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Verneri Anttila, Verneri Anttila, Brendan Bulik-Sullivan, Brendan Bulik-Sullivan ...+717 more authors

Institutions: Harvard University, Broad Institute, University College London, Cardiff University ...+266 more institutions

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Analysis of shared heritability in common disorders of the brain

Brainstorm Consortium

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RESEARCH ARTICLE SUMMARY

PSYCHIATRIC GENOMICS

Analysis of shared heritability in common disorders of the brain

The Brainstorm Consortium†

INTRODUCTION: Brain disorders may exhibit shared symptoms and substantial epidemiological comorbidity, inciting debate about their etiologic overlap. However, detailed study of phenotypes with different ages of onset, severity, and presentation poses a considerable challenge. Recently developed heritability methods allow us to accurately measure correlation of genome-wide common variant risk between two phenotypes from pools of different individuals and assess how connected they, or at least their genetic risks, are on the genomic level. We used genome-wide association data for 265,218 patients and 784,643 control participants, as well as 17 phenotypes from a total of 1,191,588 individuals, to quantify the degree of overlap for genetic risk factors of 25 common brain disorders.

RATIONALE: Over the past century, the classification of brain disorders has evolved to reflect the medical and scientific communities' assessments of the presumed root causes of clinical phenomena such as behavioral change, loss of motor function, or alterations of consciousness. Directly observable phenomena (such as the presence of emboli, protein tangles, or unusual electrical activity patterns) generally define and separate neurological disorders from

psychiatric disorders. Understanding the genetic underpinnings and categorical distinctions for brain disorders and related phenotypes may inform the search for their biological mechanisms.

RESULTS: Common variant risk for psychiatric disorders was shown to correlate significantly, especially among attention deficit hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder (MDD), and schizophrenia. By contrast, neurological disorders appear more distinct from one another and from the psychiatric disorders, except for migraine, which was significantly correlated to ADHD, MDD, and Tourette syndrome. We demonstrate that, in the general population, the personality trait neuroticism is significantly correlated with almost every psychiatric disorder and migraine. We also identify significant genetic sharing between disorders and early life cognitive measures (e.g., years of education and college attainment) in the general population, demonstrating positive correlation with several psychiatric disorders (e.g., anorexia nervosa and bipolar disorder) and negative correlation with several neurological phenotypes (e.g., Alzheimer's disease and ischemic stroke), even though the latter are considered to result from specific

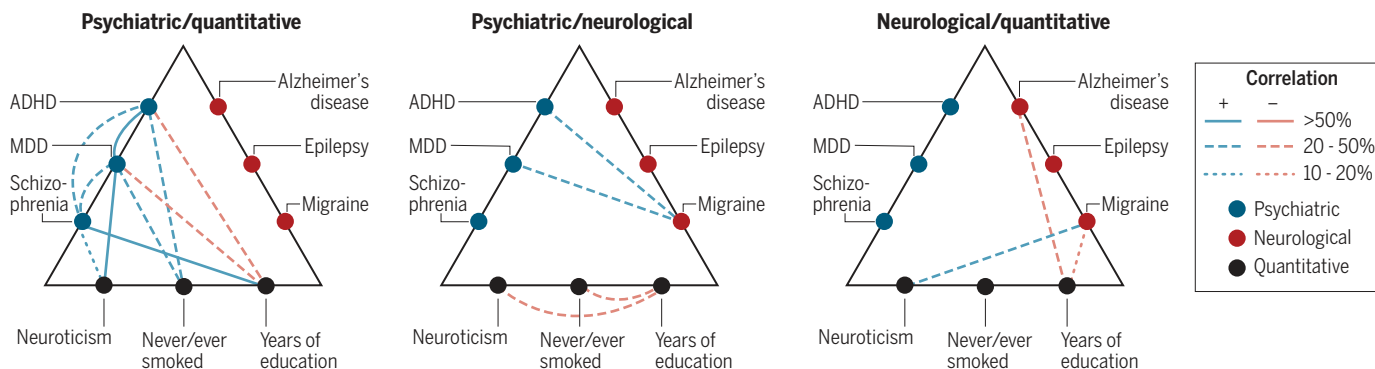
processes that occur later in life. Extensive simulations were also performed to inform how statistical power, diagnostic misclassification, and phenotypic heterogeneity influence genetic correlations.

CONCLUSION: The high degree of genetic correlation among many of the psychiatric disorders adds further evidence that their current clinical boundaries do not reflect distinct underlying pathogenic processes, at least on the genetic level. This suggests a deeply interconnected nature for psychiatric disorders, in contrast to neurological disorders, and underscores the need to refine psychiatric diagnostics. Genetically informed analyses may provide important “scaffolding” to support such restructuring of psychiatric nosology, which likely requires incorporating many levels of information. By contrast, we find limited evidence for widespread common genetic risk sharing among neurological disorders or across neurological and psychiatric disorders. We show that both psychiatric and neurological disorders have robust correlations with cognitive and personality measures. Further study is needed to evaluate whether overlapping genetic contributions to psychiatric pathology may influence treatment choices. Ultimately, such developments may pave the way toward reduced heterogeneity and improved diagnosis and treatment of psychiatric disorders. ■

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The list of author affiliations is available in the full article online.
†Corresponding authors: Verner Anttila (verneri.anttila@gmail.com); Aiden Corvin (acorvin@tcd.ie); Benjamin M. Neale (bneale@broadinstitute.org)
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Subsection of genetic risk correlations among brain disorders and quantitative phenotypes. Heritability analysis of brain disorders points to pervasive sharing of genetic risk among psychiatric disorders. These correlations are largely absent among neurological disorders but are present for both groups in relation to neurocognitive quantitative phenotypes. Only significant correlations shown. Line color and solidity indicate direction and magnitude of correlation, respectively.

RESEARCH ARTICLE

PSYCHIATRIC GENOMICS

Analysis of shared heritability in common disorders of the brain

The Brainstorm Consortium^{*†}

Disorders of the brain can exhibit considerable epidemiological comorbidity and often share symptoms, provoking debate about their etiologic overlap. We quantified the genetic sharing of 25 brain disorders from genome-wide association studies of 265,218 patients and 784,643 control participants and assessed their relationship to 17 phenotypes from 1,191,588 individuals. Psychiatric disorders share common variant risk, whereas neurological disorders appear more distinct from one another and from the psychiatric disorders. We also identified significant sharing between disorders and a number of brain phenotypes, including cognitive measures. Further, we conducted simulations to explore how statistical power, diagnostic misclassification, and phenotypic heterogeneity affect genetic correlations. These results highlight the importance of common genetic variation as a risk factor for brain disorders and the value of heritability-based methods in understanding their etiology.

The classification of brain disorders has evolved over the past century, reflecting the medical and scientific communities' assessments of the presumed root causes of clinical phenomena such as behavioral change, loss of motor function, spontaneous movements, or alterations of consciousness. Directly observable phenomena (such as the presence of emboli, protein tangles, or unusual electrical activity patterns) generally define and separate neurological disorders from psychiatric disorders (1). Understanding the genetic underpinnings and categorical distinctions between brain disorders may be helpful in informing the search for the biological pathways underlying their pathophysiology (2, 3).

Studies of twins and families have indicated that, in general, brain disorders (excepting those caused by trauma, infection, or cancer) show substantial heritability (4). Epidemiological and twin studies have explored patterns of phenotypic overlaps (5–7), and comorbidity has been reported for many pairs of disorders, including bipolar disorder and migraine (8), stroke and major depressive disorder (MDD) (9), epilepsy and autism spectrum disorder (ASD), and epilepsy and attention deficit hyperactivity disorder (ADHD) (10, 11). Furthermore, direct etiological links may also exist—e.g., mutations in the same ion channel genes confer pleiotropic risk for multiple distinct brain phenotypes (12–14). Genome-wide association studies (GWASs) have demonstrated that individual common risk variants can overlap across traditional diagnostic boundaries (15, 16) and that disorders such as schizophrenia, MDD, and bipolar disorder can have genetic correlations (17).

GWASs have also demonstrated that common genetic variation contributes to the heritability of brain disorders. Generally, this occurs via the combination of many common variants—examples include Alzheimer's disease (18), bipolar disorder (19), migraine (20), Parkinson's disease (21), and schizophrenia (22)—each with a small individual effect. In addition to locus discovery, the degree of distinctiveness (23) across neurological and psychiatric phenotypes can be evaluated with the introduction of novel heritability-based methods (24) and sufficiently large sample sizes for robust heritability analysis. These analyses can shed light on the nature of these diagnostic boundaries and explore the extent of shared common variant genetic influences.

Study design

The Brainstorm Consortium, a collaboration among GWAS meta-analysis consortia for 25 disorders (Table 1), was assembled to perform a comprehensive heritability and correlation analysis of brain disorders. We included meta-analyses of any common brain disorders for which we could identify a GWAS meta-analysis consortium of sufficient size for heritability analysis. The total study sample consists of 265,218 cases of different brain disorders and 784,643 controls (Table 1) and includes at least one representative of most ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems) blocks covering mental and behavioral disorders and diseases of the central nervous system (CNS). Also included are 1,191,588 samples for 13 behavioral-cognitive phenotypes ($n = 744,486$ individuals) traditionally viewed as brain-related, as well as 4 additional phenotypes ($n = 447,102$ individuals) selected to represent known, well-delineated etiological processes {immune disorders (Crohn's disease), vascular disease

(coronary artery disease), and anthropomorphic measures [height and body mass index (BMI)]} (Table 2).

GWAS summary statistics for the 42 disorders and phenotypes were centralized and underwent uniform quality control and processing (25). To avoid potential bias arising from ancestry differences, we used European-only meta-analyses for each disorder and generated new meta-analyses for those datasets where the original sample sets had diverse ancestries. Clinically relevant subtypes from three disorders (epilepsy, migraine, and ischemic stroke) were also included; in these cases, the subtype datasets are parts of the top-level dataset (Table 1).

We have developed a heritability estimation method, linkage disequilibrium score (LDSC) regression (24), which was used to calculate heritability estimates and correlations, as well as to estimate their statistical significance from block jackknife-based standard errors. More formally, we estimate the common variant heritability (h^2_g) of each disorder, defined as the proportion of phenotypic variance in the population that could theoretically be explained by an optimal linear predictor formed using the additive effects of all common (minor allele frequency >5%) autosomal single-nucleotide polymorphisms (SNPs). The genetic correlation for a pair of phenotypes is then defined as the correlation between their optimal genetic predictors. Heritability for binary disorders and phenotypes was transformed to the liability scale. We further performed a weighted least-squares regression analysis to evaluate whether differences relating to study makeup (such as sample size) were correlated with the magnitude of the correlation estimates. Finally, we performed a heritability partitioning analysis (25) by means of stratified LD score regression to examine whether the observed heritability for the disorders or phenotypes was enriched into any of the tissue-specific regulatory regions or functional category partitions of the genome, using 10 top-level tissue-type and 53 functional partitions from Finucane *et al.* (26). Simulated phenotype data was then generated under different scenarios by permuting 120,267 genotyped individuals from the UK Biobank (25) to evaluate statistical power and aid in interpreting the results (25).

Heritability estimates and their error sources

We observed a similar range of heritability estimates among the disorders and the behavioral-cognitive phenotypes (fig. S1, A and B, and table S1 and S2), roughly in line with previously reported estimates from smaller datasets (table S3). Three ischemic stroke subtypes (cardioembolic, large-vessel disease, and small-vessel disease) as well as the “agreeableness” personality measure from the NEO Five-Factor Inventory (27) had insufficient evidence of additive heritability for robust analysis and thus were excluded from further examination (25). The only observed correlation between heritability estimates and factors relating to study makeup (table S4 and fig. S1,

^{*}All authors with their affiliations are listed at the end of this paper.

[†]Collaborators and affiliations are listed in the supplementary materials.

Table 1. Brain disorder phenotypes used in the Brainstorm project.

Indented phenotypes are part of a larger whole (e.g., the epilepsy study contains the samples from both focal epilepsy and generalized epilepsy). “Anxiety disorders” refers to a meta-analysis of five subtypes (generalized anxiety disorder, panic disorder, social phobia, agoraphobia, and specific phobias). References are listed in table S1 and data availability in table S13. PGC-ADD2, Psychiatric Genomics Consortium (PGC) Attention Deficit Disorder Working Group; PGC-ED, PGC Eating Disorder Working Group; ANGST, Anxiety Neuro Genetics Study; PGC-AUT, PGC Autism Spectrum Disorder Working Group; PGC-BIP2, PGC Bipolar Disorder Working Group;

PGC-MDD2, PGC Major Depressive Disorder Working Group; PGC-OCDS, PGC Obsessive Compulsive Disorder and Tourette Syndrome Working Group; PGC-PTSD, PGC Posttraumatic Stress Disorder Working Group; PGC-SCZ2, PGC Schizophrenia Working Group; IGAP, International Genomics of Alzheimer’s Project; ILAE, International League Against Epilepsy Consortium on Complex Epilepsies; ISGC, International Stroke Genetics Consortium; METASTROKE, a consortium of the ISGC; IHGC, International Headache Genetics Consortium; IMSGC, International Multiple Sclerosis Genetics Consortium; IPDGC, International Parkinson’s Disease Genomics Consortium. “ indicates same as above.

Psychiatric disorders				Neurological disorders			
Disorder	Source	Cases	Controls	Disorder	Source	Cases	Controls
Attention deficit hyperactivity disorder	PGC-ADD2	12,645	84,435	Alzheimer’s disease	IGAP	17,008	37,154
Anorexia nervosa	PGC-ED	3495	10,982	Epilepsy	ILAE	7779	20,439
Anxiety disorders	ANGST	5761	11,765	Focal epilepsy	"	4601*	17,985*
Autism spectrum disorder	PGC-AUT	6197	7377	Generalized epilepsy	"	2525*	16,244*
Bipolar disorder	PGC-BIP2	20,352	31,358	Intracerebral hemorrhage	ISGC	1545	1481
Major depressive disorder	PGC-MDD2	66,358	153,234	Ischemic stroke	METASTROKE	10,307	19,326
Obsessive-compulsive disorder	PGC-OCDS	2936	7279	Cardioembolic stroke	"	1859*	17,708*
Posttraumatic stress disorder	PGC-PTSD	2424	7113	Early onset stroke	"	3274*	11,012*
Schizophrenia	PGC-SCZ2	33,640	43,456	Large-vessel disease	"	1817*	17,708*
Tourette syndrome	PGC-OCDS	4220	8994	Small-vessel disease	"	1349*	17,708*
				Migraine	IHGC	59,673	316,078
				Migraine with aura	"	6332*	142,817*
				Migraine without aura	"	8348*	136,758*
				Multiple sclerosis	IMSGC	5545	12,153
				Parkinson’s disease	IPDGC	5333	12,019
Total psychiatric		158,028	365,993	Total neurologic		107,190	418,650

*Sample count for a phenotype that is part of a larger group.

C to F) was a modest correlation between age of disorder onset and heritability, suggesting that early onset brain disorders tend to be more heritable. Because some of our interpretation of the results depends on lack of observed correlation, we explored the behavior of observed correlation versus power (fig. S2A), standard errors (fig. S2B), and the individual results (fig. S2, C and D) to identify where we can be reasonably robust in claiming lack of correlation.

The common variant heritability estimates for the psychiatric and neurological disorders were generally somewhat lower than previously reported estimates from common variants (table S5). When comparing estimates reported here with those previously reported in studies with smaller sample sizes (28), a similar pattern was observed for the behavioral-cognitive traits, with the exception of “openness,” “neuroticism,” and “never/ever smoked” (defined as those who have never smoked versus those who have smoked at some point) suggesting that some attenuation in heritability is observed when moving to larger sample sizes. Measures related to cognitive ability, such as childhood cognitive performance [heritability estimate of 0.19 (SE: 0.03)] and years of education [heritability estimate of 0.30 (SE: 0.01)], yielded estimates that were more consistent with previous estimates of the herita-

bility of intelligence (29, 30), suggesting that the cognitive measures may be less prone to phenotypic measurement error and/or have a higher heritability overall than the personality measures.

These heritability estimates should be interpreted somewhat cautiously, as they reflect the phenotype ascertained in each study and will be deflated in the presence of diagnostic heterogeneity, ascertainment errors, or unusual contributions of high-impact rare variants. To evaluate potential sources of these differences, we explored three approaches (25): evaluating the differences in real data, simulation work (table S5), and quantifying the magnitude of effect for potentially implied misclassification (table S6).

In comparison with heritability estimates obtained using twin and family data, the more diverse selection and survival biases in the underlying data may attenuate the heritability estimates and correlations, as may increased within-disorder heterogeneity introduced by the larger meta-analyses. A related explanation for the lower estimates of heritability may be that increasing sample sizes have led to expanded inclusion criteria, meaning that less severely affected cases with a lower overall burden of risk factors (both genetic and environmental) might be included, which in turn would attenuate estimates of heritability. However, the successful identification

of genome-wide significant loci suggests that these larger samples are nevertheless very useful for genetic studies, and the simulation results suggest that this has, at most, a limited effect on estimated genetic correlations (fig. S9). Even so, some of the pairs of phenotypes included here lack sufficient power for robust estimation of genetic correlations. Moreover, our analyses examine only the properties of common variant contributions; extending these analyses to include the effects of rare variants may further inform the extent of genetic overlap. For example, epilepsy and ASD show substantial overlap in genetic risk from de novo loss-of-function mutations (37), in contrast to the limited common variant sharing observed in this study. This may suggest that the rare and common variant contributions to genetic overlap may behave differently and that incorporating the two variant classes into a single analysis may provide further insight into brain disorder pathogenesis.

To address the possibility of methodological differences contributing to the differences in the estimates, and although LDSC and GREML have previously been shown to yield similar estimates from the same data (24), we performed our own comparison in Alzheimer’s disease data (32) (selected on the basis of data availability). In Alzheimer’s disease, the previously published heritability estimate [0.24 (SE: 0.03)] is significantly different

Table 2. Behavioral-cognitive and additional phenotypes used in the study. Indented phenotypes are part of a larger whole (e.g., samples in the college attainment analysis are a subset of those in the analysis for years of education). (d), dichotomous phenotype; (q), quantitative phenotype. References and phenotype definitions are listed in table S2, and data availability in table S13. SSGAC, Social Science Genetic Association Consortium; CTG, Complex Trait Genetics Lab; GPC, Genetics of Personality Consortium; TAG, Tobacco and Genetics Consortium; GIANT, Genetic Investigation of ANthropometric Traits consortium; Cardiogram, CARDIoGRAMplusC4D Consortium; IIBDGC, International Inflammatory Bowel Disease Genetics Consortium.

Phenotype	Source	Samples
Behavioral-cognitive phenotypes		
Cognitive		
Years of education (q)	SSGAC	293,723
College attainment (d)	"	120,917*
Cognitive performance (q)	"	17,989*
Intelligence (d)	CTG	78,308
Personality measures		
Subjective well-being	SSGAC	298,420
Depressive symptoms	"	161,460*
Neuroticism (q)	"	170,911*
Extraversion (q)	GPC	63,030*
Agreeableness (q)	"	17,375*
Conscientiousness (q)	"	17,375*
Openness (q)	"	17,375*
Smoking-related		
Never/ever smoked (d)	TAG	74,035
Cigarettes per day (q)	TAG	38,617*
Additional phenotypes		
BMI (q)	GIANT	339,224
Height (q)	"	253,288*
Coronary artery disease (d)	Cardiogram	86,995
Crohn's disease	IIBDGC	20,883
Total		1,124,048

*Sample counts represent overlap with preceding dataset.

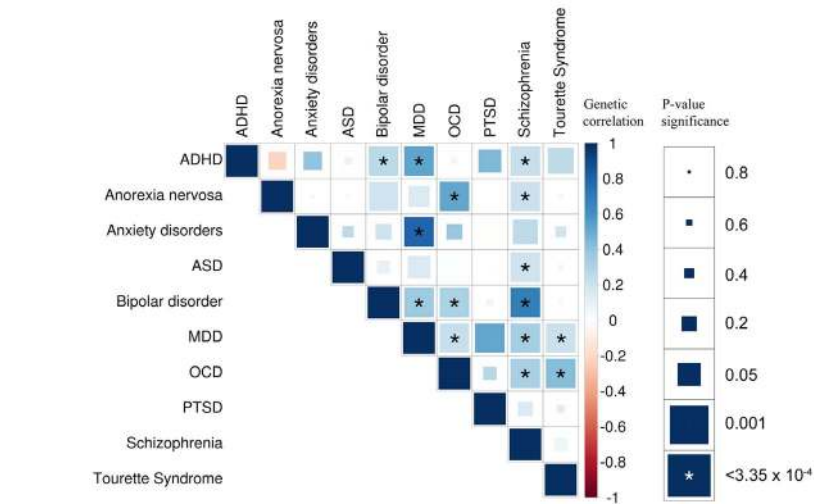


Fig. 1. Genetic correlations across psychiatric phenotypes. The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

from the estimate in the current study [0.13 (SE: 0.02)]. These differences may reflect implicit heterogeneity in a much larger case collection used in the current study (effective sample size 10,494 versus 46,669) and the potential reasons listed above, but they could also be due to methodological variability (most of the previous approximations listed in table S3 are estimated with a different methodology). To evaluate this, we applied the same analytical process used in this paper to the summary statistics of the GERAD (Genetic and Environmental Risk in Alzheimer's Disease) cohort (3941 cases and 7848 controls) from the Alzheimer's disease meta-analysis, where the previous heritability estimate was calculated. There, we obtained a heritability estimate of 0.25 (SE: 0.04), which agrees closely with the published estimate of 0.24 (SE: 0.03), suggesting that the different approximations may reflect differences between datasets rather than methodological variability.

Correlations among brain disorders

We observed widespread sharing across psychiatric disorders (Fig. 1 and fig. S3) by expanding the number of brain disorder pairs studied beyond those previously reported (17), but similar sharing was not observed among neurological disorders. Among the psychiatric disorders, schizophrenia showed significant genetic correlation with most of the psychiatric disorders, whereas MDD was positively (though not necessarily significantly) correlated with every other disorder tested. Further, schizophrenia, bipolar disorder, anxiety disorders, MDD, and ADHD each showed a high degree of correlation to the four others [average genetic correlation (r_g) = 0.40] (table S7A). Anorexia nervosa, obsessive-compulsive disorder (OCD), and schizophrenia also demonstrated significant sharing among themselves (Fig. 1), as did Tourette syndrome (TS), OCD, and MDD, as well as ASD and schizophrenia. Post-traumatic stress disorder (PTSD) showed no significant correlation with any of the other psychiatric phenotypes (though some correlation to ADHD and MDD was observed), and both ASD and TS appear to potentially be more distinct from the other psychiatric disorders. The modest power of the ASD, PTSD, and TS meta-analyses, however, limits the strength of this conclusion (fig. S2C).

Neurological disorders showed a more limited extent of genetic correlation than that of the psychiatric disorders (Fig. 2, fig. S4, and table S7A), suggesting greater diagnostic specificity and/or more distinct etiologies. Parkinson's disease, Alzheimer's disease, generalized epilepsy, and multiple sclerosis (MS) showed little to no correlation with other brain disorders. The highest degree of genetic correlation among the neurological disorders was observed for focal epilepsy (average r_g = 0.46, excluding the other epilepsy datasets), though none of the correlations were significant, reflecting the relatively modest power of the current focal epilepsy meta-analysis (fig. S2C). However, the modest heritability and the broad pattern of sharing observed for focal epilepsy may be consistent with heterogeneity and

potentially even diagnostic misclassification across a range of neurological conditions.

In the cross-category correlation analysis, the observed pattern is consistent with limited sharing across the included neurological and psychiatric disorders (Fig. 3; average $r_g = 0.03$). The only significant cross-category correlations were with migraine, suggesting that this disorder may share some of its genetic architecture with psychiatric disorders: migraine and ADHD ($r_g = 0.26$, $P = 8.81 \times 10^{-6}$), migraine and TS ($r_g = 0.19$, $P = 1.80 \times 10^{-5}$), and migraine and MDD ($r_g = 0.32$, $P = 1.42 \times 10^{-22}$ for all migraine; $r_g = 0.23$, $P = 5.23 \times 10^{-5}$ for migraine without aura; $r_g = 0.28$, $P = 1.00 \times 10^{-4}$ for migraine with aura).

We observed several significant genetic correlations between the behavioral-cognitive or additional phenotypes and brain disorders (Fig. 4 and table S7B). Results for cognitive traits were dichotomous among psychiatric phenotypes (fig. S5A), with ADHD, anxiety disorders, MDD, and TS showing negative correlations to the cognitive measures and anorexia nervosa, ASD, bipolar disorder, and OCD showing positive correlations. Schizophrenia showed more mixed results, with a significantly negative correlation to intelligence but a positive correlation to years of education. Among neurological phenotypes (fig. S5B), the correlations were either negative or null, with Alzheimer's disease, epilepsy, intracerebral hemorrhage (ICH), ischemic stroke, early onset stroke, and migraine showing significantly negative correlations. Correlations between college attainment and years of education with bipolar disorder (24), Alzheimer's disease, and schizophrenia have been previously reported (33).

Among the personality and symptom measures, significant positive correlations were observed between neuroticism and anorexia nervosa, anxiety disorders, migraine, migraine without aura, MDD, OCD, schizophrenia, and TS [fig. S6, A and B; replicating previously reported correlations with MDD and schizophrenia (34)]; between depressive symptoms and ADHD, anxiety disorder, bipolar disorder, MDD, and schizophrenia; and between subjective well-being and anxiety disorder, bipolar disorder, and MDD. For smoking-related measures, the only significant genetic correlations were between never/ever smoked and MDD ($r_g = 0.33$, $P = 3.10 \times 10^{-11}$) as well as ADHD ($r_g = 0.37$, $P = 3.15 \times 10^{-6}$).

Among the additional phenotypes, the two examples of disorders with well-defined etiologies had different results. Crohn's disease, representing immunological pathophysiology, showed no correlation with any of the study phenotypes, whereas the phenotype representing vascular pathophysiology (coronary artery disease) showed significant correlation to MDD ($r_g = 0.19$, $P = 8.71 \times 10^{-5}$) as well as the two stroke-related phenotypes ($r_g = 0.69$, $P = 2.47 \times 10^{-6}$ to ischemic stroke and $r_g = 0.86$, $P = 2.26 \times 10^{-5}$ to early onset stroke), suggesting shared genetic effects across these phenotypes. Significant correlations were also observed for BMI, which was positively correlated with ADHD and MDD, and negatively correlated with anorexia nervosa [as previous-

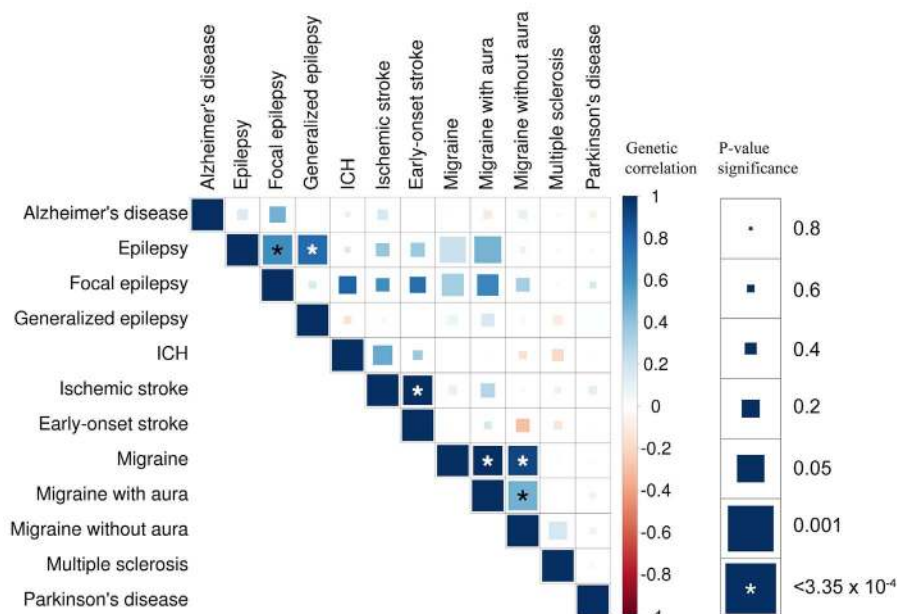


Fig. 2. Genetic correlations across neurological phenotypes. The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction. Some phenotypes have substantial overlaps (Table 1)—for instance, all cases of generalized epilepsy are also cases of epilepsy. Asterisks indicate significant genetic correlation after multiple testing correction.

ly reported with a different dataset (24)] and schizophrenia.

Our enrichment analysis (fig. S7 and tables S8 to S12) demonstrated significant heritability enrichments between the CNS and generalized epilepsy, MDD, TS, college attainment, intelligence, neuroticism, and the never/ever smoked trait; between depressive symptoms and adrenal/pancreatic cells and tissues; as well as between hematopoietic cells (including immune system cells) and MS (fig. S7, A and B, and tables S8 and S9). We replicated the reported (CNS) enrichment for schizophrenia, bipolar disorder, and years of education (tables S8 and S9) and observed the reported enrichments for BMI (CNS), years of education (CNS), height (connective tissues and bone, cardiovascular system, and other), and Crohn's disease (hematopoietic cells) from the same datasets (fig. S7, C and D) (26). The psychiatric disorders with large numbers of identified GWAS loci (bipolar disorder, MDD, and schizophrenia) and migraine, which was the only cross-correlated neurological disorder, show enrichment to conserved regions (tables S10 and S12), whereas the other neurological disorders with similar numbers of loci (MS, Alzheimer's disease, and Parkinson's disease) do not (fig. S7, A and B). Enrichment to conserved regions was also observed for neuroticism, intelligence, and college attainment and to H3K9ac peaks for BMI (tables S11 and S12).

Discussion

By integrating and analyzing the genome-wide association summary statistic data from consor-

tia of 25 brain disorders, we find that psychiatric disorders broadly share a considerable portion of their common variant genetic risk, especially across schizophrenia, MDD, bipolar disorder, anxiety disorder, and ADHD, whereas neurological disorders are more genetically distinct. Across categories, psychiatric and neurologic disorders share relatively little common genetic risk, suggesting that multiple different and largely independently regulated etiological pathways may give rise to similar clinical manifestations [e.g., psychosis, which manifests in both schizophrenia (35) and Alzheimer's disease (36)]. Except for migraine, which appears to share some genetic architecture with psychiatric disorders, the existing clinical delineation between neurology and psychiatry is corroborated at the level of common variant risk for the studied disorders.

On the basis of the observed results, we performed some exploratory analyses to address concerns about diagnostic overlap and misclassification, which are particularly relevant to psychiatric disorders, owing to their spectral nature. Given that the broad and continuous nature of psychiatric disorder spectra has long been clinically recognized (37–39) and that patients can, in small numbers, progress from one diagnosis to another (40), we evaluated to what extent this kind of diagnostic overlap could explain the observed correlations. Genetic correlation could arise if, for example, patients progress through multiple diagnoses over their lifetime or if some specific diagnostic boundaries between phenotype pairs are particularly porous to misclassification (table S5). Although, for instance, migraine and

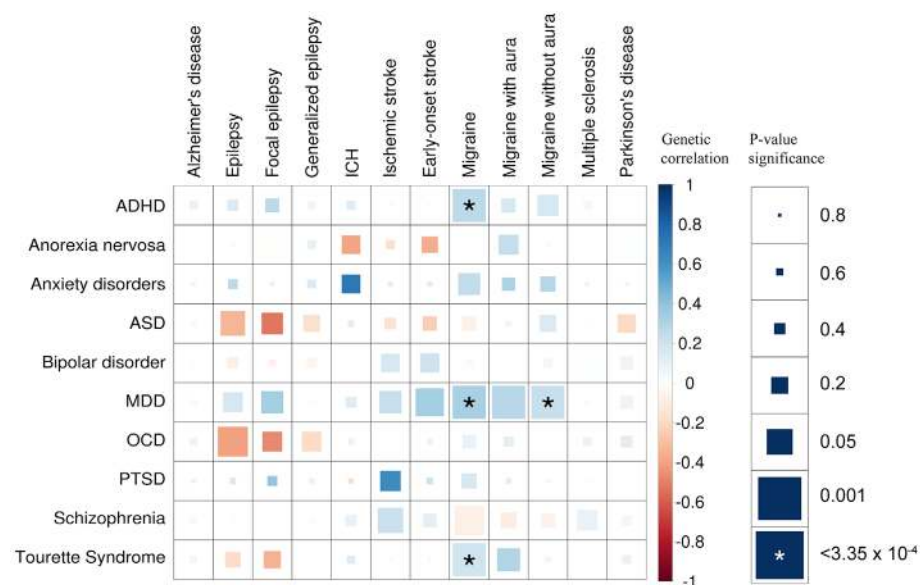


Fig. 3. Genetic correlations across neurological and psychiatric phenotypes. The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

schizophrenia are unlikely to be mistaken for one another; there may be more substantial misclassification between particular psychiatric disorders, consistent with the clinical controversies in classification. Previous work (41) suggests that substantial misclassification (on the order of 15 to 30%, depending on whether it is uni- or bidirectional) is required to introduce false levels of genetic correlation. We found that the observed levels of correlation are unlikely to appear in the absence of underlying genetic correlation (table S6), as it is apparent that a very high degree of misclassification (up to 79%) would be required to produce the observed correlations in the absence of any true genetic correlation and that reasonably expected misclassification would have limited impact on the observed r_g (fig. S8). Therefore, these results suggest true sharing of a substantial fraction of the common variant genetic architecture among psychiatric disorders as well as between behavioral-cognitive measures and brain disorders. We also performed large-scale simulations to explore the effect of sample size, polygenicity, and degree of correlation on power to detect significant correlations. First, we established that the observed heritability of the simulated misclassified traits in the UK Biobank data behaves as would be theoretically expected (fig. S9A) and that the effects on observed correlation (fig. S9, B and C) are in line with the estimates from family data (41). Reasonably low levels of misclassification or changes to the exact level of heritability appear unlikely to induce significant correlations, as observed in the power analysis (fig. S10), though a lower observed heritability caused by substantial misclassification (fig. S9A) will decrease the power to estimate true genetic overlap.

The high degree of genetic correlation among the psychiatric disorders adds further evidence that current clinical diagnostics do not reflect specific genetic etiology for these disorders and that genetic risk factors for psychiatric disorders do not respect clinical diagnostic boundaries. Rather, this finding suggests a more interconnected genetic etiology, in contrast to that of neurological disorders, and underscores the need to refine psychiatric diagnostics. This study may provide important “scaffolding” to support a framework for investigating mental disorders, incorporating many levels of information to understand basic dimensions of brain function.

The observed positive genetic correlations are consistent with a few hypothetical scenarios. For example, this observation may reflect the existence of some portion of common genetic risk factors conferring risks for multiple psychiatric disorders and where other distinct additional factors, both genetic and nongenetic, contribute to the eventual clinical presentation. The presence of significant genetic correlation may also reflect the phenotypic overlap between any two disorders; for example, the sharing between schizophrenia and ADHD might reflect underlying difficulties in executive functioning, which are well-established in both disorders (42), and that the shared risk arises from a partial capture of its shared genetic component. Similarly, we might speculate that a shared mechanism underlying cognitive biases may extend from overvalued ideas to delusions (ranging from anorexia nervosa and OCD to schizophrenia), and that this heritable intermediate trait confers pleiotropic risk to multiple outcomes. This kind of latent variable could give rise to the observed genetic

correlation between disorders, owing to the shared portion of variation affecting that variable. Though a combination of these is likely, more genome-wide significant loci are needed to evaluate these overlaps at the locus level.

Conversely, the low correlations observed across neurological disorders suggest that the current classification reflects relatively specific genetic etiologies, although the limited sample size for some of these disorders and the lack of inclusion of disorders conceived as “circuit-based” (e.g., restless legs syndrome, sleep disorders, and possibly essential tremor) constrain the full generalizability of this conclusion. On the basis of our observations, degenerative disorders (such as Alzheimer’s and Parkinson’s diseases) would therefore not be expected to share their polygenic risk profiles with a neuroimmunological disorder (such as MS) or neurovascular disorder (such as ischemic stroke). Similarly, we see limited evidence for the reported comorbidity between migraine with aura and ischemic stroke (43) ($r_g = 0.29$, $P = 0.099$); however, the standard errors of this comparison are too high to draw strong conclusions. At the disorder subtype level, migraine with and without aura ($r_g = 0.48$, $P = 1.79 \times 10^{-5}$) show substantial genetic correlation, whereas focal and generalized epilepsy ($r_g = 0.16$, $P = 0.388$) show much less.

The few significant correlations across neurology and psychiatry—namely, between migraine and ADHD, MDD, and TS—suggest modest shared etiological overlap across the neurology-psychiatry distinction. The comorbidity of migraine with MDD, TS, and ADHD has been previously reported in epidemiological studies (44–47), whereas the previously reported comorbidity between migraine and bipolar disorder seen in epidemiological studies (48) was not reflected in our estimate of genetic correlation ($r_g = -0.03$, $P = 0.406$).

Several phenotypes show only very low-level correlations with any of the other disorders and phenotypes that we studied, despite large sample size and robust evidence for heritability, which suggests that their common variant genetic risk may largely be unique. Alzheimer’s disease, Parkinson’s disease, and MS show extremely limited sharing with the other phenotypes and with each other. Neuroinflammation has been implicated in the pathophysiology of each of these conditions (49–51), as it has for migraine (52) and many psychiatric conditions, including schizophrenia (53), but no considerable shared heritability was observed with either of those conditions nor with Crohn’s disease, nor did we observe enrichment for immune-related tissues in the functional partitioning (fig. S7) as observed for Crohn’s disease. Although this does not preclude the sharing of individual neuroinflammatory mechanisms in these disorders, the large-scale lack of shared common variant genetic influences supports the distinctiveness of disorder etiology. Further, we observed significant enrichment of heritability for immunological cells and tissues in MS only, showing that inflammation-specific regulatory marks in the genome do not show overall enrichment for common variant risk for either Alzheimer’s or Parkinson’s diseases [though this does not preclude

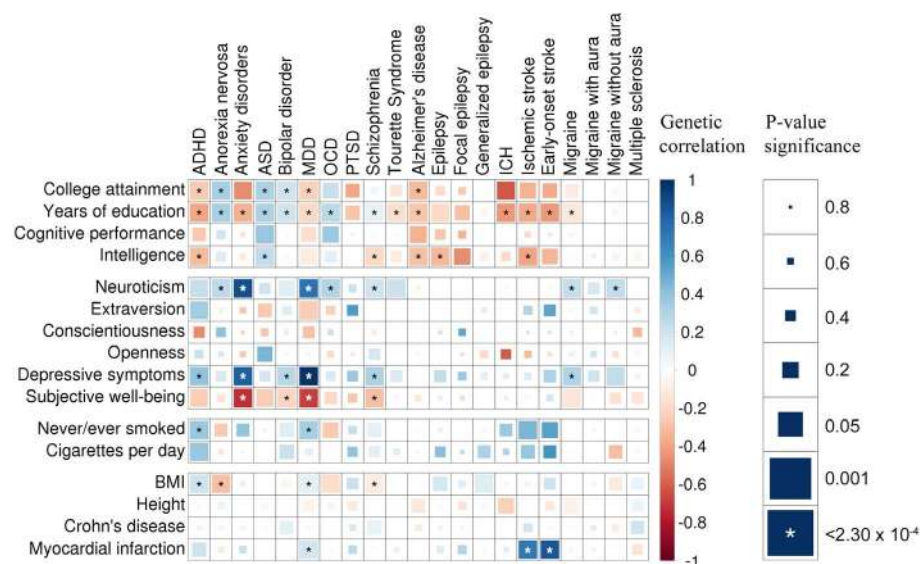


Fig. 4. Genetic correlations across brain disorders and behavioral-cognitive phenotypes. The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

the effects of specific, not particularly polygenic neuroinflammatory mechanisms [54]. Among psychiatric disorders, ASD and TS showed a similar absence of correlation with other disorders, although this may reflect small sample sizes.

Analysis of the Big Five personality measures suggest that the current sample sizes may be large enough for correlation testing. Neuroticism, which has by far the largest sample size, shows several significant correlations. Most significant of these was to MDD ($r_g = 0.737$, $P = 5.04 \times 10^{-96}$), providing evidence for the link between these phenotypes, as reported for polygenic risk scores [55] and twin studies [56, 57]; as well as other psychiatric disorders (Fig. 4 and table S7B). The correlation between MDD and anxiety disorders, with a similar pattern of correlation and the dimensional measures of depressive symptoms, subjective well-being, and neuroticism suggests that they all tag a similar underlying etiology. The significant correlation between coronary artery disease and MDD supports the link between MDD and CAD [58], and the observed correlation between ADHD and smoking initiation ($r_g = 0.374$, $P = 3.15 \times 10^{-6}$) is consistent with the epidemiological evidence of overlap [59] and findings from twin studies [60].

For the neurological disorders, five (Alzheimer's disease, intracerebral hemorrhage, ischemic and early onset stroke, and migraine) showed significant negative genetic correlation to the cognitive measures, whereas two (epilepsy and focal epilepsy) showed moderate negative genetic correlation (fig. S5). For Alzheimer's disease, poor cognitive performance in early life has been linked to increased risk for developing the disorder [61], but to our knowledge no such connection has been reported for other phenotypes.

Among the psychiatric disorders, ADHD, anxiety disorders, and MDD show a significant negative correlation to cognitive and education attainment measures, whereas the remaining five of the eight psychiatric disorders (anorexia nervosa, ASD, bipolar disorder, OCD, and schizophrenia) showed significant positive genetic correlation with one or more cognitive measures. These results suggest the existence of a link between cognitive performance in early life and the genetic risk for both psychiatric and neurological brain disorders. The basis of the genetic correlations between education, cognition, and brain disorders may have a variety of root causes, including indexing performance differences on the basis of behavioral dysregulation (e.g., ADHD relating to attentional problems during cognitive tests), or may reflect ascertainment biases in certain disorders conditional on impaired cognition (e.g., individuals with lower cognitive reserve being more rapidly identified for Alzheimer's disease), but the results could also suggest a direct link between the underlying etiologies.

BMI shows significant positive genetic correlation to ADHD, consistent with a meta-analysis linking ADHD to obesity [62], and negative genetic correlation with anorexia nervosa, OCD, and schizophrenia. This is consistent with evidence for enrichment of BMI heritability in CNS tissues [26] that suggest neuronal involvement [63]; this may also provide a partial genetic explanation for lower BMI in anorexia nervosa patients even after recovery [64]. Given that no strong correlations were observed between BMI and any of the neurological phenotypes, BMI's brain-specific genetic architecture may be more closely related to behavioral phenotypes. Ischemic stroke and BMI show surprisingly little genetic correlation in this

analysis ($r_g = 0.07$, $P = 0.26$), suggesting that although BMI is a risk factor for stroke [65], there is little evidence for shared common genetic effects. These analyses also suggest that the reported reduced rates of cardiovascular disease in individuals with histories of anorexia nervosa [66, 67] are more likely due to BMI-related secondary effects. The limited evidence of genetic correlation of anorexia nervosa with intracerebral hemorrhage, ischemic stroke, early onset stroke, and coronary artery disease suggests that any lower cardiovascular mortality is more likely due to direct BMI-related effects rather than to genetic risk variants.

The genetic correlation results presented here indicate that the clinical boundaries for the studied psychiatric phenotypes do not reflect distinct underlying pathogenic processes. This suggests that genetically informed analyses may provide a basis for restructuring of psychiatric nosology, consistent with twin- and family-based results. In contrast, neurological disorders show greater genetic specificity, and although it is important to emphasize that while some brain disorders are underrepresented here, our results demonstrate the limited evidence for widespread common genetic risk sharing between psychiatric and neurological disorders. However, we provide strong evidence that both psychiatric and neurological disorders show robust correlations with cognitive and personality measures, indicating avenues for follow-up studies. Further analysis is needed to evaluate whether overlapping genetic contributions to psychiatric pathology may influence treatment choices. Ultimately, such developments are promising steps toward reducing diagnostic heterogeneity and eventually improving the diagnostics and treatment of psychiatric disorders.

Materials and methods summary

We collected GWAS meta-analysis summary statistics for 25 brain disorders and 17 other phenotypes from various consortia and, where necessary, generated new, non-sex-stratified European cohort-only versions of the meta-analyses [25]. All datasets underwent uniform quality control [25]. For each trait, by using the LDSC framework [24], the total additive common SNP heritability present in the summary statistics (h^2_g) was estimated by regressing the association χ^2 statistic of a SNP against the total amount of common genetic variation tagged by that SNP, for all SNPs. Genetic correlations (r_g ; i.e., the genome-wide average shared genetic risk) for pairs of phenotypes were estimated by regressing the product of z -scores, rather than the χ^2 statistic, for each phenotype and for each SNP. Significance was assessed by Bonferroni multiple testing correction via estimating the number of independent brain disorder phenotypes via matrix decomposition [25]. Functional and partitioning analyses for the GWAS datasets were also performed using LDSC regression. Power analyses and simulation work to aid in interpretation of the results were conducted using genotype data from the UK Biobank resource [25].

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The Brainstorm Consortium

Veneri Anttila^{1,2,3*}, Brendan Bulik-Sullivan^{1,3}, Hilary K. Finucane^{2,3,4,5}, Raymond K. Walters^{1,2,3}, Jose Bras^{6,7}, Laramie Duncan^{1,2,3,8}, Valentina Escott-Price^{9,10}, Guido J. Falcone^{11,12,13}, Padraig Gormley^{1,2,3,11}, Rainer Malik¹⁴, Nikolaos A. Patsopoulos^{3,15}, Stephan Ripke^{12,3,16}, Zhi Wei¹⁷, Dongmei Yu^{2,11}, Phil H. Lee^{2,11}, Patrick Turley^{1,3}, Benjamin Grenier-Boley^{18,19,20}, Vincent Chouraki^{18,19,20,21}, Yoichiro Kamatani^{22,23}, Claudine Berr^{24,25,26}, Luc Letenneur^{27,28}, Didier Hanquinn^{29,30}, Philippe Amouyel³¹, Anne Boland³¹, Jean-François Deleuze³¹, Emmanuelle Duron^{32,33}, Badri N. Vardarajan³⁴, Christiane Reitz³⁵, Alison M. Goate³⁶, Matthew J. Huentelman³⁷, M. Ilyas Kambah³⁸, Eric B. Larson³⁹, Ekaterina Rogavaev⁴⁰, Peter St. George-Hyslop^{41,42}, Hakon Hakonarson^{43,44,45}, Walter A. Kukull⁴⁶, Lindsay A. Farrer⁴⁷, Lisa L. Barnes^{48,49,50}, Thomas G. Beach⁵¹, F. Yesim Demirci³⁸, Elizabeth Head⁵², Christine M. Hulette⁵³, Gregory A. Jicha⁵⁴, John S.K. Kauwe⁵⁵, Jeffrey A. Kaye⁵⁶, James B. Leverenz⁵⁷, Allan I. Levey⁵⁸, Andrew P. Lieberman⁵⁹, Vernon S. Pankratz⁶⁰, Wayne W. Poon⁶¹, Joseph F. Quinn^{62,63}, Andrew J. Saykin⁶⁴, Lon S. Schneider⁶⁵, Amanda G. Smith⁶⁶, Joshua A. Sonnen^{67,68}, Robert A. Stern⁶⁹, Viannina M. Van Deerlin⁷⁰, Linda J. Van Eldik⁵², Denise Harold⁷¹, Giancarlo Russo⁷², David C. Rubinstein^{73,74}, Anthony Bayer⁷⁵, Magda Toloski^{76,77}, Petra Proitsch⁷⁸, Nick C. Fox^{79,80}, Harald Hampel^{80,81,82,83}, Michael J. Owen^{84,85}, Simon Mead⁸⁶, Peter Passmore⁸⁷, Kevin Morgan⁸⁸, Markus M. Nöthen^{89,90}, Martin Rosser⁹¹, Michelle K. Lupton^{92,93}, Per Hoffmann^{90,94,95}, Johannes Kornhuber⁹⁶, Brian Lawlor⁹⁷, Andrew McQuillin⁹⁸, Ammar Al-Chalabi⁹⁹, Joshua C. Bis¹⁰⁰, Agustín Ruiz^{102,103}, Mercè Boada¹⁰⁴, Sudha Seshadri^{104,105,106}, Alexa Beiser^{107,108,109}, Kenneth Rice¹⁰⁹, Sven J. van der Lee¹¹⁰, Philip L. De Jager¹¹¹, Daniel H. Geschwind¹¹², Matthias Riemschneider¹¹⁵, Steffi Riedel-Heller¹¹⁶, Jerome I. Rotter¹¹⁷, Gerhard Ramsay¹¹⁸, Bradley T. Hyman^{12,13}, Carlos Cruchaga¹²⁰, Montserrat Alegret¹⁰², Bendik Winsvold^{121,122}, Priit Palta¹²³, Kai-How Farh^{124,125}, Ester Cuenca-Leon^{11,3,2}, Nicholas Furlotte¹²⁶, Tobias Kurth¹²⁷, Lannie Ligthart¹²⁸, Gisela M. Terwindt¹²⁹, Tobias Freilinger¹³⁰, Caroline Ran¹³², Scott D. Gordon⁹², Guntram Bork¹³³, Hieab H.H. Adams^{130,134}, Terho Lehtimäki¹³⁵, Juho Wedenoja^{136,137}, Julie E. Buring¹³⁸, Markus Schürks¹³⁹, Maria Hrafnisdóttir¹⁴⁰, Jouke-Jan Hottenga^{128,141}, Brenda Penninx¹⁴²

Ville Arto¹⁴³, Mari Kaunisto¹²³, Salli Vepsäläinen¹⁴³, Nicholas G. Martin⁹², Grant W. Montgomery^{32,144}, Mitja I. Kurki^{1,3,11,12,3}, Eija Hämaläinen¹²³, Hailiang Huang^{1,2,145}, Jie Huang^{146,147}, Cynthia Sandor¹⁴⁸, Caleb Webber^{148,10}, Bertram Muller-Mylsoul^{149,150,151}, Stefan Schreiber^{152,153}, Veikko Salomaa¹⁵⁴, Elizabeth Loehner¹⁵⁵, Hartmut Gobel¹⁵⁶, Alfons Macaya¹⁵⁷, Patricia Pozo-Rosich^{158,159}, Thomas Hansen^{160,161}, Thomas Werger^{161,162,163}, Jaakko Kaprio^{123,137}, Andres Metspalu¹²⁴, Christian Kubisch¹⁶⁴, Michel D. Ferrari¹²⁹, Andrea C. Belin¹³², Arn M. J. M. van den Maagdenberg^{166,129}, John-Anker Zwart¹⁶⁷, Dorret Boomsma^{168,128}, Nicholas Eriksson¹²⁶, Jes Olesen¹⁶⁰, Daniel I. Chasman^{169,171}, Dale R. Nyholt¹⁷⁰, Andreja Avbersek¹⁷¹, Larry Baum¹⁷², Samuel Berkovic¹⁷³, Jonathan Bradfield¹⁷⁴, Russell Buono^{175,176,177}, Claudia B. Catarino^{171,178}, Patrick Cossette¹⁷⁹, Peter De Jonghe¹⁸⁰, Chantal Depondt¹⁸¹, Dennis Dobbie^{184,185}, Thomas N. Ferraro^{186,187}, Jacqueline French¹⁸⁸, Helle Hjalgrim¹⁸⁹, Jennifer Jannadas-Khoda^{171,190}, Reetta Kälviäinen^{192,193}, Wolfram S. Kunz^{194,195}, Holger Lerche¹³⁶, Costin Leu¹⁹⁶, Dick Lindhout^{197,198}, Warren Lo^{199,200}, Daniel Lowenstein²⁰¹, Mark McCormack^{202,203}, Rikke S. Møller^{204,205}, Anne Molloy²⁰⁶, Ping-Wing Ng²⁰⁷, Karen Oliver²⁰⁹, Michael Privitera^{210,211}, Rodney Radtke²¹², Ann-Kathrin Ruppert²¹³, Thomas Sander²¹³, Steven Schachter^{214,12,13}, Christoph Schankin^{215,216}, Ingrid Scheffer^{217,218,219}, Susanne Schoch²²⁰, Sanjay M. Sisodiya^{221,222}, Philip Smith²²³, Michael Sperling²²⁴, Pasquale Striano²²⁵, Rainer Surges^{226,227}, G. Neil Thomas²²⁸, Frank Visscher²²⁹, Christopher D. Whelan²⁰², Federico Zaro²³⁰, Erin L. Heinzen²³¹, Anthony Marson^{232,233}, Felicitas Becker^{234,235}, Hans Stronk²³⁶, Fritz Zimprich²³⁷, Thomas Gasse^{238,239}, Raphael Gibbs²⁴⁰, Peter Heutink^{239,238}, Maria Martinez^{241,242}, Huw R. Morris²²¹, Manu Sharma²⁴³, Mina Rytén²²¹, Kin Y. T²⁴⁵, Sara Pulit^{246,247}, Steve Bevan²⁴⁸, Elizabeth Holliday²⁴⁹, John Attia^{250,251}, Thomas Battey^{11,253}, Giorgio Boncoraglio^{254,255}, Vincent Thijp^{219,256}, Wei-Min Chen²⁵⁷, Braxton Mitchell^{258,259}, Peter Rothwell²⁶⁰, Pankaj Sharma^{261,262}, Cathie Sudlow²⁶³, Astrid Vicente^{264,265}, Hugh Markus²⁶⁶, Christina Kourkoulis^{3,119,11}, Joana Pera²⁶⁷, Miriam Raffeld^{3,119,268}, Scott Sillman²⁶⁹, Vesna Boraska Perica²⁷⁰, Laura M. Thornton²⁷¹, Laura M. Huckins²⁷², N. William Rayner^{273,274,275}, Cathryn M. Lewis²⁷⁶, Monica Gratacos²⁷⁷, Filip Rybakowski²⁷⁸, Anna Keski-Rahkonen²⁷⁹, Anu Raevuori^{280,279}, James I. Hudson²⁸¹, Ted Reichborn-Kjennerud^{282,283}, Palmiero Monteleone²⁸⁴, Andreas Karwautz²⁸⁵, Katrin Mannik²⁸⁶, Jessica H. Baker²⁷¹, Julie K. O'Toole²⁸⁷, Sara E. Trace²⁸⁸, Oliver S. P. Davis²⁸⁹, Sietske G. Helder^{290,276}, Stefan Ehrlich²⁹¹, Beate Herpertz-Dahlmann²⁹², Unna N. Danner^{293,294}, Annemarie A. van Elburg^{293,294}, Maurizio Clemente²⁹⁵, Monica Forzan²⁹⁶, Elisa Docampo^{297,298}, Jolanta Lissowska²⁹⁹, Joanna Hauser³⁰⁰, Alfonso Tortorella³⁰¹, Mario Maj³⁰², Fragiskos Gonidakis³⁰³, Konstantinos Tziouvas³⁰⁴, Hana Papozova^{305,306}, Zeynep Yilmaz³⁰⁷, Gudrun Wagner³⁰⁷, Sarah Cohen-Woods³⁰⁸, Stefan Herms^{309,94,95}, Antonio Juliá³¹¹, Raquel Rabinot³¹², Danielle M. Dick³¹⁶, Samuli Ripatti^{123,137,317}, Ole A. Andreassen^{318,319}, Thomas Espeseth^{318,320,321}, Astri J. Lundervold^{322,321}, Vidar M. Steen^{323,324}, Dalila Pinto^{325,326,327,328}, Stephen W. Scherer^{330,331}, Harald Aschauer³³², Alexandra Schommer^{333,334}, Lars Alfredsson³³⁵, Leonid Padyukov³³⁶, Katherine A. Halmi³³⁷, James Mitchell^{338,339}, Michael Strober³⁴⁰, Andrew W. Bergen^{341,342}, Walter Kaye³⁴³, Jin Peng Szatkiewicz²⁷¹, Bru Cormand^{312,313,344}, Josep Antoni Ramos-Quiroga^{345,346,348,347}, Cristina Sánchez-Mora^{346,345,348}, Marta Ribases³⁴⁹, Miguel Casas^{349,350,345,351}, Amaia Hervás³⁵², Maria Jesús Arranz³⁵³, Jan Haavik^{354,355}, Tetyana Zayats^{354,1}, Stefan Johansson^{356,324}, Nigel Williams⁹, Astrid Dempfle³⁵⁷, Aribert Rothenberger³⁵⁸, Janina Kunts³⁵⁹, Robert D. Oades³⁶⁰, Tobias Banaschewski³⁶¹, Barbara Franke^{362,363,364}, Jan K. Buitelaar^{365,366}, Alejandro Arias Vasquez³⁶⁷, Alysa E. Doyle^{119,113}, Andreas Reif³⁶⁸, Klaus-Peter Lesch^{369,370,371}, Christine Freitag³⁷², Olga Rivero³⁷¹, Haukur Palmason¹⁴⁰, Marcel Romanos³⁷³, Kate Langley^{374,84}, Marcella Rietsche³⁷⁵, Stephanie H. Witt³⁷⁶, Soeren Dalsgaard^{376,163,377}, Anders D. Borglum^{378,163,379,380}, Irwin Waldman³⁸¹, Beth Wilcox³⁸², Nikolas Molly³⁸³, Claiton H.D. Bau^{384,385}, Jennifer Corley^{386,387}, Rossella Schachar^{388,387}, Sandra K. Loo³⁸⁹, James J. McGough³⁹⁰, Eugenio H. Grevet^{389,392}, Sarah E. Medland⁹², Elise Robinson^{1,2,5}, Lauren A. Weiss^{393,394,395}, Elena Bacchelli³⁹⁶, Anthony Bailey^{397,398}, Vanessa Bal^{393,394,395}, Agatino Battaglia³⁹⁹, Catalina Betancur⁴⁰⁰, Patrick Bolton^{399,401}, Rita Cantor⁴⁰², Patricia Celestino-Soper⁴⁰³, Geraldine Dawson⁴⁰⁴, Silvia De Rubeis^{325,326,407}, Frederico Dwyer^{406,405}, Andrew Green^{408,409}, Sabine M. Klauck⁴¹⁰, Marion Leboyer^{411,412,413}, Pat Levitt^{414,415}, Elena Maestri³⁹⁶, Shrikant Mane^{415,416}, Daniel Moreno-De-Luca⁴¹⁷, Jeremy Parr^{418,419,420}, Regina Regan^{409,421}, Abraham Reichenberg²⁷², Sven Sandin^{325,326,422}, Jacob Vorstman^{423,424}, Thomas Wassink⁴²⁵, Ellen Wijsman^{426,109}, Edwin Cook⁴²⁷, Susan Santangelo^{429,430}, Richard Delorme^{431,432}

Bernadette Rogé^{433,434,435}, Tiago Magalhaes^{421,436}, Dan Arking⁴³⁷, Thomas G. Schulze^{438,439,375,440,441}, Robert C. Thompson^{442,443}, Jana Strohmaier^{475,444}, Keith Matthews^{445,446}, Ingrid Melle^{447,448}, Derek Morris⁴⁴⁹, Douglas Blackwood⁴⁵⁰, Andrew McIntosh⁴⁵⁰, Sarah E. Bergen¹²², Martin Schalling^{451,452}, Stéphane Jamain^{411,412,413}, Anna Maase^{30,89}, Sascha B. Fischer^{34,458}, Céline S. Reinbold^{494,458}, Janice M. Fullerton^{454,455}, José Guzman-Parra^{456,457}, Fermin Mayoral^{456,457}, Peter R. Schofield^{544,455}, Sven Cichon^{94,458,460}, Thomas W. Mühleisen^{460,458}, Franziska Degenhardt⁴⁶¹, Johannes Schumacher⁴⁶¹, Michael Bauer⁴⁶², Philip B. Mitchell^{463,464}, Elliot S. Gershon⁴⁶⁰, John Rice⁴⁶⁵, James B. Potash⁴⁶⁰, Peter P. Zandi⁴⁶⁷, Nick Craddock⁸⁴, I. Nicol Ferrier⁴¹⁸, Martin Alda^{468,469}, Guy A. Rouleau^{470,471}, Gustavo Turecki⁴⁷², Roel Ophoff^{474,475}, Carlos Pato⁴⁷⁶, Adebayo Anjorin⁴⁷³, Eli Stahl⁴⁷⁷, Markus Leber⁴⁷⁷, Piotr M. Czerski⁴⁷⁸, Cristiana Cruceanu^{479,480}, Ian R. Jones⁴⁸¹, Danielle Posthuma^{482,483}, Till F.M. Andlauer^{149,484}, Andreas J. Forstner^{90,89,95,94,486}, Fabian Streit³⁷⁵, Bernhard T. Baune⁴⁸⁷, Tracy Air⁴⁸⁷, Conrad Sinnaman^{489,490}, Naomi R. Wray^{444,488}, Donald J. MacIntyre⁴⁹¹, David Porteous⁴⁹², Georg Homuth⁴⁹³, Margarita Rivera^{494,276}, Jackie Grove^{163,379,378,495}, Christel M. Middeldorp^{496,497,128}, Ian Hickie⁴⁹⁸, Michele Pergadia⁴⁹⁰, Divya Mehta^{499,500}, Johannes H. Smith^{442,502,503}, Rick Jansen⁴⁴², Eco de Geus^{128,502}, Erin Dunn^{11,501}, Qingqin S. Li⁵⁰⁴, Matthias Nauck^{505,506}, Robert A. Schoevers⁵⁰⁷, Aartjan TF Beekman^{142,508}, James A. Knowles⁵⁰⁹, Alexander Viktorin⁴²², Paul Arnold^{510,511,424}, Cathy L. Barr^{512,388,387}, Gabriel Bedyoya-Berrio⁵¹³, O. Joseph Bienvu⁵¹⁴, Helena Brentani⁵¹⁵, Christie Burton³⁸⁸, Beatriz Camarena⁵¹⁶, Carolina Capri⁵¹⁵, Danielle Cath⁵¹⁷, Maria Cavallini⁵²⁰, Daniele Cusi⁵²¹, Sabrina Darwish⁵²², Damiana Denys^{524,525}, Eske M. Derks³², Andrea Dietrich^{517,526}, Thomas Fernandez⁵²³, Martijn Fige^{524,325}, Nelson Freimer⁴⁷⁴, Gloria Gerber¹¹, Marco Grados⁴⁴⁰, Erica Greenberg¹¹⁹, Gregory L. Hanna⁴⁴³, Andreas Hartmann^{527,528,529}, Matthew E. Hirschtritt^{393,395}, Pieter J. Hoekstra⁵²⁶, Alden Huang^{530,390}, Chaim Huyser^{531,532}, Cornelia Illmann¹¹⁹, Michael Jenike¹³, Samuel Kuperman⁵³³, Bennett Leventhal⁶²², Christine Lochner⁵³⁴, Ghoslin J. Lyon⁵³⁵, Fabio Macciardi⁵³⁶, Marcos Madruga-Garrido⁵³⁸, Irene A. Malaty⁵³⁷, Athanasios Maras⁵³⁹, Lauren McGrath⁵⁴⁰, Euripedes C. Miguel⁵⁴¹, Pablo Mir^{542,543}, Gerald Nestadt⁴⁴⁰, Humberto Nicolini^{444,545}, Michael S. Okun^{546,547,548}, Andrew Pakstis⁴¹⁶, Peristera Paschos⁵⁵⁰, John Piacentini⁵⁵¹, Christopher Pittenger⁵⁴⁹, Kerstin Plessen⁵⁵², Vasily Ramensky⁵⁵³, Eliana M. Ramos⁵⁵⁴, Victor Reus^{393,399}, Margaret A. Richte^{555,556}, Mark A. Riddle⁵⁵⁴, Mary M. Robertson⁵⁵⁷, Veit Roessner⁵⁵⁸, Maria Rosario^{559,560}, Jack F. Samuels⁴⁴⁰, Paul Sander^{560,561,562}, Dan J. Stein^{563,534}, Fotis Tsetsos⁵⁶⁴, Filip Van Nieuwerburgh⁵⁶⁵, Sarah Weatherall¹¹, Jens R. Wendland⁵⁶⁶, Tomasz Wolanczyk⁵⁶⁷, Yulia Worob^{568,569,570}, Gwyneth Zai⁵⁶⁶, Fernando S. Go⁵⁴⁰, Nicole McLaughlin^{571,572}, Paul S. Nestadt⁴⁴⁰, Hans-Jorgen Grabe⁵⁷³, Christel Depienne^{574,575,576}, Anuar Konkashbaev⁵⁷⁷, Nuria Lanzagorta⁵⁴⁵, Ana Valencia-Duarte^{578,579}, Elvira Bramon⁵⁸, Nancy Buccola⁵⁸⁰, Wiepke Cahn⁵⁸¹, Murray Cairns^{582,583,584}, Siow A. Chong⁵⁸⁵, David Cohen⁵⁸⁶, Benedicto Crespo-Facorro⁵⁸⁷, James Crowley²⁸⁸, Michael Davidson^{589,590}, Lynn Delisi^{591,13}, Timothy Dinan^{592,593}, Gary Donohoe⁵⁹⁴, Elodie Drapeau^{572,325,326}, Jubao Duan^{595,596}, Lieuw Haan^{524,597}, David Hougaard⁵⁹⁸, Sena Karachanak-Yankova⁵⁹⁹, Andrey Khruinin⁶⁰⁰, Janis Klovinis⁶⁰¹, Vaidutis Kučinskis⁶⁰², Jimmy Lee Chee Keong⁶⁰³, Svetlana Limborska⁶⁰⁴, Carmel Loughland^{605,250}, Jouko Lönnqvist^{614,606}, Brian Maher⁴⁶⁷, Manuel Mattheisen^{607,608,609}, Colm McDonald^{610,611}, Kieran C. Murphy⁶¹², Igor Nenadic^{613,614}, Jim van Os^{581,615,616}, Christos Pantelis^{617,618,219}, Michele Pato⁴⁷⁶, Tracey Petryshen^{2,11}, Digby Quested^{619,620}, Panos Roussos²⁷², Alan R. Sanders^{621,596}, Ulrich Schall⁶²⁰, Sibylle G. Schwab⁶²², Kang Sim^{623,624,585}, Hon-Cheng So⁶²⁵, Elisabeth Stögmanner²³⁷, Mythily Subramanian^{626,627}, Draga Toncheva⁵⁹⁹, John Waddington²⁰², James Walters^{94,85}, Mark Weiser^{590,628}, Wei Cheng²⁷¹, Robert Cloninger⁶²⁹, David Curtis^{630,631}, Pablo V. Gejman^{596,621}, Frans Henskens^{632,633,251}, Morten Mattingsdal^{447,634}, Sang-Yun Oh^{635,636}, Rodney Scott^{250,251,637}, Bradley Webb⁶³⁸, Gerome Breen^{639,640}, Claire Churchhouse^{12,3}, Cynthia M. Bulik^{641,422}, Mark Daly^{1,2,3}, Martin Dichgans^{14,350}, Stephen V. Faraone⁶⁴², Rita Guerreiro⁶⁴³, Peter Holmans⁶⁴⁴, Kenneth S. Kendler⁶⁴³, Bobby Koelman⁶⁴⁴, Carol A. Mathews^{645,548}, Alkes Price^{3,5}, Jeremiah Schaff^{2,3,11,646,12,13}, Pamela Sklar²⁷², Julie Williams³¹⁰, Nicholas W. Wood^{7,630}, Chris Cotsapas^{3,647}, Aarno Palotie^{12,3,11,12,13,123}, Jordan W. Smoller^{2,11}, Patrick Sullivan^{641,648}, Jonathan Rosand^{3,11,12,13}, Leiden Corvin^{2,649,*}, Benjamin M. Neale^{12,3,*}

¹Analytic Translational Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA.

²Stanley Center for Psychiatric Research, Broad Institute of MIT and

- Harvard, Cambridge, Massachusetts, USA. ³Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. ⁴Department of Mathematics, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. ⁵Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA. ⁶UK Dementia Research Institute, University College London, London, UK. ⁷Department of Molecular Neuroscience, Institute of Neurology, University College London, London, UK. ⁸Department of Psychiatry and Behavioral Science, Stanford University, Stanford, California, USA. ⁹Cardiff University, Medical Research Council Center for Neuropsychiatric Genetics & Genomics, Institute of Psychology, Medicine & Clinical Neuroscience, Cardiff, UK. ¹⁰Dementia Research Institute, Cardiff University, Cardiff, UK. ¹¹Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. ¹²Department of Neurology, Massachusetts General Hospital, Boston, MA, USA. ¹³Harvard Medical School, Boston, MA, USA. ¹⁴Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany. ¹⁵Department of Neurology, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA. ¹⁶Charité Universitätsmedizin Berlin, Berlin, Germany. ¹⁷Department of Computer Science, New Jersey Institute of Technology, New Jersey, USA. ¹⁸INSERM U1167 LabEx DISTALZ, Lille, France. ¹⁹Institut Pasteur de Lille, U1167, Lille, France. ²⁰Université de Lille, U1167, RID-AGE, Risk Factors and Molecular Determinants of Aging-Related Diseases, Lille, France. ²¹Centre Hosp. Univ Lille, Lille, France. ²²Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. ²³Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. ²⁴INSERM U1061 - Neuropsychiatry: Epidemiological and Clinical Research, Montpellier, France. ²⁵University of Montpellier, Montpellier, France. ²⁶Memory Research and Resources Center, Department of Neurology, Montpellier University Hospital Gui de Chauliac, Montpellier, France. ²⁷INSERM, UMR 1219, Bordeaux, France. ²⁸University of Bordeaux, Bordeaux, France. ²⁹Rouen University Hospital, Rouen, France. ³⁰Inserm U1245, Rouen, France. ³¹Centre National de Recherche en Génomique Humaine (CNRGH), Institut de biologie François Jacob, CEA, Evry, France. ³²Department of Gerontology, Hôpital Broca, AD-HP, Paris, France. ³³Hôpital Paul Brousse Université Paris Sud XI, Le Kremlin-Bicêtre, Paris, France. ³⁴Gertrude H. Sergievsky Center and Dept of Neurology, Columbia University, New York, NY, USA. ³⁵Columbia University, New York, NY, USA. ³⁶Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ³⁷Translational Genomics Research Institute, Neurogenetics Division, Phoenix, AZ, USA. ³⁸University of Pittsburgh, Pittsburgh, PA, USA. ³⁹Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA. ⁴⁰Department of Medicine, University of Washington, WA, USA. ⁴¹Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada. ⁴²Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK. ⁴³Center for Applied Genomics of The Children's Hospital of Philadelphia, Philadelphia, PA, USA. ⁴⁴Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ⁴⁵Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁴⁶National Alzheimer Coordinating Center (NACC), Department of Epidemiology, University of Washington, Seattle, WA, USA. ⁴⁷Department of Medicine, Boston University School of Medicine, Boston, MA, USA. ⁴⁸Rush Alzheimers Disease Center, Chicago, IL, USA. ⁴⁹Department of Neurological Sciences, Rush Medical College, Chicago, IL, USA. ⁵⁰Department of Behavioral Sciences, Rush Medical College, Chicago, IL, USA. ⁵¹Banner Sun Health Research Institute, Sun City, AZ, USA. ⁵²Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA. ⁵³Department of Pathology, Duke University School of Medicine, Durham, NC, USA. ⁵⁴College of Medicine, University of Kentucky, Lexington, KY, USA. ⁵⁵Department of Biology, Brigham Young University, Provo, UT, USA. ⁵⁶Layton Aging & Alzheimer's Disease Center, Oregon Health & Science University, Portland, OR, USA. ⁵⁷Lou Ruvo Center for Brain Health, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA. ⁵⁸Department of Neurology, School of Medicine, Emory University, Atlanta, GA, USA. ⁵⁹Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, USA. ⁶⁰University of New Mexico Health Sciences Center, Albuquerque, NM, USA. ⁶¹Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, CA, USA. ⁶²Department of Neurology, Oregon Health and Science University, Portland, OR, USA. ⁶³Department of Neurology and Parkinson's Disease Research Education and Clinical Care Center (PADRECC), Portland Veterans Affairs Medical Center, Portland, OR, USA. ⁶⁴Indiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, IN, USA. ⁶⁵Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA. ⁶⁶Byrd Alzheimer's Institute, University of South Florida, Tampa, FL, USA. ⁶⁷Department of Pathology, University of Utah, Salt Lake City, UT, USA. ⁶⁸Department of Pathology, University of Washington, Seattle, WA, USA. ⁶⁹Boston University School of Medicine, Boston, MA, USA. ⁷⁰Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁷¹School of Biotechnology, Dublin City University, Glasnevin, Dublin, Ireland. ⁷²Functional Genomics Center Zurich, ETH/USZ-Zurich, Zurich, Switzerland. ⁷³Department of Medical Genetics, Cambridge Institute for Medical Research, Cambridge, UK. ⁷⁴UK Dementia Research Institute, Cambridge, UK. ⁷⁵School of Medicine, Cardiff University, Cardiff, UK. ⁷⁶1st and 3rd Departments of Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece. ⁷⁷Greek Association of Alzheimer's Disease and Related Disorders, Thessaloniki, Greece. ⁷⁸Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. ⁷⁹Dementia Research Centre, UCL Institute of Neurology, London, UK. ⁸⁰Sorbonne University, GRC n° 21, Alzheimer Precision Medicine (APM), AP-HP, Pitié-Salpêtrière Hospital, Paris, France. ⁸¹Institute of Memory and Alzheimer's Disease (IM2A), Department of Neurology, Pitié-Salpêtrière Hospital, AP-HP, Paris, France. ⁸²Brain & Spine Institute (ICM), INSERM U 1127, CNRS UMR 7225, Paris, France. ⁸³AXA Research Fund & Sorbonne University Chair, Paris, France. ⁸⁴MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK. ⁸⁵Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK. ⁸⁶Institute of Prion Diseases and MRC Prion Unit, University College London, London, UK. ⁸⁷Centre for Public Health, Queens University Belfast, Belfast, UK. ⁸⁸Human Genetics, School of Life Sciences, University of Nottingham, Nottingham UK. ⁸⁹Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany. ⁹⁰Institute of Human Genetics, School of Medicine, University of Bonn & University Hospital Bonn, Bonn, Germany. ⁹¹Department of Neurodegeneration, UCL Institute of Neurology, London, UK. ⁹²QIMR Berghofer Medical Research Institute, Brisbane, Australia. ⁹³Institute of Psychiatry Psychology and Neuroscience, Kings College London, London, UK. ⁹⁴Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. ⁹⁵Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland. ⁹⁶Department of Psychiatry and Psychotherapy, Friedrich-Alexander-Universität Erlangen-Nürnberg University Hospital, Erlangen, Germany. ⁹⁷Department of Psychiatry and Global Brain Health Institute, Trinity College, Dublin, Ireland. ⁹⁸Division of Psychiatry, Molecular Psychiatry Laboratory, University College London, London, UK. ⁹⁹Maurice Wohl Clinical Neuroscience Institute, Department of Basic and Clinical Neuroscience, King's College London, London, UK. ¹⁰⁰King's College Hospital, London, UK. ¹⁰¹Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA. ¹⁰²Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain and Universitat Internacional de Catalunya, Barcelona, Spain. ¹⁰³Facultat de Medicina i Ciències de la Salut, Universitat Internacional de Catalunya (UIC), Barcelona, Spain. ¹⁰⁴Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, Texas, USA. ¹⁰⁵Neurology and Neurogenetics Core, Framingham Heart Study, Framingham, MA, USA. ¹⁰⁶School of Medicine, Boston University, Boston, MA, USA. ¹⁰⁷School of Public Health, Boston University, Boston, MA, USA. ¹⁰⁸Framingham Heart Study, Framingham, MA, USA. ¹⁰⁹Department of Biostatistics, University of Washington, Seattle, WA, USA. ¹¹⁰Department of Epidemiology, Erasmus Medical Centre, Rotterdam, the Netherlands. ¹¹¹Center for Translational & Computational Neuroimmunology, Columbia University Medical Center, New York, NY, USA. ¹¹²Neurogenetics Program, Departments of Neurology and Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. ¹¹³Center For Autism Research and Treatment, Semel Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. ¹¹⁴Institute for Precision Health, University of California, Los Angeles, Los Angeles, CA, USA. ¹¹⁵Department of Psychiatry, Saarland University Hospital, Homburg, Germany. ¹¹⁶Institute of Social Medicine, Occupational Health and Public Health (ISAP), University of Leipzig, Leipzig, Germany. ¹¹⁷Institute for Translational Genomics and Population Sciences, Departments of Pediatrics and Medicine, LABioMed at Harbor-UCLA Medical Center, Torrance, CA, USA. ¹¹⁸Department of Neurology II, Kepler University Hospital, Johannes Kepler University, Linz, Austria. ¹¹⁹Massachusetts General Hospital, Boston, MA, USA. ¹²⁰Washington University School of Medicine, St. Louis, MO, USA. ¹²¹Communication and Research Unit for Musculoskeletal Disorders (FORMI), Oslo University Hospital, Oslo, Norway. ¹²²Department of Neurology, Oslo University Hospital, Oslo, Norway. ¹²³Institute for Molecular Medicine Finland (FIMM), HiLife, University of Helsinki, Helsinki, Finland. ¹²⁴Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia. ¹²⁵illumina Inc., San Diego, CA, USA. ¹²⁶23andMe Inc., Mountain View, CA, USA. ¹²⁷Institute of Public Health, Charité – Universitätsmedizin Berlin, Berlin, Germany. ¹²⁸Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. ¹²⁹Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands. ¹³⁰Institute for Stroke and Dementia Research, Klinikum der Universität Muenchen, Munich, Germany. ¹³¹Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany. ¹³²Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. ¹³³Institute of Human Genetics, University of Ulm, Ulm, Germany. ¹³⁴Department of Radiology and Nuclear Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands. ¹³⁵Department of Clinical Chemistry, Fimlab Laboratories and Finnish Cardiovascular Research Center-Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland. ¹³⁶Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. ¹³⁷Department of Public Health, University of Helsinki, Helsinki, Finland. ¹³⁸Brigham and Women's Hospital, Boston, MA. ¹³⁹Department of Neurology, University Hospital Essen, Germany. ¹⁴⁰Landspítali National University Hospital, Reykjavik, Iceland. ¹⁴¹Avera Institute for Human Genetics, Sioux Falls, SD, USA. ¹⁴²Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. ¹⁴³Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland. ¹⁴⁴Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia. ¹⁴⁵Department of Medicine, Harvard Medical School, Boston, MA, USA. ¹⁴⁶Boston VA Research Institute, Boston, MA, USA. ¹⁴⁷Brigham Women's Hospital Division of Aging, Harvard Medical School, Boston, MA, USA. ¹⁴⁸Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK. ¹⁴⁹Max Planck Institute of Psychiatry, Munich, Germany. ¹⁵⁰Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. ¹⁵¹Institute of Translational Medicine, University of Liverpool, Liverpool, UK. ¹⁵²Institute of Clinical Molecular Biology, Kiel University and University Hospital Schleswig-Holstein, Kiel, Germany. ¹⁵³Clinic of Internal Medicine I, University Hospital Schleswig-Holstein, Kiel, Germany. ¹⁵⁴National Institute for Health and Welfare, Helsinki, Finland. ¹⁵⁵Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ¹⁵⁶Kiel Pain and Headache Center, Kiel, Germany. ¹⁵⁷Pediatric Neurology Research Group, Vall d'Hebron Research Institute, Autonomous University of Barcelona, Barcelona, Spain. ¹⁵⁸Headache Unit, Neurology Department, Hospital Vall d'Hebron, Barcelona, Spain. ¹⁵⁹Headache Research Group, VHIR, Autonomous University of Barcelona, Barcelona, Spain. ¹⁶⁰Danish Headache Center, Rigshospitalet Glostrup and University of Copenhagen, Copenhagen, Denmark. ¹⁶¹Institute of Biological Psychiatry, Roskilde, Denmark. ¹⁶²Department of Clinical Sciences, University of Copenhagen, Copenhagen, Denmark. ¹⁶³Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark. ¹⁶⁴Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ¹⁶⁵Karolinska Institutet, Stockholm, Sweden. ¹⁶⁶Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands. ¹⁶⁷Division of Clinical Neuroscience, Oslo University Hospital and University of Oslo, Oslo, Norway. ¹⁶⁸Netherlands Twin Register, Vrije Universiteit, Amsterdam, the Netherlands. ¹⁶⁹Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA. ¹⁷⁰Statistical and Genomic Epidemiology Laboratory, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. ¹⁷¹Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK. ¹⁷²Centre for Genomic Sciences, University of Hong Kong, Hong Kong. ¹⁷³Epilepsy Research Centre, University of Melbourne, Heidelberg, Australia. ¹⁷⁴Quantinuum Research LLC, San Diego, CA, USA. ¹⁷⁵Cooper Medical School of Rowan University, Camden, NJ, USA. ¹⁷⁶Thomas Jefferson University Hospital, Philadelphia, PA, USA. ¹⁷⁷Children's Hospital of Philadelphia, Philadelphia, PA, USA. ¹⁷⁸Epilepsy Society, Chalfont-St-Peter, Bucks, UK. ¹⁷⁹Centre de Recherche du Centre Hospitalier de l'Université de Montréal and Department of Neurosciences, Université de Montréal, Montréal, Canada. ¹⁸⁰Neurogenetics Group, VIB-CMN, Antwerp, Belgium. ¹⁸¹University of Antwerp, Antwerp, Belgium. ¹⁸²Department of Neurology, Antwerp University Hospital, Antwerp, Belgium. ¹⁸³Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ¹⁸⁴Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ¹⁸⁵Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. ¹⁸⁶Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ, USA. ¹⁸⁷Department of Psychiatry, Center for Neurobiology and Behavior, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. ¹⁸⁸NYU School of Medicine, New York, NY, USA. ¹⁸⁹Amplexa Genetics A/S, Odense, Denmark. ¹⁹⁰Institute of Mental Health, University of Nottingham, Nottingham, UK. ¹⁹¹Human Genetics, School of Life Sciences,

- University of Nottingham, Nottingham UK. ¹⁹²Epilepsy Center/Neurocenter, Kuopio University Hospital, Kuopio, Finland. ¹⁹³Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland. ¹⁹⁴Department of Epileptology, University Bonn Medical Center, Bonn, Germany. ¹⁹⁵Institute of Experimental Epileptology and Cognition Research, University Bonn Medical Center, Bonn, Germany. ¹⁹⁶Department of Clinical and Experimental Epilepsy, NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, London. ¹⁹⁷Department of Genetics, University Medical Center Utrecht, the Netherlands. ¹⁹⁸Epilepsy Foundation in the Netherlands (SEIN), Heemstede, the Netherlands. ¹⁹⁹Departments of Pediatrics and Neurology, Ohio State University, Columbus, OH, USA. ²⁰⁰Nationwide Children's Hospital, Columbus, OH, USA. ²⁰¹Department of Neurology, University of California, San Francisco, CA, USA. ²⁰²Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. ²⁰³Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands. ²⁰⁴Danish Epilepsy Centre, Filadelfia, Dianalund, Denmark. ²⁰⁵Institute for Regional Health Services, University of Southern Denmark, Odense, Denmark. ²⁰⁶Trinity College Dublin, Dublin, Ireland. ²⁰⁷United Christian Hospital, Hong Kong. ²⁰⁸Hong Kong Sanatorium and Hospital, Hong Kong. ²⁰⁹Epilepsy Research Centre, University of Melbourne, Austin Health, Heidelberg, Australia. ²¹⁰Department of Neurology, University of Cincinnati, Cincinnati, OH, USA. ²¹¹UC Gardner Neuroscience Institute, Cincinnati, OH, USA. ²¹²Department of Neurology, Duke University School of Medicine, Durham, NC, USA. ²¹³Cologne Center for Genomics (CCG), University of Cologne, Cologne, Germany. ²¹⁴Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, USA. ²¹⁵Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland. ²¹⁶Department of Neurology, University of Munich Hospital, Grosshadern, University of Munich, Germany. ²¹⁷Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Victoria, Australia. ²¹⁸Department of Paediatrics, Royal Children's Hospital, The University of Melbourne, Melbourne, Victoria, Australia. ²¹⁹Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia. ²²⁰Institute of Neuropathology, Bonn University Medical School, Bonn, Germany. ²²¹UCL Institute of Neurology, London, UK. ²²²Chalfont Centre for Epilepsy, Bucks, UK. ²²³University Hospital of Wales, Cardiff, UK. ²²⁴Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA. ²²⁵Pediatric Neurology and Muscular Diseases Unit-Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health University of Genoa, "G. Gaslini" Institute, Genova, Italy. ²²⁶Department of Epileptology, University Hospital Bonn, Bonn, Germany. ²²⁷Section of Epileptology, Department of Neurology, University Hospital RWTH Aachen, Aachen, Germany. ²²⁸Institute of Applied Health Research, University of Birmingham, UK. ²²⁹Department of Neurology, Admiraal De Ruyter Hospital, Goes, The Netherlands. ²³⁰Laboratory of Neurogenetics, G. Gaslini Institute, Genova, Italy. ²³¹Institute for Genomic Medicine, Columbia University Medical Center, New York, NY, USA. ²³²University of Liverpool, Liverpool, UK. ²³³Walton Centre NHS Foundation Trust, Liverpool, UK. ²³⁴Department of Neurology and Epileptology, University Hospital Tuebingen, Tuebingen, Germany. ²³⁵Department of Neurology, University of Ulm, Ulm, Germany. ²³⁶CWZ Hospital, Nijmegen, Netherlands. ²³⁷Department of Neurology, Medical University of Vienna, Austria. ²³⁸Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany. ²³⁹German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany. ²⁴⁰Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA. ²⁴¹INSERM U1220, IRSD, Toulouse, France. ²⁴²Université Paul Sabatier, Toulouse, France. ²⁴³Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen, Germany. ²⁴⁴Department of Molecular Neuroscience, Institute of Neurology, University College London, London, UK. ²⁴⁵Division of Life Science, Hong Kong University of Science and Technology, Hong Kong Special Administrative Region, China. ²⁴⁶Department of Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands. ²⁴⁷Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK. ²⁴⁸University of Lincoln, Lincoln, UK. ²⁴⁹Faculty of Health and Medicine, University of Newcastle, Callaghan, Australia. ²⁵⁰University of Newcastle, Callaghan, Australia. ²⁵¹Hunter Medical Research Institute, Newcastle, Australia. ²⁵²Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. ²⁵³Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital, Boston, MA, USA. ²⁵⁴Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy. ²⁵⁵PhD Program in Neuroscience, University Milano-Bicocca, Monza, Italy. ²⁵⁶Austin Health, Heidelberg, Australia. ²⁵⁷University of Virginia Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA. ²⁵⁸Dept of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA. ²⁵⁹Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, MD, USA. ²⁶⁰Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK. ²⁶¹Institute of Cardiovascular Research, Royal Holloway University of London, London, UK. ²⁶²Ashford & St Peters NHS Foundation Trust, Surrey, UK. ²⁶³University of Edinburgh, Edinburgh, UK. ²⁶⁴Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal. ²⁶⁵Biosystems and Integrative Sciences Institute - BioISI, University of Lisboa, Lisboa, Portugal. ²⁶⁶Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK. ²⁶⁷Department of Neurology, Jagiellonian University Medical College, Kraków, Poland. ²⁶⁸The Warren Alpert Medical School of Brown University, Providence, RI, USA. ²⁶⁹Department of Neurology, College of Medicine-Jacksonville, University of Florida, Jacksonville, FL, USA. ²⁷⁰University of Split School of Medicine, Split, Croatia. ²⁷¹University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ²⁷²ICahn School of Medicine at Mount Sinai, New York, NY, USA. ²⁷³Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK. ²⁷⁴Oxford Centre for Diabetes, Endocrinology and Metabolism, Nuffield Department of Medicine, University of Oxford, Oxford, UK. ²⁷⁵Department of Human Genetics, Wellcome Sanger Institute, Hinxton, Cambridgeshire, UK. ²⁷⁶MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, UK. ²⁷⁷Genes and Disease Programme, Centre for Genomic Regulation (CRG), Barcelona, Spain. ²⁷⁸Department of Adult Psychiatry, Poznan University of Medical Sciences, Poland. ²⁷⁹Clinicum, Department of Public Health, University of Helsinki, Finland. ²⁸⁰Department of Adolescent Psychiatry, Helsinki University Central Hospital, Helsinki, Finland. ²⁸¹Harvard Medical School/McLean Hospital, Belmont, MA, USA. ²⁸²Norwegian Institute of Public Health, Oslo, Norway. ²⁸³University of Oslo, Oslo, Norway. ²⁸⁴Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Italy. ²⁸⁵Eating Disorders Unit, Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria. ²⁸⁶Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland. ²⁸⁷Kartini Clinic, Portland, OR, USA. ²⁸⁸Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ²⁸⁹MRC Integrative Epidemiology Unit and Bristol Medical School, University of Bristol, Bristol, UK. ²⁹⁰Zorg op Orde BV, Leidschendam, The Netherlands. ²⁹¹Division of Psychological & Social Medicine and Developmental Neurosciences, Faculty of Medicine, Technischen Universität Dresden, Dresden, Germany. ²⁹²Department of Child & Adolescent Psychiatry & Psychosomatic Medicine of University Clinics, RWTH Aachen, Aachen, Germany. ²⁹³Altrecht Eating Disorders Rintveld, Altrecht Mental Health Institute, Zeist, The Netherlands. ²⁹⁴Faculty of Social Sciences, University of Utrecht, Utrecht, the Netherlands. ²⁹⁵Medical Genetics Unit, Department SDB, University of Padova, Padova, Italy. ²⁹⁶UOC Genetica ed Epidemiologica Clinica Az. Ospedaliera, Padova, Italy. ²⁹⁷Department of Human Genetics, CHU Sart-Tilman, University of Liège, Liège, Belgium. ²⁹⁸Department of Cancer Epidemiology and Prevention, Cancer Center and M. Skłodowska-Curie Institute of Oncology, Warsaw, Poland. ²⁹⁹Department of Psychiatry, University of Medical Sciences, Poznan, Poland. ³⁰⁰Department of Psychiatry, University of Perugia, Perugia, Italy. ³⁰¹Department of Mental and Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy. ³⁰²Eating Disorders Unit, 1st Psychiatric Department, National and Kapodistrian University of Athens, Athens, Greece. ³⁰³Aglaia Kyriakou Childrens Hospital, Athens, Greece. ³⁰⁴Eating Disorders Unit, Department of Psychiatry, First Faculty of Medicine, Charles University, Prague, Czech Republic. ³⁰⁵General University Hospital, Prague, Czech Republic. ³⁰⁶Medical University of Vienna, Austria. ³⁰⁷School of Psychology, Flinders University, Adelaide, Australia. ³⁰⁸Division of Medical Genetics, University Hospital Basel, Basel, Switzerland. ³⁰⁹Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland. ³¹⁰Vall d'Hebron Research Institute, Barcelona, Spain. ³¹¹Institut de Recerca Sant Joan de Déu, Barcelona, Spain. ³¹²Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Spain. ³¹³Department of Genetics, Microbiology & Statistics, Faculty of Biology, University of Barcelona, Barcelona, Spain. ³¹⁴Centre for Genomic Regulation (CRG), Barcelona, Spain. ³¹⁵Departments of Psychology and Human & Molecular Genetics, College Behavioral and Emotional Health Institute, Virginia Commonwealth University, Richmond, Virginia. ³¹⁶Broad Institute of MIT and Harvard, Cambridge, USA. ³¹⁷NORMENT, Div. of Mental Health and Addiction, University of Oslo, Oslo, Norway. ³¹⁸Oslo University Hospital, Oslo, Norway. ³¹⁹Department of Psychology, University of Oslo, Norway. ³²⁰K. G. Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway. ³²¹Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway. ³²²NORMENT, K.G. Jebsen Center for Psychosis Research, Department of Clinical Science, University of Bergen, Norway. ³²³Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway. ³²⁴Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ³²⁵Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ³²⁶Department of Genetics and Genomic Sciences, and Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ³²⁷The Mindich Child Health & Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ³²⁸Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ³²⁹McLaughlin Centre and Department of Molecular Genetics, University of Toronto, Toronto, Canada. ³³⁰The Centre for Applied Genomics, Hospital for Sick Children, Toronto, Canada. ³³¹Biopsychosocial Corporation, Vienna, Austria. ³³²Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria. ³³³Zentren für Seelische Gesundheit, BBRZ-Med, Vienna, Austria. ³³⁴Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. ³³⁵Rheumatology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden. ³³⁶Weill Cornell Medical College, New York, New York, USA. ³³⁷School of Medicine, University of North Dakota, Grand Forks, ND, USA. ³³⁸Neuropsychiatric Research Institute, Fargo, ND, USA. ³³⁹Department of Psychiatry & Biobehavioral Sciences, Semel Institute for Neuroscience & Human Behavior, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. ³⁴⁰BioRealm, Walnut, California, USA. ³⁴¹Oregon Research Institute, Eugene, OR, USA. ³⁴²Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. ³⁴³Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III, Madrid, Spain. ³⁴⁴Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain. ³⁴⁵Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain. ³⁴⁶Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain. ³⁴⁷Biomedical Network Research Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain. ³⁴⁸Universitat Autònoma de Barcelona, Barcelona, Spain. ³⁴⁹Programa Corporatiu "Neurodevelopment Disorders along Life Span", Institut Català de la Salut, Barcelona, Spain. ³⁵⁰Clinica Galatea y PAIMM, Mental Health Program for Impaired Physicians, Barcelona, Spain. ³⁵¹Child and Adolescent Mental Health Unit, Hospital Universitario Mútua de Terrassa, Barcelona, Spain. ³⁵²Fundació Docència i Recerca Mútua Terrassa. ³⁵³K.G. Jebsen Centre for Neuropsychiatric Disorders, Department of Biomedicine, University of Bergen, Norway. ³⁵⁴Division of Psychiatry, Haukeland University Hospital, Bergen, Norway. ³⁵⁵K.G. Jebsen Centre for Neuropsychiatric Disorders, Department of Clinical Science, University of Bergen, Norway. ³⁵⁶Institute of Medical Informatics and Statistics, Kiel University, Kiel, Germany. ³⁵⁷Child and Adolescent Psychiatry/Psychotherapy, University Medical Center, Goettingen, Germany. ³⁵⁸Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. ³⁵⁹Clinic for Child and Adolescent Psychiatry and Psychotherapy, University of Duisburg-Essen, Essen, Germany. ³⁶⁰Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Mangel Faculty Mannheim, University of Heidelberg, Mannheim, Germany. ³⁶¹Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands. ³⁶²Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands. ³⁶³Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands. ³⁶⁴Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands. ³⁶⁵Karakter Child and Adolescent Psychiatry University Center, Nijmegen, The Netherlands. ³⁶⁶Department of Psychiatry & Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands. ³⁶⁷Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany. ³⁶⁸Laboratory of Psychiatric Neurobiology, Institute of Molecular Medicine, I.M. Sechenov First Moscow State Medical University, Moscow, Russia. ³⁶⁹Department of Translational Psychiatry, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, The Netherlands. ³⁷⁰Division of Molecular Psychiatry, Center of Mental Health, University of Wuerzburg, Wuerzburg, Germany. ³⁷¹Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany. ³⁷²Center of Mental Health, Department of Child and Adolescent

- Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Wuerzburg, Wuerzburg, Germany. ³⁷⁴School of Psychology, Cardiff University, UK. ³⁷⁵Central Institute of Mental Health, Department of Genetic Epidemiology in Psychiatry, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany. ³⁷⁶National Centre for Register-based Research, Aarhus University, Aarhus, Denmark. ³⁷⁷Hospital of Telemark, Kragers, Norway. ³⁷⁸Department of Biomedicine and Human Genetics, Aarhus University, Aarhus, Denmark. ³⁷⁹Center for Integrative Sequencing (iSEQ), Aarhus University, Aarhus, Denmark. ³⁸⁰Aarhus Genome Center, Aarhus, Denmark. ³⁸¹Department of Psychology, Emory University, Atlanta, GA, USA. ³⁸²Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR, USA. ³⁸³Department of Psychological and Brain Sciences, University of Iowa, Iowa City, IA, USA. ³⁸⁴Departamento de Genética, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. ³⁸⁵ADHD Outpatient Clinic, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. ³⁸⁶Neurosciences and Mental Health Program, Research Institute, Hospital for Sick Children, Toronto, Canada. ³⁸⁷University of Toronto, Toronto, Canada. ³⁸⁸Hospital for Sick Children, Toronto, Canada. ³⁸⁹Department of Psychiatry, University of California, Los Angeles, Los Angeles, CA, USA. ³⁹⁰Semel Institute for Neuroscience & Human Behavior, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. ³⁹¹ADHD Outpatient Clinic, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. ³⁹²Department of Psychiatry, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. ³⁹³Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA. ³⁹⁴Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, USA. ³⁹⁵Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, USA. ³⁹⁶Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy. ³⁹⁷Department of Psychiatry, University of British Columbia, Vancouver, Canada. ³⁹⁸Institute of Mental Health, University of British Columbia, Vancouver, Canada. ³⁹⁹Stella Maris Clinical Research Institute for Child and Adolescent Neuropsychiatry, Pisa, Italy. ⁴⁰⁰Sorbonne Université, INSERM, CNRS, Neuroscience Paris Seine, Institut de Biologie Paris Seine, Paris, France. ⁴⁰¹NIHR Biomedical Research Centre in Mental Health Maudsley Hospital, London, UK. ⁴⁰²Department of Human Genetics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. ⁴⁰³LifeOmic, Indianapolis, IN, USA. ⁴⁰⁴Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA. ⁴⁰⁵University Clinic of Pediatrics, Faculty of Medicine, University of Coimbra, Coimbra, Portugal. ⁴⁰⁶Child Developmental Center, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. ⁴⁰⁷Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁴⁰⁸Dept of Clinical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland. ⁴⁰⁹School of Medicine and Medical Science, University College Dublin, Dublin, Ireland. ⁴¹⁰Division of Molecular Genome Analysis and Division of Cancer Genome Research, German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁴¹¹Inserm U955, Psychiatrie Translationnelle, Créteil, France. ⁴¹²Faculté de Médecine, Université Paris Est, Créteil, France. ⁴¹³Fondation FondaMental, Créteil, France. ⁴¹⁴Children's Hospital Los Angeles, Los Angeles, CA, USA. ⁴¹⁵Yale Center for Genome Analysis, Yale University, New Haven, CT, USA. ⁴¹⁶Department of Genetics, Yale University School of Medicine, New Haven, CT, USA. ⁴¹⁷Division of Child and Adolescent Psychiatry, Department of Psychiatry and Human Behavior, Brown University, Providence, RI, USA. ⁴¹⁸Institute of Neuroscience, Newcastle University, Newcastle, UK. ⁴¹⁹Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK. ⁴²⁰Northumberland, Tyne & Wear NHS Foundation Trust, Northumberland, UK. ⁴²¹Genomics Medicine Ireland, Dublin, Ireland. ⁴²²Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ⁴²³Department of Psychiatry, Hospital for Sick Children and University of Toronto, Toronto, Canada. ⁴²⁴Program in Genetics and Genome Biology, Hospital for Sick Children, Toronto, Canada. ⁴²⁵Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City, IA, USA. ⁴²⁶Division of Medical Genetics, Department of Medicine, University of Washington, Seattle, WA, USA. ⁴²⁷Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA. ⁴²⁸Tufts University School of Medicine, Portland, ME, USA. ⁴²⁹Center for Psychiatric Research, Maine Medical Center Research Institute, Portland, ME, USA. ⁴³⁰Department of Psychiatry, Tufts University School of Medicine, Boston, MA, USA. ⁴³¹Child and Adolescent Psychiatry Department, Robert Debre Hospital, APHP, Paris, France. ⁴³²Human Genetics and Cognitive Functions, Institut Pasteur, Paris, France. ⁴³³Centre d'Etudes et de Recherches en Psychopathologie et Psychologie de la Santé (CERPSS), Université Toulouse Jean Jaurès, Toulouse, France. ⁴³⁴CERESA, Toulouse, France. ⁴³⁵Institut Universitaire de France, Paris, France. ⁴³⁶Academic Centre on Rare Diseases University College Dublin (ACoRD/UCD), Dublin, Ireland. ⁴³⁷McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. ⁴³⁸Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany. ⁴³⁹Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany. ⁴⁴⁰Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA. ⁴⁴¹Human Genetics Branch, National Institute of Mental Health, National Institutes of Health, US Department of Health and Human Services, Bethesda, MD, USA. ⁴⁴²Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, USA. ⁴⁴³Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA. ⁴⁴⁴SRH University Heidelberg, Academy for Psychotherapy, Heidelberg, Germany. ⁴⁴⁵Division of Neuroscience, School of Medicine, University of Dundee, Dundee, UK. ⁴⁴⁶Advanced Interventions Service, NHS Tayside, Dundee, UK. ⁴⁴⁷NORMENT, K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ⁴⁴⁸Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ⁴⁴⁹Cognitive Genetics and Cognitive Therapy Group, Neuroimaging, Cognition and Genomics (NICOG) Centre, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Galway, Ireland. ⁴⁵⁰Division of Psychiatry, University of Edinburgh, Edinburgh, UK. ⁴⁵¹Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden. ⁴⁵²Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. ⁴⁵³Université Paris Est, Faculté de Médecine, Créteil, France. ⁴⁵⁴Neuroscience Research Australia, Sydney, Australia. ⁴⁵⁵School of Medical Sciences, University of New South Wales, Sydney, Australia. ⁴⁵⁶Unidad de Salud Mental, Hospital Regional Universitario de Málaga, Málaga, Spain. ⁴⁵⁷Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, Spain. ⁴⁵⁸Department of Biomedicine, University of Basel, Basel, Switzerland. ⁴⁵⁹Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. ⁴⁶⁰Institute of Neuroscience and Medicine (INM-I), Research Centre Jülich, Jülich, Germany. ⁴⁶¹Institute of Human Genetics, University of Bonn, Bonn, Germany. ⁴⁶²Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. ⁴⁶³School of Psychiatry, University of New South Wales, Sydney, Australia. ⁴⁶⁴Black Dog Institute, Sydney, Australia. ⁴⁶⁵University of Chicago, Chicago, IL, USA. ⁴⁶⁶Washington University, St. Louis, MO, USA. ⁴⁶⁷Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. ⁴⁶⁸Department of Psychiatry, Dalhousie University, Halifax, Canada. ⁴⁶⁹National Institute of Mental Health, Klecany, Czech Republic. ⁴⁷⁰Montreal Neurological Institute, McGill University, Montréal, Canada. ⁴⁷¹Department of Neurology and Neurosurgery, McGill University, Montréal, Canada. ⁴⁷²Department of Psychiatry, McGill University, Montréal, Canada. ⁴⁷³University College London, London, UK. ⁴⁷⁴Center for Neurobehavioral Genetics, Semel Institute for Neuroscience & Human Behavior, University of California at Los Angeles, Los Angeles, CA, USA. ⁴⁷⁵UMC Utrecht, Utrecht, The Netherlands. ⁴⁷⁶SUNY Downstate Medical Center, Brooklyn, NY, USA. ⁴⁷⁷Hospital for Psychiatry and Psychotherapy, Cologne, Germany. ⁴⁷⁸Laboratory of Psychiatric Genetics, Department of Psychiatry, Poznan University of Medical Sciences, Poznan, Poland. ⁴⁷⁹Douglas Mental Health University Institute, McGill University, Montreal, Canada. ⁴⁸⁰Department of Translational Research in Psychiatry, Max-Planck Institute of Psychiatry, Munich, Germany. ⁴⁸¹National Centre for Mental Health, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK. ⁴⁸²Department Complex Trait Genetics, Center for Neurogenetics and Cognitive Research, VU University, Amsterdam, The Netherlands. ⁴⁸³Department Clinical Genetics, VU University Medical Center, Amsterdam Neuroscience, Amsterdam, The Netherlands. ⁴⁸⁴Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany. ⁴⁸⁵Institute of Human Genetics, University of Bonn, Bonn, Germany. ⁴⁸⁶Department of Psychiatry (UPK), University of Basel, Basel, Switzerland. ⁴⁸⁷Discipline of Psychiatry, University of Adelaide, Adelaide, Australia. ⁴⁸⁸Queensland Brain Institute, University of Queensland, Brisbane, Australia. ⁴⁸⁹Bela Menso Brain and Behaviour Centre, James Cook University, Varsity Lakes, Australia. ⁴⁹⁰Bond University, Faculty of Society and Design, Robina, Australia. ⁴⁹¹Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK. ⁴⁹²Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK. ⁴⁹³Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany. ⁴⁹⁴Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain. ⁴⁹⁵Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. ⁴⁹⁶Child Health Research Centre, University of Queensland, Brisbane, Australia. ⁴⁹⁷Child and Youth Mental Health Service, Children's Health Queensland Health and Hospital Service, Brisbane, Australia. ⁴⁹⁸Brain and Mind Centre, University of Sydney, Sydney, Australia. ⁴⁹⁹School of Psychology and Counselling, Faculty of Health, Institute of Health and Biomedical Innovation, Queensland University of Technology, Queensland, Australia. ⁵⁰⁰University of Queensland, Brisbane, Australia. ⁵⁰¹Department of Psychiatry, Harvard Medical School, Boston, MA, USA. ⁵⁰²Amsterdam Public Health Research Institute, VU Medical Center, Amsterdam, the Netherlands. ⁵⁰³Department of Research and Innovation, GGZ Ingeest, Specialized Mental Health Care, Amsterdam, the Netherlands. ⁵⁰⁴Janssen Research & Development LLC, Titusville, NJ, USA. ⁵⁰⁵Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany. ⁵⁰⁶German Centre for Cardiovascular Research (DZHK e.V.), Partner Site Greifswald, Greifswald, Germany. ⁵⁰⁷Research School of Behavioural and Cognitive Neurosciences, Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. ⁵⁰⁸Department of Psychiatry GGZ INGEEEST, Amsterdam, the Netherlands. ⁵⁰⁹Department of Cell Biology, SUNY Downstate Medical Center, Brooklyn, NY, USA. ⁵¹⁰Mathison Centre for Mental Health Research & Education, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada. ⁵¹¹Departments of Psychiatry and Medical Genetics, Cumming School of Medicine, University of Calgary, Calgary, Canada. ⁵¹²Krembil Research Institute, University Health Network, Toronto, Canada. ⁵¹³Grupo de Genética Molecular, Instituto de Biología, Facultad de Ciencias Exactas y Naturales, Universidad de Antioquia, Medellín, Colombia. ⁵¹⁴Johns Hopkins University School of Medicine, Baltimore, MD, USA. ⁵¹⁵Department of Psychiatry, Sao Paulo Medical School, University of Sao Paulo, Sao Paulo, Brazil. ⁵¹⁶Depto. Farmacogenética, Instituto Nacional de Psiquiatria Ramon de la Fuente Muñiz, Mexico City, Mexico. ⁵¹⁷University of Groningen, Groningen, the Netherlands. ⁵¹⁸Department of Psychiatry, University of Groningen and University Medical Center, Groningen, the Netherlands. ⁵¹⁹Department of Specialized Trainings, GGZ Drenthe Mental Health Care Services, Assen, the Netherlands. ⁵²⁰Ospedale San Raffaele, Milano, Italy. ⁵²¹Bio4Dreams Srl, Milan, Italy. ⁵²²University of California, San Francisco, CA, USA. ⁵²³Yale University School of Medicine, New Haven, CT, USA. ⁵²⁴Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. ⁵²⁵Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands. ⁵²⁶Department of Child and Adolescent Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. ⁵²⁷Centre National Maladie 'Syndrome Rare Gilles de la Tourette', Groupe Hospitalier Pitié-Salpêtrière, Paris, France. ⁵²⁸Assistance Publique-Hôpitaux de Paris, Département de Neurologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France. ⁵²⁹Sorbonne Universités, UPMC Université Paris 06, UMR S 1127, CNRS UMR 7225, ICM, Paris, France. ⁵³⁰Bioinformatics Interdepartmental Program, University of California, Los Angeles, Los Angeles, CA, USA. ⁵³¹De Bascule, Amsterdam, The Netherlands. ⁵³²Department of Child and Adolescent Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. ⁵³³Carver College of Medicine, University of Iowa, Iowa City, IA, USA. ⁵³⁴MRC Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry, University of Cape Town, Cape Town, South Africa. ⁵³⁵Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA. ⁵³⁶Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA. ⁵³⁷Department of Neurology, University of Florida, Gainesville, FL, USA. ⁵³⁸Sección de Neuropediatría, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain. ⁵³⁹Yulius Academy, Yulius Mental Health Organization, Barendrecht, The Netherlands. ⁵⁴⁰Department of Psychology, University of Denver, Denver, CO, USA. ⁵⁴¹Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, Brazil. ⁵⁴²Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain. ⁵⁴³Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain. ⁵⁴⁴National Institute of Genomic Medicine (INMEGEN), Ciudad de México, Mexico. ⁵⁴⁵Clinical Research, Grupo Médico Carracci, Mexico City, Mexico. ⁵⁴⁶Departments of Neurology and Neurosurgery, University of Florida, Gainesville, FL, USA. ⁵⁴⁷Fixel Center for Neurological Diseases, University of Florida, Gainesville, FL, USA. ⁵⁴⁸McKnight Brain Institute, University of Florida, Gainesville, FL, USA. ⁵⁴⁹Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA. ⁵⁵⁰Department of Biological Sciences, Purdue University, West Lafayette, Indiana, USA. ⁵⁵¹Division of Adolescent and Child Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland. ⁵⁵²Child and Adolescent Mental Health Centre, Mental Health Services Capital Region Copenhagen, University of

- Copenhagen, Copenhagen, Denmark. ⁵⁵³Moscow Institute of Physics and Technology, Dolgoprudny, Institutsky 9, Moscow, Russia.
- ⁵⁵⁴Department of Psychiatry, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA.
- ⁵⁵⁵Frederick W. Thompson Anxiety Disorders Centre, Sunnybrook Health Sciences Centre, Toronto, Canada. ⁵⁵⁶Department of Psychiatry, University of Toronto, Toronto, Canada. ⁵⁵⁷Division of Neuropsychiatry, University College London, London, UK.
- ⁵⁵⁸Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany.
- ⁵⁵⁹Child and Adolescent Psychiatry Unit (UPIA), Department of Psychiatry, Federal University of São Paulo, Brazil. ⁵⁶⁰Yale Child Study Center, Yale University School of Medicine, New Haven, CT, USA.
- ⁵⁶¹University Health Network, University of Toronto, Toronto, Canada.
- ⁵⁶²Youthdale Treatment Centers, Toronto, Canada. ⁵⁶³Groote Schuur Hospital, Cape Town, South Africa. ⁵⁶⁴Department of Molecular Biology and Genetics, Democritus University of Thrace, Alexandroupolis, Greece. ⁵⁶⁵Laboratory of Pharmaceutical Biotechnology, Ghent University, Ghent, Belgium. ⁵⁶⁶Pfizer, Inc., New York, NY, USA. ⁵⁶⁷Department of Child Psychiatry, Medical University of Warsaw, Warsaw, Poland. ⁵⁶⁸Sorbonne Université, Faculty of Médecine, Paris, France. ⁵⁶⁹Reference center for Gilles de la Tourette syndrome, Pitié-Salpêtrière Hospital, Paris, France. ⁵⁷⁰Department of Physiology, Saint Antoine Hospital, Paris, France. ⁵⁷¹Butler Hospital, Providence, RI, USA. ⁵⁷²Alpert Medical School of Brown University, Providence, RI, USA. ⁵⁷³Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany. ⁵⁷⁴Institute of Human Genetics, University Hospital Essen, University Duisburg-Essen, Essen, Germany. ⁵⁷⁵INSERM, U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Paris, France. ⁵⁷⁶GBMC, CNRS UMR 7104/INSERM U964/Université de Strasbourg, Illkirch, France. ⁵⁷⁷Vanderbilt University Medical Center, Nashville, TN, USA. ⁵⁷⁸Escuela de Ciencias de la Salud, Universidad Pontificia Bolivariana, Medellín, Colombia. ⁵⁷⁹Laboratorio de Genética Molecular, SIU, Universidad de Antioquia, Medellín, Colombia. ⁵⁸⁰School of Nursing, Louisiana State University Health Sciences Center, New Orleans, LA, USA. ⁵⁸¹Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands. ⁵⁸²School of Biomedical Sciences and Pharmacy, The University of Newcastle, Callaghan, Australia. ⁵⁸³Priority Research Centre for Brain and Mental Health Research, Hunter Medical Research Institute, Newcastle, Australia. ⁵⁸⁴Schizophrenia Research Institute, Sydney, Australia. ⁵⁸⁵Institute of Mental Health, Singapore, Singapore. ⁵⁸⁶Assistance Publique - Hôpitaux de Paris, GH Pitié-Salpêtrière, Paris, France. ⁵⁸⁷Sorbonne Université, CNRS UMR 7222 Institut des Systèmes Intelligents et Robotiques, Paris, France. ⁵⁸⁸Departments of Medicine and Psychiatry, School of Medicine University of Cantabria-IDIVAL, University Hospital Marqués de Valdecilla, Santander, Spain. ⁵⁸⁹Minerva Neurosciences Inc., Waltham, MA, USA. ⁵⁹⁰Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. ⁵⁹¹VA Boston Healthcare System, Boston, MA, USA. ⁵⁹²APC Microbiome Ireland, University College Cork, Cork, Ireland. ⁵⁹³Department of Psychiatry, University College Cork, Cork, Ireland. ⁵⁹⁴Neuroimaging, Cognition and Genomics (NICOG) Centre, School of Psychology, National University of Ireland Galway, Galway, Ireland. ⁵⁹⁵Center for Psychiatric Genetics, NorthShore University HealthSystem Research Institute, Evanston, IL, USA. ⁵⁹⁶Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA. ⁵⁹⁷Arkin, Amsterdam, the Netherlands. ⁵⁹⁸Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark. ⁵⁹⁹Department of Medical Genetics, Medical University, Sofia, Bulgaria. ⁶⁰⁰Department of Molecular Bases of Human Genetics, Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, Russia. ⁶⁰¹Latvian Biomedical Research and Study Centre, Riga, Latvia. ⁶⁰²Vilnius University, Vilnius, Lithuania. ⁶⁰³Institute of Mental Health, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. ⁶⁰⁴Department of Human Genetics, Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, Russia. ⁶⁰⁵Hunter New England Local Health District, Newcastle, Australia. ⁶⁰⁶Department of Psychiatry, University of Helsinki, Helsinki, Finland. ⁶⁰⁷Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Wuerzburg, Wuerzburg, Germany. ⁶⁰⁸Department of Biomedicine, Aarhus University, Aarhus, Denmark. ⁶⁰⁹Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden. ⁶¹⁰Centre for Neuroimaging and Cognitive Genomics (NICOG), National University of Ireland, Galway, Galway, Ireland. ⁶¹¹NCBES Galway Neuroscience Centre, National University of Ireland, Galway, Galway, Ireland. ⁶¹²Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland. ⁶¹³Philipps-Universität Marburg and Marburg University Hospital UKGM, Marburg, Germany. ⁶¹⁴Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany. ⁶¹⁵Maastricht University Medical Centre, Maastricht, the Netherlands. ⁶¹⁶Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, UK. ⁶¹⁷Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne & Melbourne Health, Victoria, Australia. ⁶¹⁸Centre for Neural Engineering, Department of Electrical and Electronic Engineering, University of Melbourne, Victoria, Australia. ⁶¹⁹Oxford Health NHS Foundation Trust, Oxford, UK. ⁶²⁰Department of Psychiatry, University of Oxford, Oxford, UK. ⁶²¹Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem Research Institute, Evanston, IL, USA. ⁶²²Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, Australia. ⁶²³Yong Loo Lin School of Medicine, National University of Singapore, Singapore. ⁶²⁴Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. ⁶²⁵School of Biomedical Sciences, Chinese University of Hong Kong, Shatin, Hong Kong. ⁶²⁶KIZ-CUHK Joint Laboratory of Bioresources and Molecular Research of Common Diseases, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, China. ⁶²⁷Chinese University of Hong Kong, Hong Kong. ⁶²⁸Sheba Medical Center, Ramat Gan, Israel. ⁶²⁹Departments of Psychiatry and Genetics, Washington University School of Medicine, St. Louis, MO, USA. ⁶³⁰UCL Genetics Institute, University College London, London, UK. ⁶³¹Centre for Psychiatry, Barts and the London School of Medicine and Dentistry, London, UK. ⁶³²School of Medicine & Public Health, University of Newcastle, Callaghan, Australia. ⁶³³Priority Research Centre for Health Behaviour, University of Newcastle, Callaghan, Australia. ⁶³⁴Research Unit, Sørlandet Hospital, Kristiansand, Norway. ⁶³⁵Department of Statistics and Applied Probability, University of California, Santa Barbara, CA, USA. ⁶³⁶Computational Research Division, Lawrence Berkeley National Laboratory, University of California at Berkeley, Berkeley, CA, USA. ⁶³⁷NSW Health Pathology, Newcastle, Australia. ⁶³⁸Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. ⁶³⁹Institute of Psychiatry, Psychology & Neuroscience, Social Genetics & Developmental Psychiatry Center, MRC, Kings College London, London, UK. ⁶⁴⁰NIHR Maudsley Biomedical Research Centre, South London & Maudsley NHS Trust & King's College London, London, UK. ⁶⁴¹Departments of Psychiatry and Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ⁶⁴²Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA. ⁶⁴³Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. ⁶⁴⁴Division Biomedical Genetics, University Medical Center Utrecht, Utrecht, the Netherlands. ⁶⁴⁵Department of Psychiatry and UF Genetics Institute, University of Florida, Gainesville, FL, USA. ⁶⁴⁶Division of Cognitive and Behavioral Neurology, Brigham and Women's Hospital, Boston, MA, USA. ⁶⁴⁷Department of Neurology, Yale School of Medicine, New Haven, CT, USA. ⁶⁴⁸Department of Genetics and Psychiatry, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA. ⁶⁴⁹Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Dublin, Ireland.
- *Corresponding author. Email: vermeri.anttila@gmail.com (V.A.); acorvin@tcd.ie (A.C.); bneale@broadinstitute.org (B.M.N.)**
- †These authors contributed equally to this work.

SUPPLEMENTARY MATERIALS

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