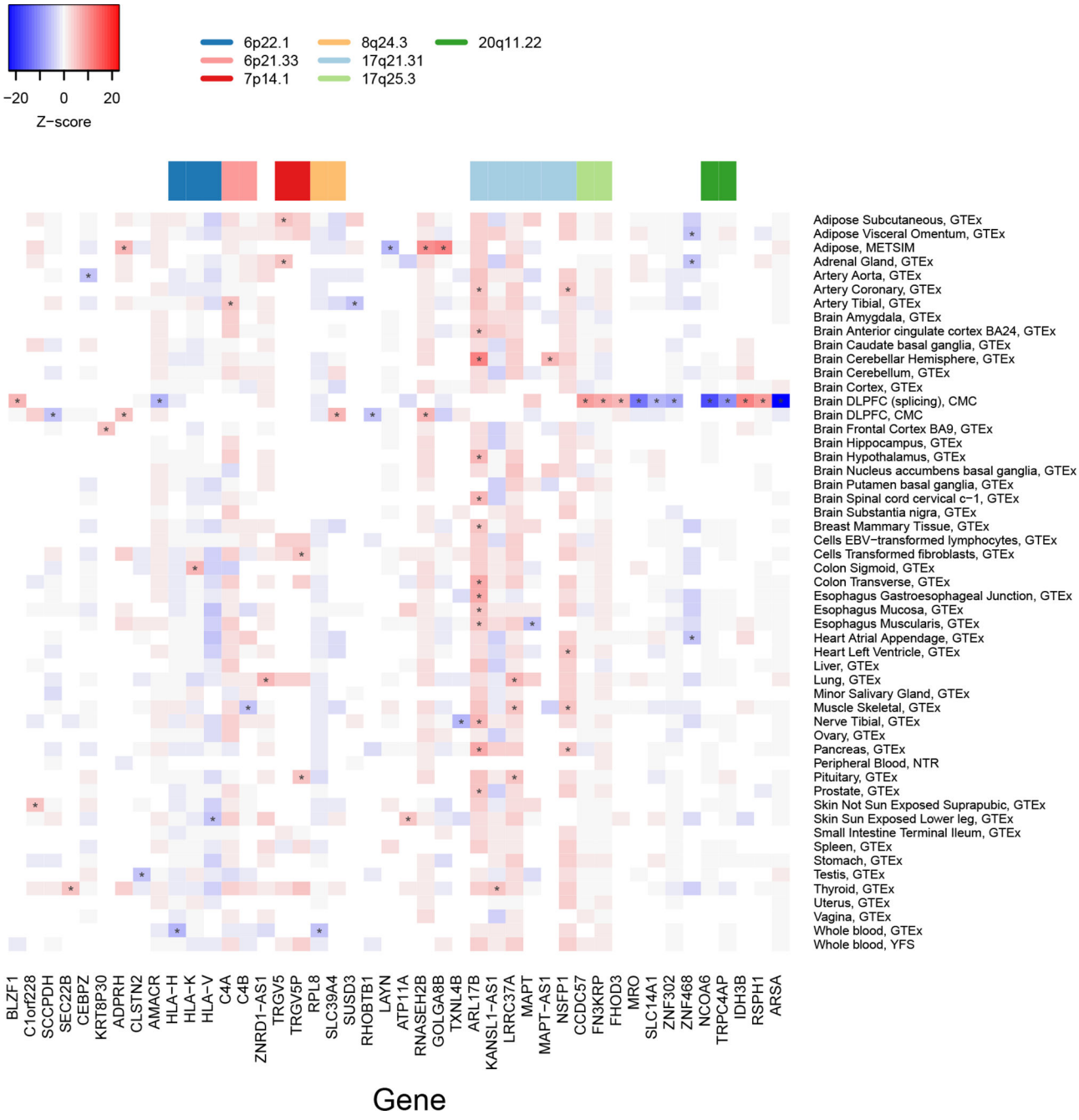

Figure 2. Heatmap of Z scores of genes with at least one transcriptome-wide significant association with FTD.

FTD transcriptome-wide associations demonstrate tissue-shared and tissue-specific effects. The association of imputed gene expression of genes located on region 17q21.31 (above depicted in light blue) with FTD seems to be preserved across most reported tissue types, albeit not statically significant. On the other hand, none out of the 13 unique (splicing) variants in the DLPFC CMC data were significant in other datasets. Transcriptome-wide significant associations (P_{FDR}<0.05) are depicted with an asterisk. Blank squares indicate that gene weights were not available in the reference panel.

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FTD; frontotemporal dementia, TWAS; transcriptome-wide association study, FDR; false-discovery rate.

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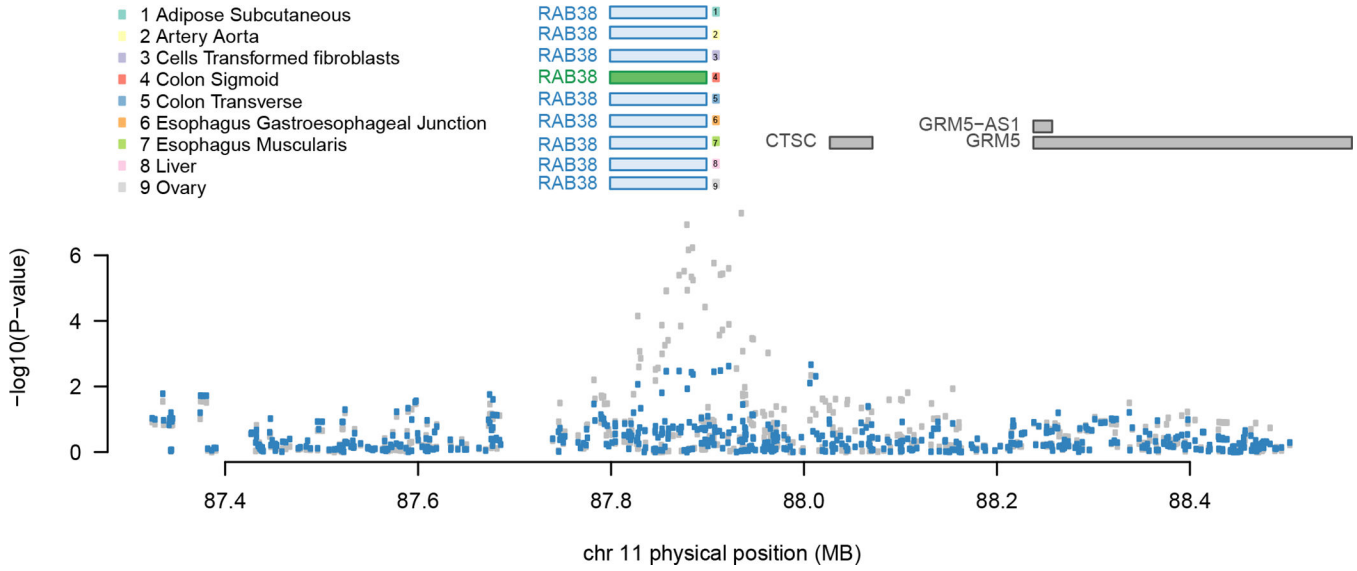

Figure 3. Regional association plot of *RAB38* for behavioral variant FTD.

The top panel shows all of the genes in the locus. The marginally TWAS associated genes are highlighted in blue, and those that are jointly significant (i.e., *RAB38* in Colon Transverse) highlighted in green. The bottom panel shows a Manhattan plot of the GWAS data before (gray) and after (blue) conditioning on the green genes. This locus goes from being genome-wide significant to non-significant after conditioning on the predicted expression of *RAB38*.

FTD; frontotemporal dementia.

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Table 1.

Descriptive statistics for tissue reference panels and TWAS results.

Study	Reference Panel	Subjects, N [a]	Genes, N [b]	FTD TWAS significant	behavioral FTD TWAS significant
CMC	Brain - Dorsolateral prefrontal cortex	452	5244	5	0
CMC	Brain - Dorsolateral prefrontal cortex (splicing)	452	7514 (3221)	19 (13)	0
GTEx	Adipose - Subcutaneous	385	7669 (7668)	1	1
GTEx	Adipose - Visceral (Omentum)	313	5765 (5763)	1	0
GTEx	Adrenal Gland	175	4252 (4251)	2	0
GTEx	Artery - Aorta	267	6040	1	0
GTEx	Artery - Coronary	152	3026	2	0
GTEx	Artery - Tibial	388	7732 (7730)	2	0
GTEx	Brain - Amygdala	88	1710	0	0
GTEx	Brain - Anterior cingulate cortex (BA24)	109	2523	1	0
GTEx	Brain - Caudate (basal ganglia)	144	3418	0	0
GTEx	Brain - Cerebellar Hemisphere	125	4131 (4130)	2	0
GTEx	Brain - Cerebellum	154	5513	0	0
GTEx	Brain - Cortex	136	3761	0	0
GTEx	Brain - Frontal Cortex (BA9)	118	2934	1	0
GTEx	Brain - Hippocampus	111	2129	0	0
GTEx	Brain - Hypothalamus	108	2147	1	0
GTEx	Brain - Nucleus accumbens (basal ganglia)	130	3032	0	0
GTEx	Brain - Putamen (basal ganglia)	111	2638	0	0
GTEx	Brain - Spinal cord (cervical c-1)	83	1892	1	0
GTEx	Brain - Substantia nigra	80	1505	0	0
GTEx	Breast - Mammary Tissue	251	4701 (4700)	1	0
GTEx	Blood - EBV-transformed lymphocytes	117	2558 (2557)	0	0
GTEx	Transformed fibroblasts	300	6957 (6956)	1	1
GTEx	Colon - Sigmoid	203	4559 (4558)	1	1
GTEx	Colon - Transverse	246	4935 (4934)	1	1
GTEx	Esophagus - Gastroesophageal Junction	213	4563 (4562)	1	1

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Study	Reference Panel	Subjects, N [a]	Genes, N [b]	FTD TWAS significant	behavioral FTD TWAS significant
GTEx	Esophagus - Mucosa	358	7551 (7549)	1	0
GTEx	Esophagus - Muscularis	335	7287 (7286)	2	1
GTEx	Heart - Atrial Appendage	264	5316	1	0
GTEx	Heart - Left Ventricle	272	4750	1	0
GTEx	Liver	153	2711	0	1
GTEx	Lung	383	7270 (7268)	2	0
GTEx	Minor Salivary Gland	85	1681	0	0
GTEx	Muscle - Skeletal	491	6990 (6989)	3	0
GTEx	Nerve - Tibial	361	9064 (9062)	2	0
GTEx	Ovary	122	2620 (2619)	0	1
GTEx	Pancreas	220	4768 (4767)	2	0
GTEx	Pituitary	157	4122 (4121)	2	0
GTEx	Prostate	132	2600	1	0
GTEx	Skin - Not Sun Exposed (Suprapubic)	335	6984 (6983)	1	0
GTEx	Skin - Sun Exposed (Lower leg)	414	8343 (8342)	2	0
GTEx	Small Intestine - Terminal Ileum	122	2664	0	0
GTEx	Spleen	146	4161	0	0
GTEx	Stomach	237	4145 (4143)	0	0
GTEx	Testis	225	8685 (8682)	1	0
GTEx	Thyroid	399	9229 (9225)	2	0
GTEx	Uterus	101	1972	0	0
GTEx	Vagina	106	1852	0	0
GTEx	Whole Blood	369	1898	2	0
METSIM	Adipose	563	4458	4	0
NTR	Peripheral Blood	1247	2356	0	0
YFS	Whole blood	1264	5568 (5567)	0	0
Total	-	-	246,320 (241,893 non-MHC, 233,420 unique)	73 (67)	8

No significant gene-tissue interactions were observed for semantic dementia (SD), progressive non-fluent aphasia (PNFA) and FTD with motor neuron diseases (FTD-MND).

FTD; frontotemporal dementia, TWAS; transcriptome-wide association study, CMC; CommonMind Consortium, GTEx; Genotype-Tissue Expression project, METSIM; Metabolic Syndrome in Men Study, NTR; Netherlands Twin Registry, YFS; Young Finns Study.

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[a] Number of subjects included in reference panel study.

[b] Number of genes that could be estimated

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Table 2.

Transcriptome-wide significant associations with supporting evidence from colocalization analysis.

Location	Min p (TWAS)	Min p (GWAS)	Jointly significant	Marginally significant
17.q21.31	1.83e–26	5.94e–05	*ARL17B, LRRC37A, NSFP1*	*ARL17B KANSL1-AS1 LRRC37A NSFP1*
13.q34	5.56e–07	2.30e–03	*ATP11A*	
6.p21.33	1.00e–05	6.49e–04	*C4A*	
3.q23	1.26e–06	3.07e–03	*CLSTN2*	
2.q35	4.57e–06	9.48e–04	*KRT8P30*	
10.q21.2	1.24e–05	2.69e–02	*RHOBTB1*	
1.p12	3.61e–07	8.88e–02	*SEC22B*	
9.q22.31	7.21e–06	6.14e–02	*SUSD3*	
7.p14.1	3.89e–07	2.24e–02	*TRGV5*	*TRGV5, TRGV5P*
19.q13.11	3.06e–12	2.63e–02	*ZNF302*	*ZNF302*
19.q13.41	9.09e–06	6.04e–02	*ZNF468*	

Min p (GWAS) represents the p value for the top SNP association within ±1Mb of transcriptional site of the gene's region.

TWAS; transcriptome-wide association study, GWAS; genome-wide association study.

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KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use "this paper" if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Deposited Data; Public Database	GWAS summary statistics on frontotemporal dementia and its clinical subtypes	PMID: 24943344, International Frontotemporal Dementia Genomics Consortium (IFGC) (https://ifgcsite.wordpress.com/)	N/A	
Deposited Data; Public Database	GWAS summary statistics on autism spectrum disorder, schizophrenia, major depressive disorder	Psychiatric Genomics Consortium	RRID:SCR_004495	
Deposited Data; Public Database	GWAS summary statistics on Alzheime's disease	PMID: 30617256	N/A	
Deposited Data; Public Database	GWAS summary statistics on amyotrophic lateral sclerosis	PMID: 29566793	N/A	
Deposited Data; Public Database	Phase 3 1000 Genomes data	PMID:26432245	RRID:SCR_008801	
Deposited Data; Public Database	Cis eQTL datasets on 53 tissue types	PMID: 26854917, downloaded from the FUSION website (http://gusevlab.org/projects/fusion)	N/A	Cis eQTL weights were calculated using data from the CommonMind Consortium (CMC, n=452), Netherlands Twin Registry (NTR, n=1,247), The Cardiovascular Risk in Young Finns Study (YFS, n=1,264), Metabolic Syndrome in Men Study (METSIM, n=562) and the Genotype Tissue Expression project (GTEx) v7 (https://gtexportal.org/home/datasets, n=752).
Software; Algorithm	FUSION	PMID:26854917	N/A	
Software; Algorithm	COLOC package in R	PMID: 19039033	N/A	
Software; Algorithm	biomaRt package in R		RRID: SCR_002987	
Software; Algorithm	stats (fisher.test) package in R	PMID: 27044131	N/A	
Software; Algorithm	Mediated Expression Score Regression (MESC) analysis (https://github.com/douglasyao/mesc)	PMID: 32424349	N/A	
Software; Algorithm	R version 4.0.3 (Bunny-Wunnies Freak out)	R Development Core team 2010	N/A	

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Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Software; Algorithm	Rstudio 1.3.1093 for macOS	R Development Core team 2010	RRID: SCR_000432	
Software; Algorithm	FUMA	PMID: 29184056	RRID: SCR_017521	
Software; Algorithm	TWAS-based gene set enrichment analysis (TWAS-GSEA, https://github.com/opain/TWAS-GSEA)	PMID: 31230729	N/A	