

Original Article

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Genetic stratification of depression by neuroticism: revisiting a diagnostic tradition

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Abstract

Background. Major depressive disorder and neuroticism (Neu) share a large genetic basis. We sought to determine whether this shared basis could be decomposed to identify genetic factors that are specific to depression.

Methods. We analysed summary statistics from genome-wide association studies (GWAS) of depression (from the Psychiatric Genomics Consortium, 23andMe and UK Biobank) and compared them with GWAS of Neu (from UK Biobank). First, we used a pairwise GWAS analysis to classify variants as associated with only depression, with only Neu or with both. Second, we estimated partial genetic correlations to test whether the depression's genetic link with other phenotypes was explained by shared overlap with Neu.

Results. We found evidence that most genomic regions (25/37) associated with depression are likely to be shared with Neu. The overlapping common genetic variance of depression and Neu was genetically correlated primarily with psychiatric disorders. We found that the genetic contributions to depression, that were not shared with Neu, were positively correlated with metabolic phenotypes and cardiovascular disease, and negatively correlated with the personality trait conscientiousness. After removing shared genetic overlap with Neu, depression still had a specific association with schizophrenia, bipolar disorder, coronary artery disease and age of first birth. Independent of depression, Neu had specific genetic correlates in ulcerative colitis, pubertal growth, anorexia and education.

Conclusion. Our findings demonstrate that, while genetic risk factors for depression are largely shared with Neu, there are also non-Neu-related features of depression that may be useful for further patient or phenotypic stratification.

Introduction

Major depressive disorder (MDD) is a leading cause of morbidity worldwide, currently affecting approximately 4% of the world's population (World Health Organization, 2017). MDD is classified by the World Health Organisation and American Psychiatric Association according to its severity, its recurrence or chronicity, and the presence or absence of psychotic symptoms. This approach aims to maximise the reliability of MDD's diagnosis while being agnostic about its underlying aetiology until robust evidence of causal mechanisms can be used to stratify the condition.

Historically, depression had been classified on the basis of pre-existing emotional instability into 'neurotic' and 'endogenous' forms (Kendell, 1977). 'Neurotic depression' was diagnosed in the presence of pre-existing emotional instability and was reported to occur in younger individuals who more frequently expressed suicidal ideation. 'Endogenous depression', in contrast, was characterised by more frequent melancholic symptoms, including disrupted sleep, impaired appetite, diurnal variation of mood and impaired cognition. Individuals with endogenous depression were described as more responsive to antidepressant treatments (Fava *et al.*, 2008).

The nosological status of neurotic and endogenous depression has, however, been very controversial (Parker, 2000). Some studies have found empirical support for the neurotic/endogenous division based upon self-report and clinical data (Zimmerman *et al.*, 1986), whereas other studies found little empirical support for the distinction and noted that

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individuals with low mood responded to antidepressant treatments regardless of their subtype (Arnouk *et al.*, 2015).

The tendency towards emotional instability, or neuroticism (Neu), is a robustly and consistently replicated dimension of personality that is relatively stable over time (Eysenck, 1947). Neu features in the most widely accepted theory of personality structure, the Five Factor model, alongside openness to experience, extraversion, conscientiousness and agreeableness (Digman, 1990). Trait Neu (sometimes also labelled as emotionality or its opposite, emotional stability) is identified consistently and is composed of items reflecting low mood, stress sensitivity, irritability and emotional control (McCrae and Costa, 1987).

Twin, family and genomic studies have shown that population variation in Neu and liability to depression are conferred by both genetic and environmental risk factors (Sullivan *et al.*, 2000; Keller *et al.*, 2005; Lubke *et al.*, 2012; Boraska *et al.*, 2014; Zeng *et al.*, 2016; Hill *et al.*, 2018). While earlier studies (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013) had difficulty in discovering specific genetic variants for depression, possibly partly because of heterogeneity (Levinson *et al.*, 2014), recent studies have identified genome-wide significantly associated loci either by focusing on more rigorously defined MDD phenotypes (CONVERGE Consortium, 2015) or by meta-analysing case-control samples with larger sample-size studies that use broader major depression (MD) phenotypes (Hyde *et al.*, 2016; Direk *et al.*, 2017; Howard *et al.*, 2018, 2019; Wray *et al.*, 2018; Amare *et al.*, 2019). Results from genome-wide association studies (GWAS) of MD primarily implicate brain-expressed genes, developmental regulatory pathways and education and body mass index (BMI) as causal factors. Recent studies of Neu have also identified over 100 genome-wide significant loci (Luciano *et al.*, 2017; Nagel *et al.*, 2018), and likewise are associated with genes involved in neuronal genesis. More recent work examining the heterogeneity of Neu has identified many more loci that are specific to the traits that make-up Neu. Confirming earlier findings from biometric studies (Fanouk *et al.*, 2002; Kendler *et al.*, 2006), these studies have shown that depression and Neu have a genetic correlation of between 0.45 and 0.7 and thus share a moderate to substantial proportion of their genetic architecture (Luciano *et al.*, 2017). Since this genetic correlation is sizeable but still less than 1, it suggests that depression and Neu are either both unreliable measures of the same underlying genetic predisposition or it indicates that depression and Neu may not be identical in terms of their genetic architecture. This may be because the effect sizes of each variant (Chesmore *et al.*, 2018) differ between depression and Neu, which includes the possibility that some variants affect one trait but not the other. A third (non-exclusive) possibility is that Neu or one of its facets is directly related to only a subtype of depression and that other subtypes will have distinct genetic aetiologies (Kendler *et al.*, 2013; Hill *et al.*, 2019).

In the current study we sought to compare genome-wide association summary statistics for depression and Neu to test whether there are specific genetic contributions to depression that are independent of Neu. First, we sought to identify loci that conferred a higher risk of depression, but not higher Neu, and vice versa. We then annotated the function of any associated loci. Second, we sought to determine whether depression and Neu have any unique genetic correlations with other traits and disorders after adjustment for the other variable.

Methods

Data sources

We used depression summary statistics from the Psychiatric Genomics Consortium (PGC) (Wray *et al.*, 2018), from the UK Biobank (Howard *et al.*, 2019) and from the 23andMe cohort (Hyde *et al.*, 2016). We also obtained PGC MD summary statistics that included the 23andMe cohort, but excluded the UK Biobank cohort ($N = 431\,394$, $116\,404$ cases and $314\,990$ controls, prevalence = 0.27, 9 030 847 variants). We compared the depression summary statistics with summary statistics for Neu (Luciano *et al.*, 2017) in UK Biobank ($N = 329\,821$, 18 485 883 variants).

Pairwise GWAS of depression and neuroticism

To identify loci that contribute to variation in liability to depression, but not Neu, we used pairwise GWAS (Pickrell *et al.*, 2016) to jointly analyse summary statistics from depression and Neu. Because this method requires that summary statistic sample overlap be minimised, we examined recent meta-analyses (Nagel *et al.*, 2018; Howard *et al.*, 2019) and identified sources of summary statistics that could yield the largest, independent sample sizes for both sets of summary statistics. We used depression summary statistics from the PGC MDD2 meta-analysis (Wray *et al.*, 2018) of PGC and 23andMe data that excluded summary statistics from the UK Biobank sample (N cases = 116 404; N controls = 314 990); for Neu we used summary statistics from the UK Biobank sample (Luciano *et al.*, 2017) ($N = 329\,821$). We used the `munge_sumstats.py` tool (Bulik-Sullivan *et al.*, 2015) to convert the summary statistics to z -scores and to align and filter effect alleles to a common reference (HapMap 3 SNPs). Using these filtered summary statistics, the `gwas-pw` program (Pickrell *et al.*, 2016) models the probability that each locus is associated with only one of the two traits, the probability that the locus has a shared association with both traits, and the probability that each of the genomic regions contains separate loci that are associated with each trait. We analysed the summary statistics by splitting them into genomic segments (1702 in total) that were approximately independent based on linkage disequilibrium (Berisa and Pickrell, 2016). To correct for potential cohort overlap, we first identified loci that were not associated with both traits using the `fgwas` program (Pickrell, 2014). We then retained segments that had a posterior probability of association < 0.2 with either trait. Using these non-associated segments, we calculated the correlation of effect sizes across the depression and Neu summary statistics, and then supplied this correlation coefficient to `gwas-pw`. The `gwas-pw` program performs a Bayesian test on each genomic region to estimate the probability of unique or overlapping association signals from the two sets of GWAS summary statistics (Pickrell *et al.*, 2016).

Using the `gwas-pw` output, we categorised each segment as being associated with depression only, Neu only, both traits or neither trait. We defined depression-only segments as those that had the highest posterior probability associated with only depression and that also had a genome-wide significant hit in the original GWAS but did not contain a genome-wide significant hit for Neu (and vice versa for Neu-only segments). We defined segments that were associated with neither trait as those that had a total posterior probability of association < 0.2 and that did not contain any genome-wide hits for either trait. To examine the depression-only signal, we excluded segments associated with

Neu or with both traits from the depression summary statistics, clumped single-nucleotide polymorphisms (SNPs) that were in linkage disequilibrium (LD) ($r^2 > 0.1$) and within 3 Mb, then used MAGMA (de Leeuw *et al.*, 2015) to identify significantly associated ($p < 2.77 \times 10^{-6}$) genes and conducted GWAS catalogue lookups using FUMA (Watanabe *et al.*, 2017). We then conducted the same set of analyses on the Neu-only segments from the Neu summary statistics and the segments associated with both depression and Neu from the depression summary statistics.

Genetic correlations with depression adjusted for neuroticism

We used cross-trait genetic correlations to identify traits that were related to MD after removing their shared genetic effects with Neu. To start, we first obtained estimates of genetic correlations from GWAS summary statistics that were downloaded from the LD Hub (Zheng *et al.*, 2017). The LD Hub results contained information on genetic correlations with MDD from the PGC (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013) and Neu from the Genetics of Personality Consortium (GPC) (de Moor *et al.*, 2012). We selected 18 traits of interest that were nominally genetically correlated ($p < 0.01$) with either MDD or Neu. These included psychiatric disorders, personality traits, cardiovascular and inflammatory diseases, anthropometric and life-history traits, education and lifestyle factors. We supplemented this list of traits with BMI since obesity has been identified as a potential stratifying factor for depression (Milaneschi *et al.*, 2017) and retained the summary statistics for GPC Neu as a check on the method. We also substituted summary statistics from larger and more recent GWAS than those listed in the LD Hub download, where available (online Supplementary Table S1). For each trait of interest, we calculated its genetic correlation using Linkage Disequilibrium Score (LDSC) regression (Bulik-Sullivan *et al.*, 2015) with the recent GWAS summary statistics for MD and Neu. For depression we used a meta-analysis of PGC, 23andMe and UK Biobank (Howard *et al.*, 2019) and for Neu we used data from UK Biobank (Luciano *et al.*, 2017).

Our goal was to determine whether depression's genetic correlation with each trait of interest is (1) explained by the genetic architecture shared between depression and Neu ('neurotic depression') or (2) specific to depression and independent of Neu ('non-neurotic depression') (and vice versa for 'depressive neuroticism' and 'non-depressive neuroticism'). We estimated the genetic covariance among MD, Neu and each trait using GenomicSEM (Grotzinger *et al.*, 2019) and fitted a multiple regression model:

$$Y_g = b_1 MD_g + b_2 Neu_g + u_Y$$

where Y_g , MD_g and Neu_g are the LDSC genetic values for trait Y , major depression and Neu, respectively; b_1 and b_2 are regression coefficients and u_Y is an error term. We used standardised estimates of the regression coefficients to obtain the partial correlations of MD after removing shared overlap with Neu, and vice versa. We first identified traits that were genetically correlated with MD but not with Neu. We then identified traits that were genetically correlated with both depression and Neu but that had a substantial partial genetic correlation with depression after adjusting for Neu (MD·adjNeu) but not with Neu after adjusting for depression (Neu·adjMD). Finally, we identified traits with the opposite patterns of having genetic correlations that were

specific to Neu or to Neu after adjusting for depression. We tested whether unadjusted and adjusted correlations were different from zero and whether adjusted correlations were smaller than their unadjusted counterparts and corrected for multiple testing using False Discovery Rate (Benjamini and Yekutieli, 2001).

Results

Pairwise GWAS of depression and neuroticism

We used pairwise GWAS (Pickrell *et al.*, 2016) between depression and Neu to partition genomic segments with association signals for MD only, for Neu only, for both traits or that contained different associations for each trait. These associations were assessed by posterior probabilities, where higher values mean more probable. The correlation in beta coefficients from the summary statistics in genomic segments that were not associated with either MD or Neu was $r = 0.005$, suggesting there was no undetected sample overlap between the two studies. We identified nine genomic segments containing loci that influence depression but do not associate with Neu (i.e. association with depression-only had the highest posterior probability) (Fig. 1, Table 1). This represented 24% of the total 37 genomic segments that contained loci previously associated with depression. The analysis indicated that there were three genomic segments that contained separate associations for depression and Neu (online Supplementary Table S2 and Figs S1–S3). There were 25 GWAS hits for depression that were also associated with Neu; in addition, there were 45 more regions that, while below the threshold of genome-wide significance for depression, the pairwise analysis indicated were associated with both depression and Neu. Finally, there were also 40 genomic segments that were significantly associated only with Neu (online Supplementary Table S2).

We used MAGMA (de Leeuw *et al.*, 2015) to identify genes associated ($p < 2.77 \times 10^{-6}$) with the partitioned genomic segments. There were 30 genes significantly associated with depression only (online Supplementary Table S3), 203 genes associated with Neu only (online Supplementary Table S4) and 104 genes associated with both depression and Neu (online Supplementary Table S5). We used FUMA (Watanabe *et al.*, 2017) to conduct GWAS catalogue lookups on these gene sets (online Supplementary Table S6). MD was uniquely associated with gene sets that are linked to N-glycan levels ($p = 1.1 \times 10^{-8}$) and to coronary heart disease ($p = 3.2 \times 10^{-3}$). Neu-only gene sets were related to traits such as intracranial volume, Parkinson's disease and high-density lipoprotein cholesterol. The gene sets shared by depression and Neu were related to cross-disorder psychiatric traits, coffee consumption and epilepsy, among other traits (online Supplementary S6).

Partial genetic correlations with depression removing neuroticism

The LD score genetic correlation between MD and Neu was 0.680 ± 0.028 s.e. We fitted multiple regression models in GenomicSEM to estimate the unadjusted genetic correlation of each trait of interest with MD and with Neu and the partial genetic correlation with depression where the shared overlap with Neu has been removed (MD·adjNeu) and with Neu where overlap with depression has been removed (Neu·adjMD) (Fig. 2, online Supplementary Table S1). We grouped traits based on the pattern of their unadjusted and adjusted genetic correlations with MD and Neu.

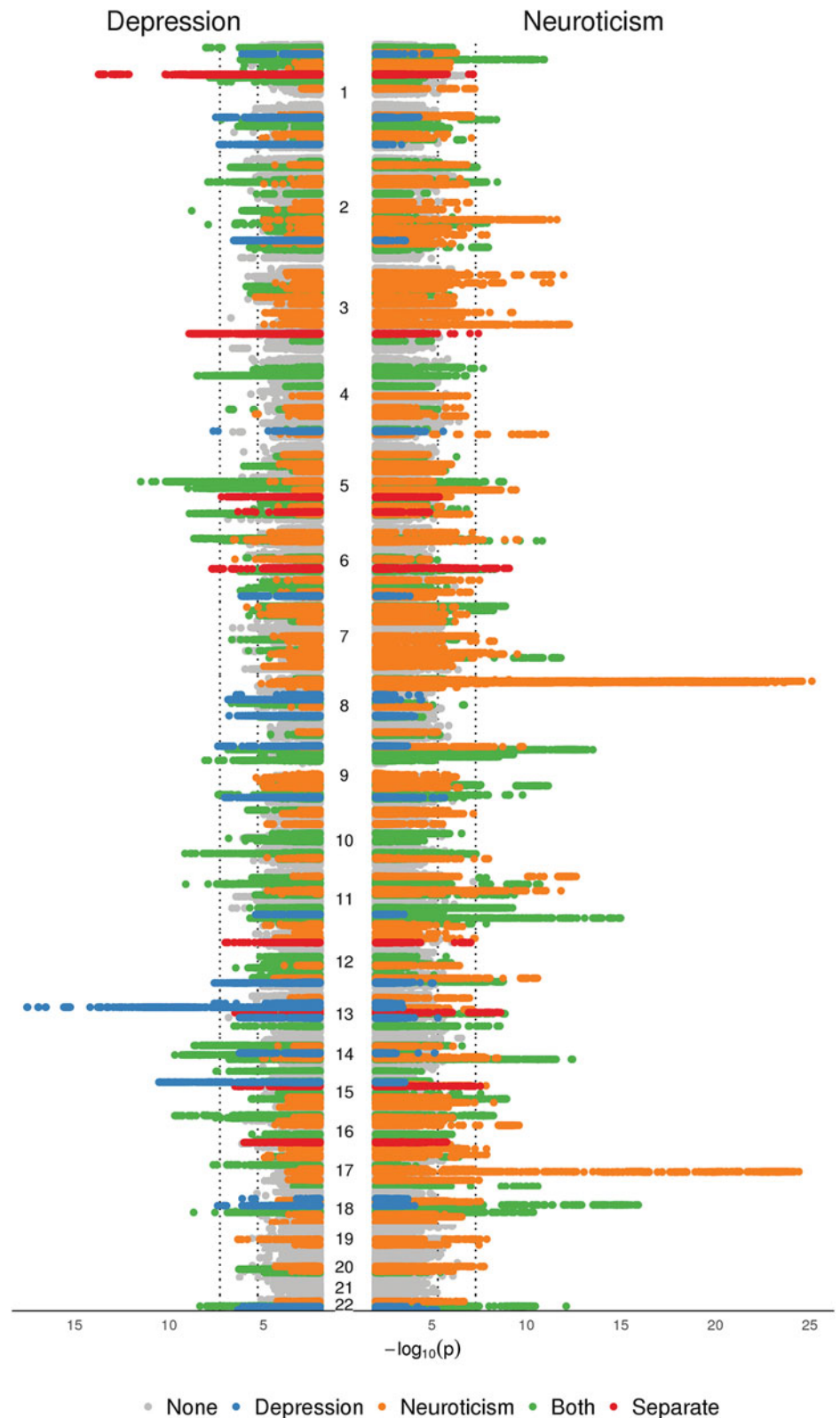


Fig. 1. Manhattan plot of pairwise GWAS of depression and Neu with genomic segments partitioned by association with depression-only (blue), Neu only (orange), both traits (green), separate associations (red) or neither trait (grey).

Two traits were genetically correlated with both MD and Neu that were slightly (depressive symptoms) or completely (sleep duration) attenuated when adjusting for the other variable. Three traits (triglycerides, BMI and conscientiousness) were genetically correlated with MD but not Neu while another two traits (ulcerative colitis

and pubertal growth) were genetically correlated with Neu but not with depression. There are two traits (apolipoprotein A-1 and bone density) that were correlated with neither MD nor Neu.

The multiple regression analyses identified traits correlated with MD and Neu but that had specific genetic correlations

Table 1. Genomic regions that are likely associated with depression but not with Neu that also contain a genome-wide significant SNP for depression

Chr	Region (Mb)	Prob (Dep only)	Prob(N only)	Prob (both)	Prob (separate)	Top SNP	BP	A1/2	Dep. GWAS p -value
1	175.090–177.433	0.533	0.001	0.287	0.094	rs10913112	175 913 828	T/C	3.02×10^{-8}
1	241.583–242.071	0.657	3×10^{-4}	0.176	0.032	rs4660091	241 628 430	T/C	4.64×10^{-8}
4	174.267–176.568	0.011	0.004	0.004	0.001	rs75990749	175 349 867	C/G	2.22×10^{-8}
9	1.920–3.185	0.449	0.001	0.413	0.053	rs7036618	2 990 717	A/C	3.92×10^{-8}
12	119.759–121.989	0.380	0.005	0.222	0.092	rs77741769	121 363 835	T/C	2.53×10^{-8}
13	43.109–44.901	0.595	0.001	0.151	0.123	rs4143229	44 327 799	A/C	2.50×10^{-8}
13	53.340–54.681	0.800	3×10^{-13}	0.108	0.120	rs1343605	53 647 048	A/C	3.09×10^{-18}
15	37.461–38.528	0.514	7×10^{-7}	0.363	0.001	rs834629	37 678 862	T/C	2.97×10^{-11}
18	36.366–37.683	0.337	0.004	0.285	0.046	chr18_36904688_1	36 904 688	D/I	3.80×10^{-8}

For each segment, the posterior probability of association (higher value means more probable) with depression only [Prob(Dep only)] is compared with Neu only [Prob(N only)], with the same association signal for both traits [Prob(both)] or with separate association signals effecting each trait [Prob(separate)]. For each region, the top SNP associated with MDD is listed along with its base pair position (BP) and GWAS p -value.

with only one of these phenotypes after adjusting for shared overlap with the other, wherein the partial correlation was maintained for the focal phenotype but went to zero or had the opposite sign for the other phenotype. MD had specific genetic correlations with attention deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, coronary artery disease and age of first birth. There were three additional traits [cigarettes smoked per day, waist-hip ratio and chronotype ('morningness')] that showed a similar pattern of full and partial correlations with MD, but where the effect sizes overlapped with those for Neu, and thus their status of having a specific relationship was less well supported. Finally, there were three traits (Neu measured in the GPC, anorexia and years of schooling) that showed specific relationships with Neu after removing shared overlap with MD.

Discussion

We conducted complementary analyses to separate the specific genetic features of MD from those that overlap with Neu and vice versa. The pairwise GWAS analysis using depression results from the PGC and 23andMe and Neu results from UK Biobank revealed nine genomic regions that were significantly associated with depression but not with Neu. Several of the associated regions contained genes of known function: rs10913112 is downstream of *RFWD2* (ring finger and WD repeat domain 2), a gene that can promote tumour growth (Dornan *et al.*, 2004); rs4660091 is near the fumarate hydratase gene (*FH*) which is involved in the Krebs cycle; rs4143229 is in an intron of the ecto-NOX disulphide-thiol exchanger 1 gene (*ENOX1*) which is expressed in the nervous systems and has been implicated in autoimmune disorders (Landouré *et al.*, 2012) and rs1343605 is near *OLFM4*, a gene that has been linked to depression (Wray *et al.*, 2018), inflammation and cancer (Liu and Rodgers, 2016).

There were 40 independent regions that were associated with Neu but not depression. These included the two large inversion polymorphisms, located on chromosomes 8 and 17, that have previously been associated with Neu (Okbay *et al.*, 2016; Luciano *et al.*, 2017). These polymorphisms are thought to influence the regulation of the genes in these regions, some of which are highly expressed in the nervous (*MAPT*, *MSRA*, *MTMR9*) and immune

(*BLK*, *MFHAS1*) systems (Okbay *et al.*, 2016). The remaining regions of interest were associated with both depression and Neu. These included the MHC region; *DRD2*, the dopamine D2 receptor involved in mood and emotion; *MEF2C*, a gene that regulates synaptic function; *TCF4*, a regulator of prefrontal neuronal excitability and *RFXO1*, a gene splicing regulator that has also been implicated in other psychiatric disorders (Okbay *et al.*, 2016; Wray *et al.*, 2018; Howard *et al.*, 2019). There were 10 regions that did not contain genome-wide significant associations in either depression or Neu summary statistics but that, when analysed jointly in the pairwise analysis, appeared to be associated with both traits. The novel loci included SNPs in or near the *DENND1B* (DENN domain containing 1B) gene, which has been implicated in childhood asthma (Sleiman *et al.*, 2010); RNF103 (ring finger protein 103), a suspected antidepressant target (Yamada *et al.*, 2000) and genes related to axon guidance (DCC netrin 1 receptor) (Kolodziej *et al.*, 1996). There was also a non-novel locus in the PCLO (piccolo presynaptic cytomatrix protein) gene involved in synaptic vesicle trafficking that, while not genome-wide significant in the PGC and 23andMe meta-analysis (Wray *et al.*, 2018) did reach genome-wide significance separately for MDD in single cohort (Mbarek *et al.*, 2017) that is included in the PGC meta-analyses.

The pairwise GWAS also suggested three regions that contained separate association signals for depression and Neu. For example, a region (71.6–74.3 Mb on chromosome 1, online Supplementary Fig. S1) contained two association signals for depression. The first signal (rs1460942) was shared with Neu and was close to the neuronal growth regulator 1 (*NEGR1*) gene. A second association signal (rs12129573) was in the intron of an uncharacterised non-protein coding RNA (*LOC105378800*). In a further region, a signal was found (97.8–100.6 Mb on chromosome 6) that showed a clear separation between the association signals for each trait (online Supplementary Fig. S3). The SNP associated with depression (rs12202410) was near the F-box and leucine-rich repeat protein 4 (*FBXL4*) gene which is related to energy homeostasis (Gai *et al.*, 2013).

Using a GWAS catalogue lookup with FUMA (Watanabe *et al.*, 2017) on the pairwise GWAS results, we found that genes associated with depression, but not with Neu, were also associated

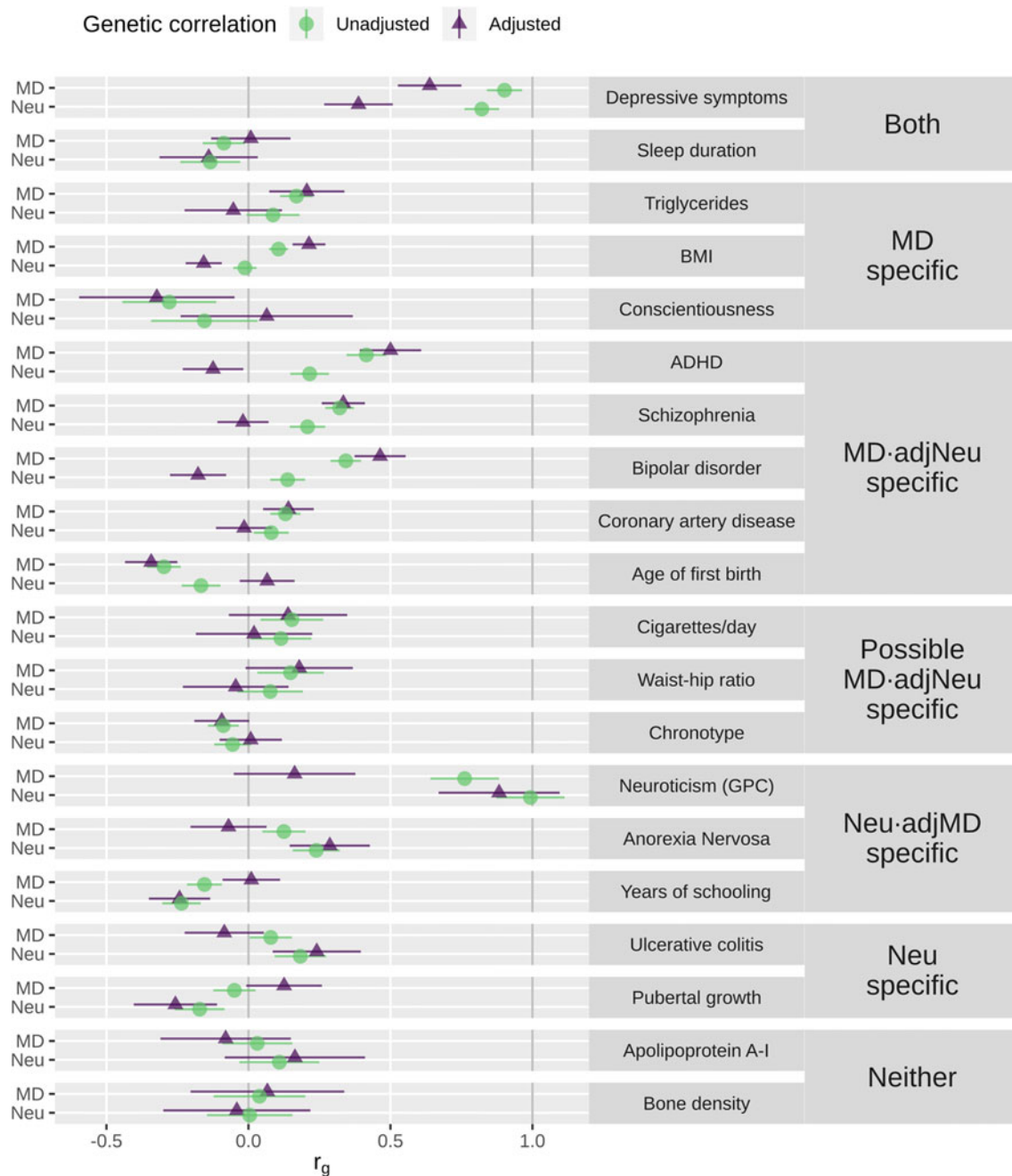


Fig. 2. Genetic correlations of traits with MD and with Neu. Full, unadjusted correlations (green circles) and partial genetic correlations after adjusting for the other variable (purple triangles) with 95% confidence intervals. We grouped traits based on the patterning of full and partial genetic correlations: both = genetically correlated with MD and Neu, with specific or entirely shared overlap; MD specific = genetically correlated with depression but not Neu; MD·adjNeu specific = fully correlated with both MD and Neu, but partially correlated with only MD; Possible MD·adjNeu specific = fully or partially correlated with depression and not Neu, but substantial overlap in effect sizes; Neu·adjMD specific = fully correlated with both MD and Neu, but partially correlated with only Neu; Neu specific = genetically correlated with Neu but not depression; neither = not genetically correlated with either depression or Neu.

with glycosylation and coronary heart disease. This suggests that there may be subtypes of depression involving inflammation and cardiovascular disease that are separate from subtypes of depression associated with Neu. In contrast, genes that were associated with both depression and Neu were also associated with psychological, behavioural and psychiatric traits such as schizophrenia, autism spectrum disorder and intelligence, suggesting that they may influence behaviour and cognitive function more generally.

Differential association of MD with other traits, once shared overlap with Neu was accounted for, was also shown in our analysis of LD score genetic correlations. We found that, unlike Neu, MD was genetically correlated with BMI, triglyceride levels and coronary artery disease, suggesting the atypical depressive subtype related to cardio-metabolic traits (Lasserre *et al.*, 2016; Milaneschi *et al.*, 2017). Even after removing shared genetic overlap with Neu, MD was still specifically related to ADHD, schizophrenia, bipolar

disorder, coronary artery disease and age of first birth; and also possibly to smoking, waist–hip ratio and chronotype ('morningness'). The robust association with schizophrenia and bipolar disorder after adjusting for overlap with Neu may indicate genetic subtype heterogeneity among depression cases or the over-inclusiveness of minimal depression phenotyping (Cai *et al.*, 2019). In contrast, the genetic architecture of depression that is shared with Neu explained all or most of the genetic correlation of depression with anorexia and years of schooling, which arise from the worry/vulnerability and anxiety/tension subfactors of Neu (Hill *et al.*, 2019).

One limitation of our study is that by using summary statistics from GWAS, we were only able to assess the overlap in genetic architecture between depression and Neu that arises from common variants. Even biobank-sized samples of millions of participants can be underpowered for detecting associations with rare variants unless such variants have very large effect sizes (Visscher *et al.*, 2017). While common variants contribute a large proportion to phenotype heritabilities (Shi *et al.*, 2016), and thus trait covariances, it is not known how the strength of any correlation will differ between rare and common polymorphisms (Shi *et al.*, 2016, 2017). Furthermore there is evidence that rare variants are associated with both Neu and depression (Zeng *et al.*, 2016; Hill *et al.*, 2018). Much will depend on the evolutionary history of both phenotypes. If, for example, antagonistic pleiotropy, where a variant has opposite effects on two phenotypes, is maintaining common variants, then rare variants might be more likely to affect both traits in the same direction (Carter and Nguyen, 2011). A second limitation is that we used summary statistics for MD that were meta-analysed from studies with varying levels of phenotyping depth and thus may be picking up on genetic overlap that is more broadly shared with other psychiatric disorders rather than specific to clinically defined MDD (Cai *et al.*, 2019). Another limitation is that our source studies used case/control definitions of depression and sum-score quantities of Neu, while other analyses of individual depressive symptoms (Thorp *et al.*, 2019) and factors of Neu (Hill *et al.*, 2019) shows that depression and Neu are composed of subfactors that themselves have unique associations with other traits.

Neu is a major risk factor for depression (Bagby *et al.*, 1995; Kendler *et al.*, 2004), the two traits are strongly genetically correlated (Jardine *et al.*, 1984; Fanous *et al.*, 2002; Luciano *et al.*, 2017), and Mendelian randomisation analysis has pinpointed high Neu as a cause of depression (Howard *et al.*, 2019). Our results confirm that the majority of specific genetic variants associated with depression are shared with Neu. However, we also identified several association signals and overlap with other traits that were unique to depression. In particular, the pairwise GWAS analysis both identified new associations with depression and separated out associations that were specific to depression while the partial genetic correlation analysis identified other phenotypes that are related to depression even after removing shared genetic overlap with Neu. This suggests that that depression and Neu are not *just* noisy measures of the same underlying liability. If these differences represent distinct genetic subtypes of depression, then most cases of depression will stem from this Neu–depression nexus, while a smaller proportion may have aetiologies that are distinct from Neu. Some of these associations, such as between depression, chronotype and metabolic phenotypes, are suggestive of endogenous depression's features but do not point to all the characteristics of this previously described subtype. Confirming known depression subtypes and identifying new subtypes will

be useful for phenotypic and clinical stratification. The unique associations of triglyceride levels and BMI with depression, but not at all with Neu, confirms that depression with comorbid obesity and other metabolic factors should be studied as a subtype when exploring aetiology and testing treatment efficacy. The partial genetic correlations that ADHD, schizophrenia and bipolar disorder have with depression after adjusting for Neu imply that polygenic risk scores for these other disorders may be useful to screen or stratify participants even if they do not manifest these other disorders.

Neither depression (Kendler *et al.*, 2013; Thorp *et al.*, 2019) nor Neu (Hill *et al.*, 2019) is completely genetically homogeneous. Because the common variant genetic overlap is high between different forms of assessing depression (clinically ascertained, brief questionnaire, hospital records) (Howard *et al.*, 2018; Wray *et al.*, 2018), our results suggest that much of the shared genetic variance, where depression and non-depression are on a continuum, is wrapped-up in the Neu–depression nexus, and that going forward additional studies based on a more refined, symptom-level analysis may be more revealing for non-Neu-related forms of depression.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291719002629>.

Data. The full MDD summary statistics from Hyde *et al.* are made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Visit <https://research.23andme.com/collaborate> for more information and to apply to access the data. Summary statistics from the Psychiatric Genomics Consortium (Wray *et al.*, 2018; Howard *et al.*, 2019) are available for download from <http://www.med.unc.edu/pgc/>. Summary statistics for Neu in UK Biobank are available from the Centre for Cognitive Aging and Cognitive Epidemiology <http://www.ccace.ed.ac.uk/node/335>.

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References

Amare AT, Vaez A, Hsu Y-H, Direk N, Kamali Z, Howard DM, McIntosh AM, Tiemeier H, Bültmann U, Snieder H and Hartman CA (2019) Bivariate genome-wide association analyses of the broad depression phenotype combined with major depressive disorder, bipolar disorder or

- schizophrenia reveal eight novel genetic loci for depression. *Molecular Psychiatry*, s41380-018-0336-6, 1–10.
- Arnold BA, Blasey C, Williams LM, Palmer DM, Rekschan W, Schatzberg AF, Etkin A, Kulkarni J, Luther JF and Rush AJ (2015) Depression subtypes in predicting antidepressant response: a report from the iSPOT-D trial. *American Journal of Psychiatry* 172, 743–750.
- Bagby RM, Joffe RT, Parker JDA, Kalemka V and Harkness KL (1995) Major depression and the five-factor model of personality. *Journal of Personality Disorders* 9, 224–234.
- Benjamini Y and Yekutieli D (2001) The control of the false discovery rate in multiple testing under dependency. *The Annals of Statistics* 29, 1165–1188.
- Berisa T and Pickrell JK (2016) Approximately independent linkage disequilibrium blocks in human populations. *Bioinformatics (Oxford, England)* 32, 283–285.
- Boraska V, Franklin CS, Floyd JA, Thornton LM, Huckins LM, Southam L, Rayner NW, Tachmazidou I, Klump KL, Treasure J, Lewis CM, Schmidt U, Tozzi F, Kiezebrink K, Hebebrand J, Gorwood P, Adan RA, Kas MJ, Favaro A, Santonastaso P, Fernandez-Aranda F, Gratacos M, Rybakowski F, Dmitrzak-Weglarz M, Kaprio J, Keski-Rahkonen A, Raevuori A, Van Furth EF, Slof-Op 't Landt MC, Hudson JJ, Reichborn-Kjennerud T, Knudsen GP, Monteleone P, Kaplan AS, Karwautz A, Hakonarson H, Berrettini WH, Guo Y, Li D, Schork NJ, Komaki G, Ando T, Inoko H, Esko T, Fischer K, Mannik K, Metspalu A, Baker JH, Cone RD, Dackor J, DeSocio JE, Hilliard CE, O'Toole JK, Pantel J, Szatkiewicz JP, Taico C, Zerwas S, Trace SE, Davis OS, Helder S, Buhren K, Burghardt R, de Zwaan M, Egberts K, Ehrlich S, Herpertz-Dahlmann B, Herzog W, Imgart H, Scherag A, Scherag S, Zipfel S, Boni C, Ramoz N, Versini A, Brandys MK, Danner UN, de Kovel C, Hendriks J, Koeleman BP, Ophoff RA, Strengman E, van Elburg AA, Bruson A, Clementi M, Degortes D, Forzan M, Tenconi E, Docampo E, Escaramis G, Jimenez-Murcia S, Lissowska J, Rajewski A, Szeszenia-Dabrowska N, Slopian A, Hauser J, Karhunen L, Meulenbelt I, Slagboom PE, Tortorella A, Maj M, Dedoussis G, Dikeos D, Gonidakis F, Tziouvas K, Tsitsika A, Papezova H, Slachтова L, Martaskova D, Kennedy JL, Levitan RD, Yilmaz Z, Huemer J, Koubek D, Merl E, Wagner G, Lichtenstein P, Breen G, Cohen-Woods S, Farmer A, McGuffin P, Cichon S, Giegling I, Herms S, Rujescu D, Schreiber S, Wichmann HE, Dina C, Sladek R, Gambaro G, Soranzo N, Julia A, Marsal S, Rabionet R, Gaborieau V, Dick DM, Palotie A, Ripatti S, Widen E, Andreassen OA, Espeseth T, Lundervold A, Reinvang I, Steen VM, Le Hellard S, Mattingsdal M, Ntalla I, Bencko V, Foretova L, Janout V, Navratilova M, Gallinger S, Pinto D, Scherer SW, Aschauer H, Carlberg L, Schosser A, Alfredsson L, Ding B, Klareskog L, Padyukov L, Courtet P, Guillaume S, Jaussent I, Finan C, Kalsi G, Roberts M, Logan DW, Peltonen L, Ritchie GR, Barrett JC, Estivill X, Hinney A, Sullivan PF, Collier DA, Zeggini E and Bulik CM (2014) A genome-wide association study of anorexia nervosa. *Molecular Psychiatry* 19, 1085–1094.
- Bulik-Sullivan BK, Loh P-R, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson N, Daly MJ, Price AL and Neale BM (2015) LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics* 47, 291–295.
- Cai N, Revez JA, Adams MJ, Andlauer TFM, Breen G, Byrne EM, Clarke T-K, Forstner AJJ, Grabe HJJ, Hamilton SP, Levinson DF, Lewis CM, Lewis G, Martin NG, Milaneschi Y, Mors O, Muller-Myhsok B, Penninx BWJH, Perlis RH, Pistis G, Potash JB, Preisig M, Shi J, Smoller JW, Streit F, Tiemeier H, Uher R, Van der Auwera S, Viktorin A, Weissman MM, Kendler KS and Flint J (2019) Minimal phenotyping yields GWAS hits of low specificity for major depression. *bioRxiv* 440735, 1–34.
- Carter AJR and Nguyen AQ (2011) Antagonistic pleiotropy as a widespread mechanism for the maintenance of polymorphic disease alleles. *BMC Medical Genetics* 12, 160.
- Chesmore K, Bartlett J and Williams SM (2018) The ubiquity of pleiotropy in human disease. *Human Genetics* 137, 39–44.
- CONVERGE Consortium (2015) Sparse whole-genome sequencing identifies two loci for major depressive disorder. *Nature* 523, 588–591.
- de Leeuw CA, Mooij JM, Heskes T and Posthuma D (2015) MAGMA: generalized gene-set analysis of GWAS data. *PLoS Computational Biology* 11, e1004219.
- de Moor MH, Costa PT, Terracciano A, Krueger RF, de Geus EJ, Toshiko T, Penninx BW, Esko T, Madden PA, Derringer J, Amin N, Willemsen G, Hottenga JJ, Distel MA, Uda M, Sanna S, Spinhoven P, Hartman CA, Sullivan P, Realo A, Allik J, Heath AC, Pergadia ML, Agrawal A, Lin P, Grucza R, Nutile T, Ciullo M, Rujescu D, Giegling I, Konte B, Widen E, Cousminer DL, Eriksson JG, Palotie A, Peltonen L, Luciano M, Tenesa A, Davies G, Lopez LM, Hansell NK, Medland SE, Ferrucci L, Schlessinger D, Montgomery GW, Wright MJ, Aulchenko YS, Janssens AC, Oostra BA, Metspalu A, Abecasis GR, Deary IJ, Raikonen K, Bierut LJ, Martin NG, van Duijn CM and Boomsma DI (2012) Meta-analysis of genome-wide association studies for personality. *Molecular Psychiatry* 17, 337–349.
- Digman JM (1990) Personality structure: emergence of the five-factor model. *Annual Review of Psychology* 41, 417–440.
- Direk N, Williams S, Smith JA, Ripke S, Air T, Amare AT, Amin N, Baune BT, Bennett DA, Blackwood DHR, Boomsma D, Breen G, Buttenschon HN, Byrne EM, Borglum AD, Castelao E, Cichon S, Clarke T-K, Cornelis MC, Dannlowski U, De Jager PL, Demirkan A, Domenici E, van Duijn CM, Dunn EC, Eriksson JG, Esko T, Faul JD, Ferrucci L, Fornage M, de Geus E, Gill M, Gordon SD, Grabe HJ, van Grootheest G, Hamilton SP, Hartman CA, Heath AC, Hek K, Hofman A, Homuth G, Horn C, Jan Hottenga J, Kardina SLR, Kloiber S, Koenen K, Kutalik Z, Ladwig K-H, Lahti J, Levinson DF, Lewis CM, Lewis G, Li QS, Llewellyn DJ, Lucae S, Lunetta KL, MacIntyre DJ, Madden P, Martin NG, McIntosh AM, Metspalu A, Milaneschi Y, Montgomery GW, Mors O, Mosley TH, Murabito JM, Müller-Myhsok B, Nöthen MM, Nyholt DR, O'Donovan MC, Penninx BW, Pergadia ML, Perlis R, Potash JB, Preisig M, Purcell SM, Quiroz JA, Räikkönen K, Rice JP, Rietschel M, Rivera M, Schulze TG, Shi J, Shyn S, Sinnamoni GC, Smit JH, Smoller JW, Snieder H, Tanaka T, Tansey KE, Teumer A, Uher R, Umbricht D, Van der Auwera S, Ware EB, Weir DR, Weissman MM, Willemsen G, Yang J, Zhao W, Tiemeier H and Sullivan PF (2017) An analysis of two genome-wide association meta-analyses identifies a new locus for broad depression phenotype. *Biological Psychiatry* 82, 322–329.
- Dornan D, Wertz I, Shimizu H, Arnold D, Frantz GD, Dowd P, O'Rourke K, Koeppen H and Dixit VM (2004) The ubiquitin ligase COP1 is a critical negative regulator of p53. *Nature* 429, 86–92.
- Eysenck HJ (1947) *Dimensions of Personality*. London: Routledge.
- Fanous A, Gardner C, Prescott C, Cancro R and Kendler K (2002) Neuroticism, major depression and gender: a population-based twin study. *Psychological Medicine* 32, 719–728.
- Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, Biggs MM, Zisook S, Leuchter A, Howland R, Warden D and Trivedi MH (2008) Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *American Journal of Psychiatry* 165, 342–351.
- Gai X, Ghezzi D, Johnson Mark A, Biagosch Caroline A, Shamseldin Hanan E, Haack Tobias B, Reyes A, Tsukikawa M, Sheldon Claire A, Srinivasan S, Gorza M, Kremer Laura S, Wieland T, Strom Tim M, Polyak E, Place E, Consugar M, Ostrovsky J, Vidoni S, Robinson Alan J, Wong L-J, Sondheimer N, Salih Mustafa A, Al-Jishi E, Raab Christopher P, Bean C, Furlan F, Parini R, Lamperti C, Mayr Johannes A, Konstantopoulou V, Huemer M, Pierce Eric A, Meitinger T, Freisinger P, Sperl W, Prokisch H, Alkuraya Fowzan S, Falk Marni J and Zeviani M (2013) Mutations in FBXL4, encoding a mitochondrial protein, cause early-onset mitochondrial encephalomyopathy. *American Journal of Human Genetics* 93, 482–495.
- Grotzinger AD, Rhemtulla M, de Vlaming R, Ritchie SJ, Mallard TT, Hill WD, Ip HF, Marioni RE, McIntosh AM, Deary IJ, Koellinger PD, Harden KP, Nivard MG and Tucker-Drob EM (2019) Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. *Nature Human Behaviour* 3, 513–525.

- Hill WD, Arslan RC, Xia C, Luciano M, Amador C, Navarro P, Hayward C, Nagy R, Porteous DJ, McIntosh AM, Deary IJ, Haley CS and Penke L (2018) Genomic analysis of family data reveals additional genetic effects on intelligence and personality. *Molecular Psychiatry* 23, 2347–2362.
- Hill WD, Weiss A, Liewald DC, Davies G, Porteous DJ, Hayward C, McIntosh AM, Gale CR and Deary IJ (2019) Genetic contributions to two special factors of neuroticism are associated with affluence, higher intelligence, better health, and longer life. *Molecular Psychiatry*, s41380-019-0387-3, 1–19.
- Howard DM, Adams MJ, Shirali M, Clarke T-K, Marioni RE, Davies G, Coleman JRI, Alloza C, Shen X, Barbu MC, Wigmore EM, Gibson J, Agee M, Alipanahi B, Auton A, Bell RK, Bryc K, Elson SL, Fontanillas P, Furlotte NA, Hinds DA, Huber KE, Kleinman A, Litterman NK, McCreight JC, McIntyre MH, Mountain JL, Noblin ES, Northover CAM, Pitts SJ, Sathirapongsasuti JF, Sazonova OV, Shelton JF, Shringarpure S, Tian C, Tung JY, Vacic V, Wilson CH, Hagenaars SP, Lewis CM, Ward J, Smith DJ, Sullivan PF, Haley CS, Breen G, Deary IJ and McIntosh AM (2018) Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nature Communications* 9, 1470.
- Howard DM, Adams MJ, Clarke T-K, Hafferty JD, Gibson J, Shirali M, Coleman JRI, Hagenaars SP, Ward J, Wigmore EM, Alloza C, Shen X, Barbu MC, Xu EY, Whalley HC, Marioni RE, Porteous DJ, Davies G, Deary IJ, Hemani G, Berger K, Teismann H, Rawal R, Arolt V, Baune BT, Dannlowski U, Domschke K, Tian C, Hinds DA, Trzaskowski M, Byrne EM, Ripke S, Smith DJ, Sullivan PF, Wray NR, Breen G, Lewis CM, McIntosh AM and 23andMe Research Team, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (2019) Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience* 22, 343–352.
- Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, Tung JY, Hinds DA, Perlis RH and Winslow AR (2016) Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nature Genetics* 48, 1031–1036.
- Jardine R, Martin NG, Henderson AS and Rao DC (1984) Genetic covariation between neuroticism and the symptoms of anxiety and depression. *Genetic Epidemiology* 1, 89–107.
- Keller MC, Coventry WM, Heath AC and Martin NG (2005) Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. *Behavior Genetics* 35, 707–721.
- Kendell R (1977) The classification of depression. A review of contemporary confusion. In Burrows GD (ed.), *Handbook of Studies on Depression*. Amsterdam: Excerpta Medica, pp. 3–20.
- Kendler KS, Kuhn J and Prescott CA (2004) The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry* 161, 631–636.
- Kendler KS, Gatz M, Gardner CO and Pedersen NL (2006) Personality and major depression: a Swedish longitudinal, population-based twin study. *Archives of General Psychiatry* 63, 1113–1120.
- Kendler KS, Aggen SH and Neale MC (2013) Evidence for multiple genetic factors underlying DSM-IV criteria for major depression. *JAMA Psychiatry* 70, 599–607.
- Kolodziej PA, Timpe LC, Mitchell KJ, Fried SR, Goodman CS, Jan LY and Jan YN (1996) *frizzled* encodes a drosophila member of the DCC immunoglobulin subfamily and is required for CNS and Motor Axon Guidance. *Cell* 87, 197–204.
- Landouré G, Knight MA, Stanescu H, Taye AA, Shi Y, Diallo O, Johnson JO, Hernandez D, Traynor BJ, Biesecker LG, Elkhouloun A, Rinaldi C, Vincent A, Willcox N, Kleta R, Fischbeck KH and Burnett BG (2012) A candidate gene for autoimmune myasthenia gravis. *Neurology* 79, 342–347.
- Lasserre AM, Strippoli MPF, Glaus J, Gholam-Rezaee M, Vandeleur CL, Castela E, Marques-Vidal P, Waeber G, Vollenweider P and Preisig M (2016) Prospective associations of depression subtypes with cardio-metabolic risk factors in the general population. *Molecular Psychiatry* 22, 1026–1034.
- Levinson DF, Mostafavi S, Milaneschi Y, Rivera M, Ripke S, Wray NR and Sullivan PF (2014) Genetic studies of major depressive disorder: why are there no genome-wide association study findings and what can we do about it? *Biological Psychiatry* 76, 510–512.
- Liu W and Rodgers GP (2016) Olfactomedin 4 expression and functions in innate immunity, inflammation, and cancer. *Cancer Metastasis Review* 35, 201–212.
- Lubke GH, Hottenga JJ, Walters R, Laurin C, de Geus EJC, Willemsen G, Smit JH, Middeldorp CM, Penninx BWJH, Vink JM and Boomsma DI (2012) Estimating the genetic variance of major depressive disorder due to all single nucleotide polymorphisms. *Biological Psychiatry* 72, 707–709.
- Luciano M, Hagenaars SP, Davies G, Hill WD, Clarke T-K, Shirali M, Harris SE, Marioni RE, Liewald DC, Fawns-Ritchie C, Adams MJ, Howard DM, Lewis CM, Gale CR, McIntosh AM and Deary IJ (2017) Association analysis in over 329 000 individuals identifies 116 independent variants influencing neuroticism. *Nature Genetics* 50, 6–11.
- Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium (2013) A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular Psychiatry* 18, 497–511.
- Mbarek H, Milaneschi Y, Hottenga J-J, Ligthart L, de Geus EJC, Ehli EA, Willemsen G, Davies GE, Smit JH, Boomsma DI and Penninx BWJH (2017) Genome-wide significance for PCLO as a gene for major depressive disorder. *Twin Research and Human Genetics* 20, 267–270.
- McCrae RR and Costa Jr. PT (1987) Validation of the five-factor model of personality across instruments and observers. *Journal of Personality and Social Psychology* 52, 81–90.
- Milaneschi Y, Lamers F, Peyrot WJ, Baune BT, Breen G, Dehghan A, Forstner AJ, Grabe HJ, Homuth G, Kan C, Lewis C, Mullins N, Nauck M, Pistis G, Preisig M, Rivera M, Rietschel M, Streit F, Strohmaier J, Teumer A, Van der Auwera S, Wray NR, Boomsma DI, Penninx BWJH, Charge Inflammation Working Group, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (2017) Genetic association of major depression with atypical features and obesity-related immunometabolic dysregulations. *JAMA Psychiatry* 74, 1214–1225.
- Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, Savage JE, Hammerschlag AR, Skene NG, Muñoz-Manchado AB, Agee M, Alipanahi B, Auton A, Bell RK, Bryc K, Elson SL, Fontanillas P, Furlotte NA, Hinds DA, Hromatka BS, Huber KE, Kleinman A, Litterman NK, McIntyre MH, Mountain JL, Noblin ES, Northover CAM, Pitts SJ, Sathirapongsasuti JF, Sazonova OV, Shelton JF, Shringarpure S, Tian C, Tung JY, Vacic V, Wilson CH, White T, Tiemeier H, Linnarsson S, Hjerling-Leffler J, Polderman TJC, Sullivan PF, van der Sluis S, Posthuma D and 23andMe Research Team (2018) Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nature Genetics* 50, 920–927.
- Okbay A, Baselmans BM, De Neve JE, Turley P, Nivard MG, Fontana MA, Meddens SF, Linner RK, Rietveld CA, Derringer J, Gratten J, Lee JJ, Liu JZ, de Vlaming R, Ahluwalia TS, Buchwald J, Cavadino A, Frazier-Wood AC, Furlotte NA, Garfield V, Geisel MH, Gonzalez JR, Haitjema S, Karlsson R, van der Laan SW, Ladwig KH, Lahti J, van der Lee SJ, Lind PA, Liu T, Matteson L, Mihailov E, Miller MB, Minica CC, Nolte IM, Mook-Kanamori D, van der Most PJ, Oldmeadow C, Qian Y, Raitakari O, Rawal R, Realo A, Rueedi R, Schmidt B, Smith AV, Stergiakouli E, Tanaka T, Taylor K, Thorleifsson G, Wedenoja J, Wellmann J, Westra HJ, Willems SM, Zhao W, Amin N, Bakshi A, Bergmann S, Bjornsdottir G, Boyle PA, Cherny S, Cox SR, Davies G, Davis OS, Ding J, Direk N, Eibich P, Emery RT, Fatemifar G, Faul JD, Ferrucci L, Forstner AJ, Gieger C, Gupta R, Harris TB, Harris JM, Holliday EG, Hottenga JJ, De Jager PL, Kaakinen MA, Kajantie E, Karhunen V, Kolcic I, Kumari M, Launer LJ, Franke L, Li-Gao R, Liewald DC, Koini M, Loukola A, Marques-Vidal P, Montgomery GW, Mosing MA, Paternoster L, Pattie A, Petrovic KE, Pulkki-Raback L, Quaye L, Raikonen K, Rudan I, Scott RJ, Smith JA, Sutin AR, Trzaskowski M, Vinkhuyzen AE, Yu L, Zabaneh D, Attia JR, Bennett DA, Berger K, Bertram L, Boomsma DI, Snieder H, Chang SC, Cucca F, Deary IJ,

- van Duijn CM, Eriksson JG, Bultmann U, de Geus EJ, Groenen PJ, Gudnason V, Hansen T, Hartman CA, Haworth CM, Hayward C, Heath AC, Hinds DA, Hypponen E, Iacono WG, Jarvelin MR, Jockel KH, Kaprio J, Kardina SL, Keltikangas-Jarvinen L, Kraft P, Kubzansky LD, Lehtimäki T, Magnusson PK, Martin NG, McGue M, Metspalu A, Mills M, de Mutsert R, Oldehinkel AJ, Pasterkamp G, Pedersen NL, Plomin R, Polasek O, Power C, Rich SS, Rosendaal FR, den Ruijter HM, Schlessinger D, Schmidt H, Svento R, Schmidt R, Alizadeh BZ, Sorensen TI, Spector TD, Starr JM, Stefansson K, Steptoe A, Terracciano A, Thorsteinsdottir U, Thurik AR, Timpson NJ, Tiemeier H, Uitterlinden AG, Vollenweider P, Wagner GG, Weir DR, Yang J, Conley DC, Smith GD, Hofman A, Johannesson M, Laibson DI, Medland SE, Meyer MN, Pickrell JK, Esko T, Krueger RF, Beauchamp JP, Koellinger PD, Benjamin DJ, Bartels M and Cesarini D (2016) Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nature Genetics* **48**, 624–633.
- Parker G (2000) Classifying depression: should paradigms lost be regained? *American Journal of Psychiatry* **157**, 1195–1203.
- Pickrell JK (2014) Joint analysis of functional genomic data and genome-wide association studies of 18 human traits. *American Journal of Human Genetics* **94**, 559–573.
- Pickrell JK, Berisa T, Liu JZ, Séguire L, Tung JY and Hinds DA (2016) Detection and interpretation of shared genetic influences on 42 human traits. *Nature Genetics* **48**, 709.
- Shi H, Kichaev G and Pasaniuc B (2016) Contrasting the genetic architecture of 30 complex traits from summary association data. *American Journal of Human Genetics* **99**, 139–153.
- Shi H, Mancuso N, Spendlove S and Pasaniuc B (2017) Local genetic correlation gives insights into the shared genetic architecture of complex traits. *American Journal of Human Genetics* **101**, 737–751.
- Sleiman PMA, Flory J, Imielinski M, Bradfield JP, Annaiah K, Willis-Owen SAG, Wang K, Rafaels NM, Michel S, Bonnelykke K, Zhang H, Kim CE, Frackelton EC, Glessner JT, Hou C, Otieno FG, Santa E, Thomas K, Smith RM, Glaberson WR, Garris M, Chiavacci RM, Beaty TH, Ruczinski I, Orange JS, Allen J, Spergel JM, Grundmeier R, Mathias RA, Christie JD, von Mutius E, Cookson WOC, Kabesch M, Moffatt MF, Grunstein MM, Barnes KC, Devoto M, Magnusson M, Li H, Grant SFA, Bisgaard H and Hakonarson H (2010) Variants of DENND1B associated with asthma in children. *New England Journal of Medicine* **362**, 36–44.
- Sullivan PF, Neale MC and Kendler KS (2000) Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry* **157**, 1552–1562.
- Thorp JG, Marees A, Ong J-S, An J, MacGregor S and Derks E (2019) Investigating genetic heterogeneity in major depression through item-level genetic analyses of the PHQ-9. *bioRxiv*, 528067, 1–31.
- Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA and Yang J (2017) 10 years of GWAS discovery: biology, function, and translation. *American Journal of Human Genetics* **101**, 5–22.
- Watanabe K, Taskesen E, van Bochoven A and Posthuma D (2017) Functional mapping and annotation of genetic associations with FUMA. *Nature Communications* **8**, 1826.
- World Health Organization (2017) *Depression and Other Common Mental Disorders: Global Health Estimates*. Geneva: World Health Organization.
- Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TMF, Bacanu S-A, Bækvad-Hansen M, Beekman AFT, Bigdeli TB, Binder EB, Blackwood DRH, Bryois J, Buttenschön HN, Bybjerg-Grauholm J, Cai N, Castelao E, Christensen JH, Clarke T-K, Coleman JIR, Colodro-Conde L, Couvy-Duchesne B, Craddock N, Crawford GE, Crowley CA, Dashti HS, Davies G, Deary IJ, Degenhardt F, Derks EM, Direk N, Dolan CV, Dunn EC, Eley TC, Eriksson N, Escott-Price V, Kiadeh FHF, Finucane HK, Forstner AJ, Frank J, Gaspar HA, Gill M, Giusti-Rodríguez P, Goes FS, Gordon SD, Grove J, Hall LS, Hannon E, Hansen CS, Hansen TF, Herms S, Hickie IB, Hoffmann P, Homuth G, Horn C, Hottenga J-J, Hougaard DM, Hu M, Hyde CL, Ising M, Jansen R, Jin F, Jorgenson E, Knowles JA, Kohane IS, Kraft J, Kretschmar WW, Krogh J, Kutalik Z, Lane JM, Li Y, Li Y, Lind PA, Liu X, Lu L, MacIntyre DJ, MacKinnon DF, Maier RM, Maier W, Marchini J, Mbarek H, McGrath P, McGuffin P, Medland SE, Mehta D, Middeldorp CM, Mihailov E, Milanecchi Y, Milani L, Mill J, Mondimore FM, Montgomery GW, Mostafavi S, Mullins N, Nauck M, Ng B, Nivard MG, Nyholt DR, O'Reilly PF, Oskarsson H, Owen MJ, Painter JN, Pedersen CB, Pedersen MG, Peterson RE, Pettersson E, Peyrot WJ, Pistis G, Posthuma D, Purcell SM, Quiroz JA, Qvist P, Rice JP, Riley BP, Rivera M, Saeed Mirza S, Saxena R, Schoevers R, Schulte EC, Shen L, Shi J, Shyn SI, Sigurdsson E, Sinnamoni GBC, Smit JH, Smith DJ, Stefansson H, Steinberg S, Stockmeier CA, Streit F, Strohmaier J, Tansey KE, Teismann H, Teumer A, Thompson W, Thomson PA, Thorgeirsson TE, Tian C, Traylor M, Treutlein J, Trubetskoy V, Uitterlinden AG, Umrbricht D, Van der Auwera S, van Hemert AM, Viktorin A, Visscher PM, Wang Y, Webb BT, Weinsheimer SM, Wellmann J, Willemsen G, Witt SH, Wu Y, Xi HS, Yang J, Zhang F, Arolt V, Baune BT, Berger K, Boomsma DI, Cichon S, Dannlowski U, de Geus ECJ, DePaulo JR, Domenici E, Domschke K, Esko T, Grabe HJ, Hamilton SP, Hayward C, Heath AC, Hinds DA, Kendler KS, Kloiber S, Lewis G, Li QS, Lucae S, Madden PFA, Magnusson PK, Martin NG, McIntosh AM, Metspalu A, Mors O, Mortensen PB, Müller-Myhsok B, Nordentoft M, Nöthen MM, O'Donovan MC, Paciga SA, Pedersen NL, Penninx BWJH, Perlis RH, Porteous DJ, Potash JB, Preisig M, Rietschel M, Schaefer C, Schulze TG, Smoller JW, Stefansson K, Tiemeier H, Uher R, Völzke H, Weissman MM, Werge T, Winslow AR, Lewis CM, Levinson DF, Breen G, Børglum AD and Sullivan PF (2018) Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics* **50**, 668–681.
- Yamada M, Yamada M, Yamazaki S, Takahashi K, Nishioka G, Kudo K, Ozawa H, Yamada S, Kiuchi Y, Kamijima K, Higuchi T and Momose K (2000) Identification of a novel gene with RING-H2 finger motif induced after chronic antidepressant treatment in rat brain. *Biochemical and Biophysical Research Communications* **278**, 150–157.
- Zeng Y, Navarro P, Xia C, Amador C, Fernandez-Pujals AM, Thomson PA, Campbell A, Nagy R, Clarke T-K, Hafferty JD, Smith BH, Hocking LJ, Padmanabhan S, Hayward C, MacIntyre DJ, Porteous DJ, Haley CS and McIntosh AM (2016) Shared genetics and couple-associated environment are major contributors to the risk of both clinical and self-declared depression. *EBioMedicine* **14**, 161–167.
- Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, Hemani G, Tansey K, Laurin C, Pourcain BS, Warrington NM, Finucane HK, Price AL, Bulik-Sullivan BK, Anttila V, Paternoster L, Gaunt TR, Evans DM and Neale BM (2017) LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics (Oxford, England)* **33**, 272–279.
- Zimmerman M, Coryell W, Pfuhl B and Stangl D (1986) The validity of four definitions of endogenous depression: II. Clinical, demographic, familial, and psychosocial correlates. *Archives of General Psychiatry* **43**, 234–244.