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1 Association analysis in over 329,000 individuals identifies 116 independent variants
2 influencing neuroticism.

3

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25

26 Neuroticism is a relatively stable personality trait characterised by negative emotionality
27 (e.g., worry, guilt) ¹; twin study heritability ranges 30 to 50% ², and SNP-based heritability
28 ranges 6 to 15% ³⁻⁶. Increased neuroticism is associated with poorer mental and physical
29 health ^{7,8}, translating to high economic burden ⁹. Genome-wide association (GWA) studies of
30 neuroticism have identified up to 11 genetic loci ^{3,4}. Here we report 116 significant
31 independent loci from a GWA of neuroticism in 329,821 UK Biobank participants; 15 of
32 these replicated at $P < .00045$ in an unrelated cohort ($N = 122,867$). Genetic signals were
33 enriched in neuronal genesis and differentiation pathways, and substantial genetic
34 correlations were found between neuroticism and depressive symptoms ($r_g = .82$, $SE = .03$),
35 major depressive disorder (MDD; $r_g = .69$, $SE = .07$) and subjective wellbeing ($r_g = -.68$,
36 $SE = .03$) alongside other mental health traits. These discoveries significantly advance our
37 understanding of neuroticism and its association with MDD.

38 **Main**

39 Understanding why people differ in neuroticism will provide an important
40 contribution to understanding people's liability to poor mental health throughout the life
41 course. The strong genetic correlation between neuroticism and mental health, especially
42 anxiety and major depressive disorder ^{10,11}, means that exploring the genetic contribution to
43 differences in neuroticism is one way to understand more about these common and
44 burdensome, but aetiologically intractable illnesses. In the largest GWA study of major
45 depressive disorder (MDD; 130,664 cases vs 330,470 controls), 44 independent genetic loci
46 were identified ¹².

47 UK Biobank has health, medical and genetic information for over 500,000 individuals
48 aged 39-73 years from the United Kingdom, assessed between 2006 and 2010 ^{13,14}. We
49 performed a GWA analysis of trait neuroticism in 329,821 unrelated White British adults
50 (152,710 male (46.3%)) with high-quality genotype data (Online Methods). Neuroticism was

51 measured by the total score of the 12-item Eysenck Personality Questionnaire-Revised Short
52 Form (EPQ-R-S) ¹⁵; missing item data (ranging 1.8% to 4.7%) were imputed with reference
53 to age and sex, and individuals with greater than 4 missing items were excluded
54 (Supplementary Note, Supplementary Table 1 and Supplementary Fig. 1). For analysis, the
55 score was residualized for the effects of age, sex, assessment centre, genotype batch, array,
56 and 40 genetic principal components. This score was tested against 18,485,882 bi-allelic
57 single nucleotide polymorphism (SNP) variants, based on the Haplotype Reference
58 Consortium panel ¹⁶, with a minor allele frequency ≥ 0.0005 and an information/imputation
59 quality score of ≥ 0.1 under an additive model. The distribution of obtained versus expected
60 results under the null hypothesis showed some genomic inflation, with a lambda of 1.15
61 (quantile-quantile plot shown in Supplementary Fig. 2). Univariate linkage disequilibrium
62 score (LDSC) regression ¹⁷ estimates indicated that 96.8% of this inflation was due to the
63 presence of a large polygenic signal with the intercept being close to 1 (1.02, SE = .01). SNP-
64 based heritability of neuroticism was estimated at .108 (SE=.005) using LDSC.

65 Genome-wide significance ($P < 5 \times 10^{-8}$) was demonstrated for 10,353 genetic
66 variants with a further 17,668 variants at a suggestive level ($P < 1 \times 10^{-5}$) (Supplementary
67 Table 2). The Manhattan plot is shown in Figure 1 and gene annotation for the significant
68 SNPs in Supplementary Table 3. SNPs identified in previous neuroticism GWA studies were
69 mostly significant in our sample (Supplementary Note and Supplementary Table 2) and
70 substantial overlap with MDD SNPs (75%) and genes was found (Supplementary Note and
71 Supplementary Table 4). The major histocompatibility complex (MHC) region has been
72 previously linked to schizophrenia, a psychiatric comorbidity trait (including MDD) ^{18,19} and
73 MDD ¹². It contained 3 significant independent genetic loci associated with neuroticism, two
74 were in genes (*GABBR1*, *TNXB*) connected with schizophrenia ^{20,21}. The primary associated
75 SNP, rs2021722, for schizophrenia ¹⁸, was present in our study and nominally significant ($P =$

76 9.42 x 10⁻⁵). Supplementary Figure 3 indicates the previous MHC associations in relation to
77 our findings.

78 116 of the significant SNPs were independent ($r^2 > 0.1$ and within 500kb of the
79 significant index SNP); these lead SNPs are shown in Supplementary Table 5 with the
80 number of associated SNPs, region size, and genes within the LD interval. 73 lead SNPs were
81 located within genes, 5 were exonic (in *MSRA*, *NOS1*, *PINX1*, *ZCCHC14*, and *C12orf49*) and
82 a further 2 were coding SNPs in *RPP21* (a missense mutation) and *AGBL1* (synonymous), 55
83 were intronic and 10 were noncoding RNA variants; 42 were intergenic. For the 116
84 independent SNPs, evidence of expression quantitative trait loci (eQTL) was explored using
85 the GTEx database, 44 were eQTLs (Supplementary Table 5). A Regulome DB score was
86 used to identify SNPs with a likely regulatory function. 33 of the 116 SNPs were included in
87 the Regulome DB database and 8 of these had a score < 3, indicating that they are likely to be
88 involved in gene regulation (Supplementary Table 5).

89 Replication of the significant association signals in UK Biobank was sought from the
90 results of a GWA meta-analysis of neuroticism that we performed using 23andMe (N =
91 59,206)²² and the Genetics of Personality Consortium (GPC-2; N = 63,661)²³. Of the 10,353
92 genome-significant SNPs in UK Biobank, 10,171 were available in the replication cohorts,
93 and 8,774 of these increased in significance when the replication cohorts were meta-analysed
94 with UK Biobank. This indicated a consistent direction of allelic effect (Supplementary Table
95 6).

96 INSERT FIGURE 1 ABOUT HERE

97

98 Of the 116 independent associated SNPs, 111 were present in the replication cohort,
99 with 51 nominally significant ($P < .05$; Supplementary Table 5), and 15 at a Bonferroni-
100 corrected level ($P < .00045$; Table 1). One of these, *rs2953805*, was previously associated

101 with morning chronotype ²⁴, a trait relating to lower neuroticism ²⁵ and showing allelic effects
102 in the expected direction. The low replication rate (13.5%) at a strict corrected level reflects
103 the finding that effect sizes are extremely small (up to .02 of a SD increase in neuroticism
104 score per allele) and will thus require similarly large replication samples to confirm their
105 effects. Figure 2a-c shows the regional association plot for chromosomes 8, 11 and 22 in
106 which multiple genes were present in the associated LD region. Of the five chromosome 8
107 loci only one lead SNP tagged a well-known inversion, previously linked to neuroticism
108 (Supplementary Note and Supplementary Fig. 4), although associations in the broad region
109 had been attributed to the inversion ⁴ and so might cautiously be considered as a single locus.

110 All 69 genes located within the 15 replicated loci were classified in terms of their
111 molecular function, biological process and protein class using the Protein Analysis Through
112 Evolutionary Relationships Classification System which includes 14,710 protein families
113 categorised into 76,032 functionally distinct subfamilies ²⁶. Supplementary Figure 4 shows
114 that a large number of genes 1) coded for nucleic acid binding and transcription factors, 2)
115 contributed to metabolic and cellular processes, and 3) had a role in binding and catalytic
116 activity molecular functioning. Transcription factors, in particular, have been implicated in
117 the aetiology of depression ^{27,28}, and miRNAs—which have been linked with anxiety²⁹ and
118 depression ³⁰—might target genes with roles in binding (e.g., *POLR3H*). The PsyGeNET
119 (v2.0) database showed that of the 69 genes, four have been associated with psychiatric
120 disorder (Supplementary Table 7): *DRD2* (bipolar, depression, substance use/dependence,
121 delirium), *EP300* (alcoholic intoxication), *TEF* (depression) and *MSRA* (schizophrenia).
122 Variants in *CACNA1E* have been associated with cross-psychiatric disorder overlap and
123 migraine ^{18,31}.

124 A GTEx database search for the 15 replicated SNPs showed that 9 were associated
125 with significant regulation of 60 genes expressed in a variety of tissues (Supplementary Table

126 8). Of the 30 brain expression associations, half of these were in the cerebellum: 4 SNPs
127 regulating 10 genes. Interestingly, MRI studies have shown associations between cerebellar
128 volume and neuroticism, and cerebellar blood flow in response to negative emotional cues
129 ^{32,33}. In the BRAINEAC search, all SNPs were identified as eQTLs in at least one brain
130 region at a nominal significance level ($P < .05$) and 10 were supported at a Bonferroni-
131 corrected level of $P < .0003$ (Supplementary Table 9). Of potential interest, rs7107356, a
132 novel SNP in an intergenic region of chromosome 11, regulates *MTCH2* in the cerebellar
133 cortex ($P = 4.5 \times 10^{-6}$). *MTCH2* is involved in metabolic pathways and cell function ³⁴ and
134 variants of this gene have been associated with BMI ³⁵.

135 Gene-based analysis of the GWA results was performed using MAGMA ³⁶; 249
136 genes were significantly associated at a Bonferroni-corrected level ($\alpha = 0.05 / 18,080$; $P <$
137 2.77×10^{-6} ; Supplementary Table 10). Three of these were genes (*STH*, *HIST1H3J*,
138 *HIST1H4L*) containing a single SNP. Of the replicated independent GWA SNPs that were in
139 genes, the following significant genes were corroborated in the gene-based results:
140 *CACNA1E*, *XKR6*, *MSRA*, *LINGO2*, *CELF4*, *ZC3H7B* and *BAIAP2*. SNP rs6981523,
141 previously identified in 23andMe for neuroticism ²², was an intergenic SNP near *XKR6*; this
142 gene was the second most significant gene in our gene-based analysis ($P = 6.55 \times 10^{-32}$).
143 *L3MBTL2* and *CHADL*, wherein 23andMe's other significant SNP, rs9611519, resided,
144 showed respective gene-based p-values of 2.40×10^{-6} and 1.15×10^{-6} .

145 Pathway analysis in MAGMA highlighted 5 significant gene ontology pathways
146 (family-wise error $P < 1.21 \times 10^{-6}$): neuron spine (cellular), homophilic cell adhesion via
147 plasma membrane adhesion molecules (biological), neuron differentiation (biological), cell
148 cell adhesion via plasma membrane adhesion molecules (biological), and neurogenesis
149 (biological). See Table 2 for further details. Of note is the neurogenesis pathway, a
150 hypothesis of which exists for depression (and to a lesser extent, anxiety) based on stress

151 reducing neurogenesis in the hippocampus and on the action of antidepressants on brain
152 circuitry^{37,38}. Further, variants in *PLXNA2*, potentially involved in adult neurogenesis, have
153 been associated with anxiety and neuroticism³⁹. Cell adhesion molecules have been
154 implicated in neuropsychiatric disorder⁴⁰, and protocadherins specifically with neuroticism
155 and risk of mood disorder⁴¹, which supports the importance of cell adhesion pathways. A
156 further gene-set analysis of genes expressing proteins that can bind to anti-depressant drug
157 molecules was significant ($P = .005$) re-affirming the dependency of neuroticism and
158 depression on shared biological pathways. This is consistent, for example, with findings for
159 *CRHRI* (highlighted in our SNP and gene-based analysis), a gene involved in normal
160 hormonal responses to stress (the glucocorticoid pathway being a relevant and well-known
161 target) and associated with anxiety, depression and neuroticism^{3,42,43}. That genes influencing
162 neuroticism reveal pathways involved in currently prescribed and effective antidepressant
163 action suggests that neuroticism could be a potentially useful clinical stratifying factor for
164 effective antidepressant action. There may also be clinical utility in knowing a person's level
165 of neuroticism after the occurrence of a stressful life event and therefore pre-empting onset of
166 depression via drug therapy in those high in neuroticism. Because our GWA of neuroticism
167 reveals signals associated with the known biological action of existing antidepressants, it may
168 be useful as a means of discovering (or re-purposing) new pharmacological interventions for
169 MDD.

170 LD score regression⁴⁴ was used to estimate the genetic correlation between
171 neuroticism and a variety of health traits (Supplementary Tables 11 and 12). The strongest
172 correlation was observed for depressive symptoms ($r_g = .82$, $SE = .03$). Major depressive
173 disorder, subjective wellbeing, and tiredness showed moderate-to-strong correlations (.62-
174 .69). The stronger correlation for depressive symptoms than depressive disorder might be
175 indicative of improved sensitivity of continuous versus dichotomous traits but might also

176 point to inventory item overlap (greater conceptual similarity) for depressive symptoms
177 and/or noise in MDD diagnosis. Genetic correlations with neuroticism were moderate for
178 self-rated health (.41), moderate-to-low for schizophrenia, ADHD, anorexia nervosa and
179 educational attainment ($\sim|.20|$), and low for bipolar disorder and smoking status ($|.11|$). The
180 genetic correlation of one between Eysenck neuroticism and other neuroticism scales (used
181 by 23andMe and the GPC) confirms that GWA meta-analysis based on different
182 measurement instruments is valid. Mendelian randomization was used to determine whether
183 the genetic correlation between neuroticism and non-psychiatric variables (less likely to be
184 influenced by pleiotropy), smoking status and educational attainment, represented a causal
185 relationship from neuroticism. For smoking status, the beta of 0.23 was significant in the
186 inverse variance weighted model ($P = .00002$) which is preferred in the presence of
187 heterogeneity ($P = .001$); the MR Egger regression did not show significant directional
188 pleiotropy (intercept = 0.02, $P = .10$) thus supporting a causal relationship. For educational
189 attainment, the beta of -0.09 was significant ($P = 8.35 \times 10^{-6}$) in the inverse variance
190 weighted model (heterogeneity $P = 5.87 \times 10^{-7}$), with no evidence of directional pleiotropy
191 (intercept = 0, $P = .23$). Although theoretically less plausible, the reverse causal direction
192 should be investigated in UK Biobank once a large number of significant SNPs influencing
193 smoking status and educational attainment have been estimated in non-overlapping samples.

194 Polygenic profile analyses based on the SNP inclusion threshold with the optimal
195 signal-to-noise ratio ($P < .05$) indicated that the neuroticism polygenic score explained 2.79%
196 of the variance in neuroticism ($\beta = .19$, $P = 2.65 \times 10^{-47}$) and 0.8% of the variance in
197 depression status ($OR = 1.25$, $P = 1.53 \times 10^{-8}$) in Generation Scotland (GS; $N = 7,388$)⁴⁵.
198 Results for polygenic scores in GS based on other SNP significance inclusion thresholds
199 (0.01, 0.05, 0.1, 0.5 and 1) from the UK Biobank GWA can be found in Supplementary Table
200 13.

201 The combination, in UK Biobank, of a large ethnically homogenous sample and a
202 well-validated neuroticism scale has afforded the discovery of 15 stringently replicated
203 genetic loci that influence neuroticism levels, four of them novel. Most lead variants were
204 associated with gene regulation, with half of these expressed in the brain; single variant and
205 gene associations overlapped substantially with MDD findings, and genes in antidepressant-
206 targeted pathways were over-represented. There was also support for neuroticism having
207 causal effects on socio-economic markers. These discoveries promise paths to understand the
208 mechanisms whereby some people become depressed, and of broader human differences in
209 happiness, and they are a resource for those seeking novel drug targets for major depression.
210 After millennia in which scholars and researchers have sought the sources of individual
211 differences in proneness to dysphoria ⁴⁶, the present study adds significantly to explaining the
212 (genetic) anatomy of melancholy.

213

214 **URLs**

215 UK Biobank Resource: <http://www.ukbiobank.ac.uk>

216 BGENIE: <https://jmarchini.org/bgenie/>

217 BRAINEAC: <http://www.braineac.org/>

218 Druggable genome: <http://dgidb.genome.wustl.edu/>

219 Genotype-Tissue Expression Portal: <http://www.gtexportal.org>

220 Gene Ontology: <http://geneontology.org>

221 GPC-2 Summary Statistics: <http://www.tweelingenregister.org/GPC/>

222 Linkage Disequilibrium Score Regression: <https://github.com/bulik/ldsc/wiki>

223 METAL: <http://csg.sph.umich.edu/abecasis/metal/index.html>

224 PANTHER: <http://pantherdb.org/>

225 PLINK V2: <https://www.cog-genomics.org/plink2>

226 PsyGeNet: <http://www.psygenet.org/web/PsyGeNET/menu/home>

227 Regulome Database: <http://www.regulomedb.org/>

228

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248

249 **Author Disclosure**

250 IJD was a participant in UK Biobank. The other authors declare no conflict of interest.

251

252 **Author Contributions**

253 M.L. drafted the manuscript with contributions from W.D.H. and I.J.D. G.D., D.C.L.,
254 R.E.M., M.J.A. and D.M.H. performed quality control of UK Biobank data and/or Generation
255 Scotland. M.L, G.D, S.P.H., and M.S. analysed the data. T-K.C., C.F-R., W.D.H. and S.E.H.
256 performed/assisted with downstream analysis. C.R.G, C.M.L., and A.M.M provided critical
257 comments on the manuscript draft and analysis. M.L. and I.J.D. co-ordinated the work. All
258 authors commented on and approved the manuscript.

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261 **References for Main text**

- 262 1. Matthews, G., Deary, I.J. & Whiteman, M.C. *Personality Traits*, (Cambridge
263 University Press, 2009).
- 264 2. Vukasovic, T. & Bratko, D. Heritability of personality: A meta-analysis of behavior
265 genetic studies. *Psychological Bulletin*.**141**, pp (2015).
- 266 3. Smith, D.J. *et al.* Genome-wide analysis of over 106 000 individuals identifies 9
267 neuroticism-associated loci. *Mol Psychiatry* **21**, 749-57 (2016).
- 268 4. Okbay, A. *et al.* Genetic variants associated with subjective well-being, depressive
269 symptoms, and neuroticism identified through genome-wide analyses. *Nat Genet* **48**,
270 624-33 (2016).
- 271 5. Power, R.A. & Pluess, M. Heritability estimates of the Big Five personality traits
272 based on common genetic variants. *Transl Psychiatry* **5**, e604 (2015).
- 273 6. Vinkhuyzen, A.A. *et al.* Common SNPs explain some of the variation in the
274 personality dimensions of neuroticism and extraversion. *Transl Psychiatry* **2**, e102
275 (2012).
- 276 7. Kubzansky, L.D., Martin, L.T. & Buka, S.L. Early manifestations of personality and
277 adult health: a life course perspective. *Health Psychol* **28**, 364-72 (2009).
- 278 8. Strickhouser, J.E., Zell, E. & Krizan, Z. Does Personality Predict Health and Well-
279 Being? A Metasynthesis. *Health psychology: official journal of the Division of Health*
280 *Psychology, American Psychological Association* (2017).
- 281 9. Cuijpers, P. *et al.* Economic costs of neuroticism: a population-based study. *Arch Gen*
282 *Psychiatry* **67**, 1086-1093 (2010).
- 283 10. Few, L.R. *et al.* Genetic variation in personality traits explains genetic overlap
284 between borderline personality features and substance use disorders. *Addiction* **109**,
285 2118-27 (2014).

- 286 11. Kendler, K.S., Gatz, M., Gardner, C.O. & Pedersen, N.L. Personality and major
287 depression: a Swedish longitudinal, population-based twin study. *Arch Gen*
288 *Psychiatry* **63**, 1113-20 (2006).
- 289 12. Wray, N.R. & Sullivan, P.F. Genome-wide association analyses identify 44 risk
290 variants and refine the genetic architecture of major depression. *bioRxiv* (2017).
- 291 13. Sudlow, C. *et al.* UK biobank: an open access resource for identifying the causes of a
292 wide range of complex diseases of middle and old age. *PLoS Med* **12**, e1001779
293 (2015).
- 294 14. Bycroft, C. *et al.* Genome-wide genetic data on ~500,000 UK Biobank participants.
295 *bioRxiv* (2017).
- 296 15. Eysenck, S.B., Eysenck, H.J. & Barrett, P. A revised version of the psychoticism
297 scale. *Personality and individual differences* **6**, 21-29 (1985).
- 298 16. McCarthy, S. *et al.* A reference panel of 64,976 haplotypes for genotype imputation.
299 *Nat Genet* **48**, 1279-1283 (2016).
- 300 17. Bulik-Sullivan, B.K. *et al.* LD Score regression distinguishes confounding from
301 polygenicity in genome-wide association studies. *Nat Genet* **47**, 291-295 (2015).
- 302 18. Cross-Disorder Group of the Psychiatric Genomics, C. Identification of risk loci with
303 shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet*
304 **381**, 1371-1379 (2013).
- 305 19. Sekar, A. *et al.* Schizophrenia risk from complex variation of complement component
306 4. *Nature* **530**, 177-183 (2016).
- 307 20. Hegyi, H. GABBR1 has a HERV-W LTR in its regulatory region – a possible
308 implication for schizophrenia. *Biology Direct* **8**, 5-5 (2013).

- 309 21. Wei, J. & Hemmings, G.P. TNXB locus may be a candidate gene predisposing to
310 schizophrenia. *American Journal of Medical Genetics Part B: Neuropsychiatric*
311 *Genetics* **125B**, 43-49 (2004).
- 312 22. Lo, M.-T. *et al.* Genome-wide analyses for personality traits identify six genomic loci
313 and show correlations with psychiatric disorders. *Nat Genet* **49**, 152-156 (2017).
- 314 23. Genetics of Personality, C. *et al.* Meta-analysis of Genome-wide Association Studies
315 for Neuroticism, and the Polygenic Association With Major Depressive Disorder.
316 *JAMA Psychiatry* **72**, 642-50 (2015).
- 317 24. Hu, Y. *et al.* GWAS of 89,283 individuals identifies genetic variants associated with
318 self-reporting of being a morning person. *Nat Commun* **7**, 10448 (2016).
- 319 25. Duggan, K.A., Friedman, H.S., McDevitt, E.A. & Mednick, S.C. Personality and
320 Healthy Sleep: The Importance of Conscientiousness and Neuroticism. *PLOS ONE* **9**,
321 e90628 (2014).
- 322 26. Mi, H., Muruganujan, A. & Thomas, P.D. PANTHER in 2013: modeling the
323 evolution of gene function, and other gene attributes, in the context of phylogenetic
324 trees. *Nucleic Acids Research* **41**, D377-D386 (2013).
- 325 27. Sulser, F. The role of CREB and other transcription factors in the pharmacotherapy
326 and etiology of depression. *Annals of Medicine* **34**, 348-356 (2002).
- 327 28. Wang, H. *et al.* Forkhead box O transcription factors as possible mediators in the
328 development of major depression. *Neuropharmacology* **99**, 527-537 (2015).
- 329 29. Malan-Müller, S., Hemmings, S.M.J. & Seedat, S. Big Effects of Small RNAs: A
330 Review of MicroRNAs in Anxiety. *Molecular Neurobiology* **47**, 726-739 (2013).
- 331 30. Dwivedi, Y. Emerging role of microRNAs in major depressive disorder: diagnosis
332 and therapeutic implications. *Dialogues in Clinical Neuroscience* **16**, 43-61 (2014).

- 333 31. Ambrosini, A. *et al.* Possible Involvement of the CACNA1E Gene in Migraine: A
334 Search for Single Nucleotide Polymorphism in Different Clinical Phenotypes.
335 *Headache: The Journal of Head and Face Pain* **57**, 1136-1144 (2017).
- 336 32. Schraa-Tam, C.K.L. *et al.* fMRI activities in the emotional cerebellum: a preference
337 for negative stimuli and goal-directed behavior. *The Cerebellum* **11**, 233-245 (2012).
- 338 33. Schutter, D.J.L.G., Koolschijn, P.C.M.P., Peper, J.S. & Crone, E.A. The Cerebellum
339 Link to Neuroticism: A Volumetric MRI Association Study in Healthy Volunteers.
340 *PLOS ONE* **7**, e37252 (2012).
- 341 34. Grinberg, M. *et al.* Mitochondrial carrier homolog 2 is a target of tBID in cells
342 signaled to die by tumor necrosis factor alpha. *Mol Cell Biol* **25**, 4579-90 (2005).
- 343 35. Locke, A.E. *et al.* Genetic studies of body mass index yield new insights for obesity
344 biology. *Nature* **518**, 197-206 (2015).
- 345 36. de Leeuw, C.A., Mooij, J.M., Heskes, T. & Posthuma, D. MAGMA: Generalized
346 Gene-Set Analysis of GWAS Data. *PLoS Computational Biology* **11**(2015).
- 347 37. Lucassen, P.J., Oomen, C.A., Schouten, M., Encinas, J.M. & Fitzsimons, C.P. Chapter
348 8 - Adult Neurogenesis, Chronic Stress and Depression A2 - Canales, Juan J. in *Adult*
349 *Neurogenesis in the Hippocampus* 177-206 (Academic Press, San Diego, 2016).
- 350 38. Schoenfeld, T.J. & Cameron, H.A. Adult Neurogenesis and Mental Illness.
351 *Neuropsychopharmacology* **40**, 113-128 (2015).
- 352 39. Wray, N.R., James, M.R., Mah, S.P. & *et al.* Anxiety and comorbid measures
353 associated with *plxn2*. *Arch Gen Psychiatry* **64**, 318-326 (2007).
- 354 40. Redies, C., Hertel, N. & Hübner, C.A. Cadherins and neuropsychiatric disorders.
355 *Brain Research* **1470**, 130-144 (2012).

- 356 41. Chang, H. *et al.* The protocadherin 17 gene affects cognition, personality, amygdala
357 structure and function, synapse development and risk of major mood disorders. *Mol*
358 *Psychiatry* (2017).
- 359 42. DeYoung, C.G., Cicchetti, D. & Rogosch, F.A. Moderation of the association
360 between childhood maltreatment and Neuroticism by the corticotropin-releasing
361 hormone receptor 1 gene. *Journal of child psychology and psychiatry, and allied*
362 *disciplines* **52**, 898-906 (2011).
- 363 43. Binder, E.B. & Nemeroff, C.B. The CRF system, stress, depression and anxiety –
364 insights from human genetic studies. *Mol Psychiatry* **15**, 574-588 (2010).
- 365 44. Bulik-Sullivan, B.K. *et al.* An atlas of genetic correlations across human diseases and
366 traits. *Nat Genet* **47**, 1236-41 (2015).
- 367 45. Smith, B.H. *et al.* Cohort Profile: Generation Scotland: Scottish Family Health Study
368 (GS:SFHS). The study, its participants and their potential for genetic research on
369 health and illness. *International Journal of Epidemiology* **42**, 689-700 (2013).
- 370 46. Burton, R. *The Anatomy of Melancholy*. (eds Faulkner, T.C., Kiessling, N.K. & Blair,
371 R.L.) (Oxford University Press, 1989).
- 372

373 **Figure Legends for Main Text**

374 Figure 1. GWA results for neuroticism in 329,821 UK Biobank individuals.

375

376 Figure 2. Regional association plot for suggestive/significant signals in UK Biobank on a)

377 chromosome 8p (site of the inversion polymorphism), b) chromosome 11, and c)

378 chromosome 22. The SNP association p-value is shown on the y-axis and the SNP position

379 (with gene annotation) appears on the x-axis; for each SNP, the strength of LD with the lead

380 SNP is colour coded based on its r^2 . Plots were produced in LocusZoom.

381

383 **Table 1. Fifteen independent SNPs associated with neuroticism in UK Biobank most strongly replicated (with consistent allelic effect) in**
 384 **the meta-analysis of 23andMe and the GPC cohorts. Bolded genes were significant in the gene-based tests.**

Chr	SNP	MAF	Discovery P-value (N=329,821)	Replication P-value (N=122,867)	Nearest Gene	Distance to Gene	Genes within Range	Significant in Previous GWA Studies
1	rs169235	.25	3.97×10^{-9}	2.55E-05	CACNA1E**	0		
5	rs1422192 [^]	.17	1.68×10^{-9}	6.54E-07	<i>LINC00461</i>	0	MEF2C**	
8* [†]	rs2921036	.49	8.04×10^{-26}	3.27E-07	.	.	CLDN23, ERI1**, MFHAS1**, SGK223	
8* [†]	rs2953805	.47	3.02×10^{-22}	1.26E-08	<i>U3</i>	1292	CLDN23, ERI1**, MFHAS1**, PPP1R3B	Morning vs Evening Chronotype ²⁴
8* [†]	rs6982308	.49	6.46×10^{-21}	2.26E-08	MSRA**	0		
8* [†]	rs7005884	.45	1.92×10^{-23}	1.34E-07	XKR6	0	C8orf74, PINX1**, PRSS55**, RP1L1, SOX7**, XKR6	
8* [†]	rs10097870	.47	2.18×10^{-24}	6.51E-07	<i>LINC00208</i>	5665	BLK**, CTSB**, DEFB134**, DEFB135, DEFB136, FAM167A**, FDFT1, GATA4, LOC100133267, MTMR9, NEIL2, SLC35G5, XKR6	
9	rs1521732	.37	2.91×10^{-9}	4.01E-06	LINGO2	0		
9	rs72694263	.08	2.12×10^{-8}	0.000237	.	.		
11*	rs7107356	.50	1.52×10^{-12}	1.34E-05	AGBL2	4973	ACP2, AGBL2, CIQTNF4, CELF1, DDB2**, FAM180B, FNBP4**, KBTBD4, MADD**, MTCH2**, MYBPC3, NDUFS3, NR1H3, NUP160**, PSMC3, PTPMT1, RAPSN, SLC39A13**,	Neuroticism ⁴

								<i>SPI1</i>
11*	rs7111031	.36	1.06×10^{-15}	0.000215	.	.		<i>DRD2</i>
15*	rs7175083	.48	1.16×10^{-9}	0.000297	<i>LINGO1</i>	0		
17	rs7502590	.15	2.61×10^{-11}	0.000146	<i>BAIAP2</i>	0		<i>AATK, BAIAP2</i>
18*	rs11082011	.34	1.25×10^{-16}	2.05E-06	<i>CELF4</i>	0		
22*	rs11090045	.30	8.04×10^{-13}	5.40E-07	<i>ZC3H7B**</i>	0		<i>ACO2, C22orf46, CHADL, CSDC2**, DESI1, EP300, L3MBTL2**, MEI1, NHP2L1, PHF5A, PMM1, POLR3H, RANGAP1**, RBX1, TEF**, TOB2, XRCC6, ZC3H7B**</i>

385 ^ Genotyped SNP

386 † Located in Inversion Region

387 * Broad region implicated in previous studies ^{4,22,45}

388 ** Regulated gene expressed in brain

389

390 **Table 2. Significant gene ontology pathways for neuroticism in UK Biobank**

Pathway	Number of genes	Beta	SE	P-value	Corrected P	Definition
Neuron Spine	147	0.560	0.107	7.77×10^{-8}	0.0282	A small membranous protrusion, often ending in a bulbous head and attached to the neuron by a narrow stalk or neck.
Homophilic Cell Adhesion Via Plasma Membrane Adhesion Molecules	115	0.490	0.0938	8.81×10^{-8}	0.0289	The attachment of a plasma membrane adhesion molecule in one cell to an identical molecule in an adjacent cell.
Neuron Differentiation	1341	0.145	0.0288	2.36×10^{-7}	0.0357	The process in which a relatively unspecialized cell acquires specialized features of a neuron.
Cell Cell Adhesion Via Plasma Membrane Adhesion Molecules	828	0.183	0.0364	2.72×10^{-7}	0.0372	The attachment of one cell to another cell via adhesion molecules that are at least partially embedded in the plasma membrane.
Neurogenesis	195	0.419	0.0859	5.35×10^{-7}	0.0439	Generation of cells within the nervous system

391 **Online Methods**

392 Genome-wide association analysis in UK Biobank

393 An imputed dataset, including >92 million variants, referenced to the UK10K
394 haplotype, 1000 Genomes Phase 3, and Haplotype Reference Consortium (HRC) panels was
395 available in UK Biobank. The current analysis includes only those SNPs available in the
396 HRC reference panel⁴⁷. Quality control filters were applied (see Supplementary Note) which
397 resulted in 18,485,882 imputed SNPs for analysis in 329,821 individuals. The GWA of
398 neuroticism was conducted using BGENIE⁴⁸, a program specifically developed to analyse
399 UK Biobank data in a fast and efficient manner. Further information can be found at the
400 following URL: <https://jmarchini.org/bgenie/>. A linear SNP association model was tested
401 which accounted for genotype uncertainty. Neuroticism was pre-adjusted for age, sex,
402 genotyping batch, genotyping array, assessment centre, and 40 principal components to speed
403 up analysis.

404 The number of independent signals from the GWA analysis was determined using
405 LD-clumping in PLINK v1.90b3i⁴⁹ (see URLs). The LD structure was based on SNPs with a
406 p-value $< 1 \times 10^{-3}$ that were extracted from the imputed genotypes. Index SNPs were
407 identified ($P < 5 \times 10^{-8}$) and clumps were formed for SNPs with $P < 1 \times 10^{-5}$ that were in LD
408 ($r^2 > 0.1$) and within 500kb of the index SNP. SNPs were assigned to no more than one
409 clump.

410

411 Meta-analysis of GWA Results

412 Two meta-analyses were performed. Firstly, to check for replication of the significant
413 ($P < 5 \times 10^{-8}$) GWA signals in UK Biobank, results from a meta-analysis of 23andme⁵⁰ (the
414 full GWA summary statistics were made available from 23andMe) and the Genetics of
415 Personality Consortium (GPC-2)⁵¹ (the full GWA summary statistics were publicly available

416 see URLs) were used. This meta-analysis was conducted using METAL⁵² and due to the
417 lack of phenotype harmonisation across the cohorts, a sample size weighted meta-analysis
418 was preferred. A second meta-analysis of UK Biobank and the replication cohorts was
419 performed using the same method, but only for the SNPs that were significant in UK
420 Biobank.

421

422 Genome-wide Gene-based Analysis

423 Gene-based analysis of neuroticism was performed using MAGMA⁵³, which
424 provides gene-based statistics derived using the results of the GWA analysis. Genetic variants
425 were assigned to genes based on their position according to the NCBI 37.3 build, with no
426 additional boundary placed around the genes. This resulted in a total of 18,080 genes being
427 analysed. The European panel of the 1000 Genomes data (phase 1, release 3) was used as a
428 reference panel to account for linkage disequilibrium. A genome-wide significance threshold
429 for gene-based associations was calculated using the Bonferroni method ($\alpha=0.05/18,080$; $P <$
430 2.77×10^{-6}).

431

432 Functional annotation and gene expression

433 For the 116 independent genome-wide significant SNPs identified by LD clumping,
434 evidence of expression quantitative trait loci (eQTL) and functional annotation were explored
435 using publicly available online resources. The Genotype-Tissue Expression Portal (GTEx)
436 (see URLs) was used to identify eQTLs associated with the SNPs. Functional annotation was
437 investigated using the Regulome DB database⁵⁴ (see URLs). Further to GTEx searches, we
438 investigated whether any of the 15 replicated SNPs were brain expression quantitative loci
439 (eQTLs) by entering them into the brain eQTL database BRAINEAC (see URLs), which

440 contains gene expression data across ten brain regions (cerebellar cortex, frontal cortex,
441 hippocampus, medulla, occipital cortex, putamen, substantia nigra, temporal cortex, thalamus
442 and intralobular white matter). The genes located in the region of replicated independent loci
443 were investigated for protein function using the PANTHER database (Protein ANalysis
444 THrough Evolutionary Relationships, see URLs) which stores data on the evolution and
445 function of protein-coding genes from sequenced genomes of diverse species⁵⁵, our focus
446 here on homo sapiens. Uncharacterized gene function is predicted via phylogenetic branching
447 information and the resource enables biological pathway annotation.

448

449 Pathway Analysis

450 Biological pathway analysis was performed on the gene-based analysis results. This
451 gene-set enrichment analysis was conducted utilising gene-annotation files from the Gene
452 Ontology (GO) Consortium (see URLs)⁵⁶ taken from the Molecular Signatures Database
453 (MSigDB) v5.2. The GO consortium includes gene-sets for three ontologies; molecular
454 function, cellular components and biological function. This annotation file consisted of 5,917
455 gene-sets which were corrected for multiple testing correction using the MAGMA default
456 setting correcting for 10,000 permutations.

457 To determine whether the genetic targets of antidepressants were enriched for
458 neuroticism we performed a competitive gene-set analysis using MAGMA. Gene sets
459 corresponding to the Anatomical Therapeutic Chemical Classification System code N06A
460 *Antidepressants* (within the *Psychoanaleptics* class) were downloaded (see URLs). This
461 resulted in a set of 110 unique genes corresponding to those that are the targets of the
462 antidepressants. Enrichment for neuroticism was tested against a set of 5483 ‘druggable’
463 autosomal genes (see URLs), that is, they code for proteins which can bind to drug-like

464 molecules. Of the 110 antidepressant genes 86 were found amongst the 5483 druggable
465 genes.

466

467 Linkage Disequilibrium Score Regression

468 Univariate Linkage disequilibrium Score (LDSC) regression⁵⁷ was used to test for
469 residual stratification in our GWAS summary statistics and to derive a heritability estimate.
470 An LD regression was performed by regressing the GWA test statistics (χ^2) on to each SNP's
471 LD score (the sum of squared correlations between the minor allele frequency count of a SNP
472 with the minor allele frequency count of every other SNP). This regression allows for the
473 estimation of heritability from the slope, and a means to detect residual confounders, the
474 intercept. The percentage inflation in the test statistic due to polygenic signal can be derived
475 by subtracting the LDSC ratio ((intercept - 1)/(mean χ^2 - 1)), which represents inflation due to
476 population stratification and other confounding, from 1 and multiplying by 100. Bivariate
477 LDSC regression⁵⁸ was used to derive genetic correlations between neuroticism and 18
478 psychiatric and physical health phenotypes (see Supplementary Table 11). For Alzheimer's
479 disease, a 500-kb region surrounding *APOE* was excluded and the analysis re-run
480 (Alzheimer's disease (500kb)). The genetic correlation between neuroticism as measured by
481 different inventories was also estimated. Further details, including source of GWA summary
482 statistics can be found in the Supplementary Note. Sample overlap could not be controlled for
483 in the LDSC analyses because the exact overlap between the UK Biobank data and the health
484 traits was unknown. In such a case, constraining the intercept to a 'wrong' value could lead to
485 biased estimates. Any sample overlap in the present analyses will only affect the intercept of
486 the regression and could lead to inflated standard errors, but will not affect the genetic
487 correlation¹².

488

489 Mendelian Randomization

490 Two sample Mendelian Randomization (MR) was performed using the TwoSampleMR⁵⁹
491 package implemented in R. GWA summary statistics from the GWA of smoking status in
492 74,053 Europeans⁶⁰ was used to create outcome data for the MR between neuroticism and
493 smoking status. 77 independent SNPs associated with neuroticism were available in the
494 smoking status GWA summary data to test for a causal effect of neuroticism on smoking
495 status. There were no significant SNP signals for smoking status to test the reverse causation
496 model. GWA summary statistics from the GWA of educational attainment in 126,559
497 Caucasians⁶¹ was used to create outcome data for the MR between neuroticism and
498 educational attainment. 75 independent SNPs associated with neuroticism were available in
499 the educational attainment GWA summary data to test for a causal effect of neuroticism on
500 educational attainment. There were too few significant SNPs available for educational
501 attainment to test for a causal effect of educational attainment on neuroticism. Sensitivity
502 analyses were performed to test for heterogeneity and a further test for horizontal pleiotropy
503 was carried out.

504

505 Polygenic Prediction into Generation Scotland

506 Polygenic profile analyses were performed to predict neuroticism and depression status in
507 Generation Scotland (GS)⁶². Polygenic profiles were created in PRSice⁶³ using the UK
508 Biobank neuroticism SNP-based association results, for 7,388 unrelated individuals in GS.
509 SNPs with a MAF <0.01 were removed prior to creating the polygenic profiles. Clumping
510 was used to obtain SNPs in linkage disequilibrium with an $r^2 < 0.25$ within a 250kb window.
511 Individuals were removed from GS if they had contributed to both UK Biobank and GS (n =
512 302). Polygenic profile scores were created based on the significance of the association in
513 UK Biobank with the neuroticism phenotype, at p-value thresholds of 0.01, 0.05, 0.1, 0.5 and

514 1 (all SNPs). Linear regression models were used to examine the associations between the
515 polygenic profile and neuroticism score in GS, adjusting for age at measurement, sex and the
516 first 10 genetic principal components to adjust for population stratification. Logistic
517 regression models were used to examine depression status, adjusting for the same covariates
518 as in the neuroticism models. The false discovery rate (FDR) method was used to correct for
519 multiple testing across the polygenic profiles for neuroticism at all five thresholds⁶⁴.

520

521 **Data Availability**

522 The GWA results generated by this analysis are publicly available at

523 <http://www.ccace.ed.ac.uk>.

524

525 **References for Online Methods**

- 526 47. Haplotype Reference, C. A reference panel of 64,976 haplotypes for genotype
527 imputation. *Nat Genet* **48**, 1279-1283 (2016).
- 528 48. Bycroft, C. *et al.* Genome-wide genetic data on ~500,000 UK Biobank participants.
529 *bioRxiv* (2017).
- 530 49. Chang, C.C. *et al.* Second-generation PLINK: rising to the challenge of larger and
531 richer datasets. *GigaScience* **4**, 7 (2015).
- 532 50. Lo, M.-T. *et al.* Genome-wide analyses for personality traits identify six genomic loci
533 and show correlations with psychiatric disorders. *Nat Genet* **49**, 152-156 (2017).
- 534 51. Genetics of Personality, C. *et al.* Meta-analysis of Genome-wide Association Studies
535 for Neuroticism, and the Polygenic Association With Major Depressive Disorder.
536 *JAMA Psychiatry* **72**, 642-50 (2015).
- 537 52. Willer, C.J., Li, Y. & Abecasis, G.R. METAL: fast and efficient meta-analysis of
538 genomewide association scans. *Bioinformatics* **26**, 2 (2010).

- 539 53. de Leeuw, C.A., Mooij, J.M., Heskes, T. & Posthuma, D. MAGMA: Generalized
540 Gene-Set Analysis of GWAS Data. *PLoS Computational Biology* **11**(2015).
- 541 54. Boyle, A.P. *et al.* Annotation of functional variation in personal genomes using
542 RegulomeDB. *Genome research* **22**, 1790-1797 (2012).
- 543 55. Mi, H. *et al.* PANTHER version 11: expanded annotation data from Gene Ontology
544 and Reactome pathways, and data analysis tool enhancements. *Nucleic Acids*
545 *Research* **45**, D183-D189 (2017).
- 546 56. Gene Ontology, C. Expansion of the Gene Ontology knowledgebase and resources.
547 *Nucleic acids research* **45**, D331-D338 (2017).
- 548 57. Bulik-Sullivan, B.K. *et al.* LD Score regression distinguishes confounding from
549 polygenicity in genome-wide association studies. *Nature genetics* **47**, 291-295 (2015).
- 550 58. Bulik-Sullivan, B.K. *et al.* An atlas of genetic correlations across human diseases and
551 traits. *Nat Genet* **47**, 1236-41 (2015).
- 552 59. Hemani, G. *et al.* MR-Base: a platform for systematic causal inference across the
553 phenome using billions of genetic associations. *bioRxiv* (2016).
- 554 60. Genome-wide meta-analyses identify multiple loci associated with smoking behavior.
555 *Nat Genet* **42**, 441-447 (2010).
- 556 61. Rietveld, C.A. *et al.* GWAS of 126,559 individuals identifies genetic variants
557 associated with educational attainment. *science* **340**, 1467-1471 (2013).
- 558 62. Smith, B.H. *et al.* Cohort Profile: Generation Scotland: Scottish Family Health Study
559 (GS:SFHS). The study, its participants and their potential for genetic research on
560 health and illness. *International Journal of Epidemiology* **42**, 689-700 (2013).
- 561 63. Euesden, J., Lewis, C.M. & O'Reilly, P.F. PRSice: polygenic risk score software.
562 *Bioinformatics* **31**, 1466-1468 (2014).

563 64. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: a practical and
564 powerful approach to multiple testing. *Journal of the royal statistical society. Series B*
565 *(Methodological)*, 289-300 (1995).

566

Genome-wide association results for neuroticism in UK Biobank



