**Supplementary Note:**

**CONTENTS**

[Supplementary Note 2](#_wyaw5nqy9ft5)

[Detailed description of TWAS, FOCUS and isoTWAS eQTL analyses](#_fvpfikxioaj1) 2

[Full acknowledgements 3](#_ddw693tcj8qt)

[Funding Sources 9](#_flo8beeuh0ta)

[Consortium/Group authors and affiliations 18](#_f14iw14e1emd)

[Competing Interests 24](#_5qcnhrk1r567)

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# **Supplementary Note**

## Detailed description of TWAS, FOCUS and isoTWAS eQTL analyses

As additional eQTL integration analysis, transcriptome-wide association studies (TWAS) were performed using the FUSION software[1](https://paperpile.com/c/hv9UZw/A60Sz) with precomputed gene expression weights from the PsychENCODE dataset,[2](https://paperpile.com/c/hv9UZw/zNgRi) available online at <http://resource.psychencode.org/>. This data is derived from 1,321 postmortem human brain samples and comprises 14,750 genes with significant *cis*-SNP heritability. Monomorphic and rare (MAF < 0.01) variants were excluded from the HRC reference panels via filtering with Plink 2[3](https://paperpile.com/c/hv9UZw/jlXin). We also ran colocalization[4](https://paperpile.com/c/hv9UZw/9kk7o) tests on any gene-trait associations with a TWAS p-value less than 0.05 (--coloc\_P 0.05 flag in FUSION). After excluding the 119 MHC locus genes due to complex LD structure and genes that were skipped by FUSION due to technical reasons such as an insufficient overlap between eQTLs and GWAS SNPs, TWAS p-values were Bonferroni-corrected at a p-value threshold of 3 × 10−6, derived by taking the nominal alpha level of 0.05 and correcting for the 14,773 genes tested. Gene-trait associations with an adjusted p-value < 0.05 were filtered for COLOC posterior probability (PP4) >= 0.8 to obtain gene-trait associations with a shared causal variant between GWAS and eQTL effect.

We performed fine-mapping of TWAS results using FOCUS[5,6](https://paperpile.com/c/hv9UZw/zxUA4+x5m3Z) to model the correlation among the TWAS signals and prioritise the most likely causal gene(s) in each region. For the multi-ancestry summary statistics, we used the multi-ancestry LD blocks (37:EUR-EAS-AFR). We also applied the MA-FOCUS[5,6](https://paperpile.com/c/hv9UZw/zxUA4+x5m3Z) software implementing the joint analysis of each of the ancestry-specific summary statistics, again using the multi-ancestry LD blocks and ancestry-matched LD reference panels from the HRC, though for the gene expression weights we used the same PsychENCODE database (EUR-specific) for all ancestries. We then kept all associations that were in the credible set and had a posterior inclusion probability (PIP) >= 0.8.

We also applied the recently developed isoform-level TWAS method (isoTWAS)[7](https://paperpile.com/c/hv9UZw/bgQa), using precomputed weights per isoform derived from adult PsychENCODE data, as provided by the isoTWAS developers (<https://zenodo.org/record/6795947#.Y8mi2-zMLBI>). In total we tested the 7,530 genes, each with varying numbers of isoforms, that had positive heritability with a p-value < 0.05 within the PsychENCODE data. We subset the provided PsychENOCDE SNP-isoform weights and GWAS summary statistics SNPs to those that intersect with the HRC reference panel SNPs, then perform the isoTWAS burden test to generate z-scores for each SNP-isoform pair. We then performed probabilistic fine-mapping, filtering the resulting SNP-isoform statistics to those isoforms with a burden z-test p-value < 0.05 and a permutation p-value < 0.05. The permutation p-value was generated by performing 100 random shuffles of SNP-to-isoform weights to generate a null distribution. Credible sets were defined as SNPs passing these two p-value thresholds and having a posterior inclusion probability (PIP) >= 0.8.

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## Competing Interests

T.E.T., H.S. and K.S. are employed by deCODE Genetics/Amgen. E.A.S. is an employee of Regeneron Genetics Center and owns stocks of Regeneron Pharmaceutical Co. K-H.L. and X.W. are employed by 23andMe Inc.

Multiple additional authors work for pharmaceutical or biotechnology companies in a manner directly analogous to academic coauthors and collaborators.

A.H.Y. has given paid lectures and served on advisory boards relating to drugs used in affective and related disorders for several companies (AstraZeneca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allergan, Bionomics and Sumitomo Dainippon Pharma), was Lead Investigator for Embolden Study (AstraZeneca), BCI Neuroplasticity study and Aripiprazole Mania Study, and is an investigator for Janssen, Lundbeck, Livanova and Compass.

J.I.N. is an investigator for Janssen.

P.F.S. reports the following potentially competing financial interests: Neumora Therapeutics (advisory committee and shareholder).

G. Breen reports consultancy and speaker fees from Eli Lilly and Illumina and grant funding from Eli Lilly.

M. Landén has received speaker fees from Lundbeck.

O.A.A. has served as a speaker for Janssen, Lundbeck, and Sunovion and as a consultant for Cortechs.ai.

A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board; he is a member of the scientific advisory board of Human Longevity and the Mohn Medical Imaging and Visualization Center (Bergen, Norway); and he has received research funding from General Electric Healthcare.

E.V. has received grants and served as a consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Catalan Government (AGAUR and PERIS), the Spanish Ministry of Science, Innovation, and Universities (AES and CIBERSAM), the Seventh European Framework Programme and Horizon 2020 and the Stanley Medical Research Institute.

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A.S. is or has been a consultant/speaker for: Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier.

J.R.D. has served as an unpaid consultant to Myriad – Neuroscience (formerly Assurex Health) in 2017 and 2019 and owns stock in CVS Health.

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