

1 **Cross-disorder analysis of schizophrenia and 19 immune diseases reveals**
2 **genetic correlation**

3 **Short Title: Genetic correlation between schizophrenia and immune diseases**

4 Jennie G Pouget^{1,2,3}, Schizophrenia Working Group of the Psychiatric Genomics
5 Consortium[^], Buhm Han⁴, Yang Wu⁵, Emmanuel Mignot⁶, Hanna M Ollila^{6,7,8}, Jonathan
6 Barker^{9,10}, Sarah Spain^{9,11}, Nick Dand⁹, Richard Trembath^{9,12}, Javier Martin¹³, Maureen
7 D Mayes¹⁴, Lara Bossini-Castillo¹¹, Elena López-Isac¹³, Ying Jin^{15,16}, Stephanie A
8 Santorico^{15,17,18}, Richard A Spritz^{15,16}, Soumya Raychaudhuri^{19,20,21,22,23,24¶}, Jo
9 Knight^{1,2,3,25¶*}

10 ¹Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON,
11 Canada, ²Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada, ³Department of
12 Psychiatry, University of Toronto, Toronto, ON, Canada, ⁴Department of Biomedical Sciences, Seoul
13 National University College of Medicine, Seoul, Republic of Korea, ⁵Institute for Molecular Bioscience,
14 The University of Queensland, Brisbane, QLD 4072, Australia, ⁶Center for Sleep Sciences and Medicine,
15 Department of Psychiatry and Behavioral Sciences, Stanford University, School of Medicine, Palo Alto,
16 CA, USA, ⁷Finnish Institute for Molecular Medicine, Helsinki, Finland, ⁸Center for Genomic Medicine,
17 Massachusetts General Hospital, Boston, Massachusetts, USA and Broad Institute, Cambridge,
18 Massachusetts, USA, ⁹School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine,
19 King's College London, UK, ¹⁰St. John's Institute of Dermatology, Faculty of Life Sciences and Medicine,
20 King's College London, London, UK, ¹¹Wellcome Trust Sanger Institute, Wellcome Trust Genome
21 Campus, Hinxton, Cambridge, UK, ¹²Queen Mary University of London, Barts and the London School of
22 Medicine and Dentistry, London, UK, ¹³Institute of Parasitology and Biomedicine López-Neyra, IPBLN-
23 CSIC, Granada, Spain, ¹⁴The University of Texas Health Science Center-Houston, Houston, TX, USA,
24 ¹⁵Human Medical Genetics and Genomics Program and ¹⁶Department of Pediatrics, University of
25 Colorado School of Medicine, Aurora, CO, USA, ¹⁷Department of Mathematical and Statistical Sciences,
26 University of Colorado Denver, Denver, CO, USA, ¹⁸Department of Biostatistics and Informatics, Colorado
27 School of Public Health, University of Colorado, Aurora, CO, USA, ¹⁹Department of Medicine, Brigham
28 and Women's Hospital and Harvard Medical School, Boston, MA, USA, ²⁰Partners HealthCare Center for
29 Personalized Genetic Medicine, Boston, MA, USA, ²¹Program in Medical and Population Genetics, Broad
30 Institute of MIT and Harvard, Cambridge, MA, USA, ²²Division of Genetics, and ²³Division of
31 Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, ²⁴Faculty of
32 Medical and Human Sciences, University of Manchester, Manchester, UK, ²⁵Lancaster Medical School
33 and Data Science Institute, Lancaster University, Lancaster, UK.

34 *Corresponding authors
35 Email: soumya@broadinstitute.org (SR)
36 Email: jo.knight@lancaster.ac.uk (JK)

37 ¶These authors contributed equally to this work

38 ^Membership of the Schizophrenia Working Group of the Psychiatric Genomics Consortium is provided in
39 the **Supporting Information**.

40 Abstract

41 Epidemiological studies indicate that many immune diseases occur at different rates
42 among people with schizophrenia compared to the general population. Here, we evaluated
43 whether this phenotypic correlation between immune diseases and schizophrenia might be
44 explained by shared genetic risk factors (**genetic correlation**). We used data from a large
45 genome-wide association study (GWAS) of schizophrenia (N=35,476 cases and 46,839
46 controls) to compare the genetic architecture of schizophrenia to 19 immune diseases. First, we
47 evaluated the association with schizophrenia of 581 variants previously reported to be
48 associated with immune diseases at genome-wide significance. We identified three variants with
49 pleiotropic effects, located in regions associated with both schizophrenia and immune disease.
50 Our analyses provided the strongest evidence of pleiotropy at rs1734907 (~85kb upstream of
51 *EPHB4*), a variant which was associated with increased risk of both Crohn's disease (OR =
52 1.16, $P = 1.67 \times 10^{-13}$) and schizophrenia (OR = 1.07, $P = 7.55 \times 10^{-6}$). Next, we investigated
53 genome-wide sharing of common variants between schizophrenia and immune diseases using
54 polygenic risk scores (PRS) and cross-trait LD Score regression (LDSC). PRS revealed
55 significant genetic overlap with schizophrenia for narcolepsy ($p=4.1 \times 10^{-4}$), primary biliary
56 cirrhosis ($p=1.4 \times 10^{-8}$), psoriasis ($p=3.6 \times 10^{-5}$), systemic lupus erythematosus ($p=2.2 \times 10^{-8}$), and
57 ulcerative colitis ($p=4.3 \times 10^{-4}$). Genetic correlations between these immune diseases and
58 schizophrenia, estimated using LDSC, ranged from 0.10 to 0.18 and were consistent with the
59 expected phenotypic correlation based on epidemiological data. We also observed suggestive
60 evidence of sex-dependent genetic correlation between schizophrenia and multiple sclerosis
61 (interaction $p=0.02$), with genetic risk scores for multiple sclerosis associated with greater risk of
62 schizophrenia among males but not females. Our findings suggest that shared genetic risk
63 factors contribute to the epidemiological co-occurrence of schizophrenia and certain immune
64 diseases, and suggest that in some cases this genetic correlation is sex-dependent.

65 Author Summary

66 Immune diseases occur at different rates among patients with schizophrenia compared to
67 the general population. While the reasons for this phenotypic correlation are unclear, shared
68 genetic risk (**genetic correlation**) has been proposed as a contributing factor. Prior studies
69 have estimated the genetic correlation between schizophrenia and a handful of immune
70 diseases, with conflicting results. Here, we performed a comprehensive cross-disorder
71 investigation of schizophrenia and 19 immune diseases. We identified three individual genetic
72 variants associated with both schizophrenia and immune diseases, including a variant near
73 *EPHB4* – a gene whose protein product guides the migration of lymphocytes towards infected
74 cells in the immune system and the migration of neuronal axons in the brain. We demonstrated
75 significant genome-wide genetic correlation between schizophrenia and narcolepsy, primary
76 biliary cirrhosis, psoriasis, systemic lupus erythematosus, and ulcerative colitis. Finally, we
77 identified a potential sex-dependent pleiotropic effect between schizophrenia and multiple
78 sclerosis. Our findings point to shared genetic risk for schizophrenia and at least a subset of
79 immune diseases, which likely contributes to their epidemiological co-occurrence. These results
80 raise the possibility that the same genetic variants may exert their effects on neurons or immune
81 cells to influence the development of psychiatric and immune disorders, respectively.

82 Introduction

83 Despite recent advances in identifying key biomarkers and genetic loci for
84 schizophrenia, its pathophysiology remains poorly understood [1, 2]. One interesting
85 epidemiological observation is that the risk of developing many immune-mediated diseases is
86 increased among patients with schizophrenia [3–5], and vice versa [6, 7]. Here, we use the term
87 **immune disease** to broadly encompass both autoimmune and inflammatory disorders. While
88 there are discrepancies among studies regarding which immune diseases are most strongly
89 correlated with schizophrenia, there is converging evidence that these diseases co-occur at a
90 greater rate than is expected by chance [3–7]. A notable exception is rheumatoid arthritis (RA),
91 where a consistent inverse association with schizophrenia has been observed [5, 8].

92 Genetic factors have long been proposed as an explanation for the differing prevalence
93 of immune diseases among patients with schizophrenia compared to the general population [5,
94 6]. The recently reported role of *complement component 4* (C4) variation in schizophrenia [9]
95 illustrates a potential shared genetic mechanism in the development of immune and psychiatric
96 disorders. Genetic variants conferring increased C4 expression protect against developing
97 systemic lupus erythematosus (SLE), possibly by increased tagging of apoptotic cells – which
98 are the trigger for autoantibody development in SLE – leading to more effective clearance by
99 macrophages [10]. The same genetic mechanism may increase the risk of developing
100 schizophrenia, by increased tagging of neuronal synapses for elimination by microglia leading to
101 excessive synaptic pruning [9]. We hypothesize that similar shared genetic mechanisms may
102 occur throughout the genome, with cellular manifestations in immune cells and neurons
103 influencing the development of immune and psychiatric disorders, respectively. Previously, we
104 found that susceptibility to schizophrenia does not appear to be driven by the broad set of loci
105 harboring immune genes [11]. However, not all genetic variants conferring risk of immune

106 disease fall within immune loci. Here, we evaluated whether common genetic variants
107 influencing the risk of 19 different immune diseases may also be involved in schizophrenia.

108 Our cross-disorder genetic approach is supported by recent successes in identifying
109 shared genetic risk variants (**pleiotropy**) across a variety of human diseases [12–18]. Pleiotropy
110 is emerging as a pervasive phenomenon in the human genome [19–21], and cross-disorder
111 studies characterizing the nature of genotype-phenotype relationships have the potential to yield
112 significant insights into disease etiology. For instance, cross-trait genetic analyses have shed
113 new light on cardiovascular disease and lipid biology – and shifted attention away from HDL as
114 a potential treatment target – by demonstrating that increased HDL cholesterol levels do not
115 reduce the risk of myocardial infarction [14]. In psychiatry, cross-disorder analyses have
116 identified significant pleiotropy between schizophrenia, bipolar disorder, and major depressive
117 disorder, indicating that these diseases are not as distinct at a pathophysiological level as
118 current diagnostic criteria suggest [12, 13, 22].

119 While previous studies have investigated genome-wide pleiotropy between
120 schizophrenia and immune disorders, results have been inconsistent (**S1 Table**). Genetic
121 correlation has been reported between schizophrenia and Crohn's disease [23–27], multiple
122 sclerosis [28], primary biliary cirrhosis [25], psoriasis [29], rheumatoid arthritis [23, 24], systemic
123 lupus erythematosus [24, 25], and type 1 diabetes [23, 24, 26, 27] in some studies, but not in
124 others [8, 13, 16, 24, 30]. Interestingly, negative genetic correlation (whereby genetic risk
125 protects against developing schizophrenia) has also been reported for RA [31], in keeping with
126 the inverse epidemiological association [5, 8].

127 Additional studies are needed to reconcile the inconsistencies in existing cross-trait
128 analyses of schizophrenia and immune disorders, with careful attention towards potential
129 confounding variables (e.g. population stratification, linkage disequilibrium, non-independence
130 of genome-wide association study (GWAS) samples, and sex-specific effects). To this end we
131 have performed a comprehensive cross-disorder analysis of schizophrenia and 19 immune

132 diseases, using data from the largest available genetic studies. Our findings add to a growing
133 body of literature supporting pervasive pleiotropy between schizophrenia and immune diseases.
134 We extend existing literature by including 10 immune diseases that have not previously been
135 compared with schizophrenia, prioritizing pleiotropic genes through integrative analyses of multi-
136 omics data, estimating how much of the phenotypic correlation between schizophrenia and
137 immune diseases was explained by the genetic correlations we observed, and providing novel
138 evidence for potential sex-specific pleiotropy between schizophrenia and immune disease.

139 **Results**

140 **Defining immune risk variants**

141 We identified immune-mediated diseases with robust GWAS findings using
142 ImmunoBase (<http://www.immunobase.org>; accessed 7 June 2015), an online resource
143 providing curated GWAS data for immune-related human diseases. These included the
144 following 19 diseases: alopecia areata (AA), ankylosing spondylitis (AS), autoimmune thyroid
145 disease (ATD), celiac disease (CEL), Crohn's disease (CRO), inflammatory bowel disease
146 (IBD), juvenile idiopathic arthritis (JIA), multiple sclerosis (MS), narcolepsy (NAR), primary
147 biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), psoriasis (PSO), rheumatoid
148 arthritis (RA), Sjögren's syndrome (SJO), systemic lupus erythematosus (SLE), systemic
149 sclerosis (SSC), type 1 diabetes (T1D), ulcerative colitis (UC), and vitiligo (VIT). Notably, the
150 majority of IBD risk variants were also risk variants for CRO and/or UC. For 14 of these immune
151 diseases (see **Table 1**), we also obtained full GWAS or Immunochip summary statistics allowing
152 us to conduct additional polygenic risk scoring (PRS) [30, 32] and cross-trait Linkage
153 Disequilibrium Score regression (LDSC) analyses [16].

154 Given that human leukocyte antigen (HLA) alleles within the major histocompatibility
155 complex (MHC) region (chromosome 6: 25-34 Mb) account for a significant proportion of
156 heritability of immune and inflammatory disorders [33], we considered HLA and non-HLA risk

157 variants separately in our analyses. Within the MHC region we considered only the most
158 strongly associated HLA variant (including SNPs, imputed HLA amino acid sites, and classical
159 alleles) for each disease based on univariate analysis in previously published studies (see
160 **Table 2**), because multivariate conditional analyses reporting adjusted effect sizes of
161 independent HLA variants were not available for all immune diseases. Outside of the MHC
162 region, we considered all non-HLA variants curated in ImmunoBase for each of the 19 immune
163 diseases.

164 The number of genome-wide significant non-HLA risk loci for each of the 19 immune
165 diseases varied from three (NAR) to 144 (IBD). Several variants were associated with more
166 than one immune disease. In total we identified 581 unique variants (563 non-HLA variants and
167 18 HLA variants) associated with any immune disease at genome-wide significance. We refer to
168 these variants as **immune risk variants**.

169

170 **Identifying pleiotropic variants implicated in both immune disease and schizophrenia**

171 First, we evaluated whether there was any evidence of overall risk allele sharing
172 between each of the 19 immune diseases and schizophrenia using a binomial sign test. To do
173 this, we used previously published findings from a GWAS conducted by the Schizophrenia
174 Working Group of the Psychiatric Genomics Consortium [1, 11]. This GWAS represented a
175 meta-analysis of 52 cohorts, comprising a total of 35,476 cases and 46,839 controls, and the full
176 dataset is referred to here as the **PGC2 study**. Overall, the direction of effect for the sets of
177 non-HLA SNPs associated with each of the 19 immune diseases at genome-wide significance
178 was not shared with schizophrenia more than expected by chance (all binomial sign test $p > 0.05$,
179 **S1 Fig**). Thus, we did not observe evidence of risk allele sharing between any immune disease
180 and schizophrenia when using a stringent genome-wide significance threshold to define immune
181 risk variants. We also evaluated the collective association of 261 LD-independent, non-HLA
182 immune risk variants associated with at least one of the 19 immune-mediated diseases, for

183 which linkage disequilibrium (LD) Score and minor allele frequency (MAF) information were
184 available in the European LD Score database [16]. We found significant deviation from the
185 theoretical null in schizophrenia for immune risk SNPs ($\lambda=1.46$). However, when we compared
186 the association of immune risk SNPs to that of similar randomly selected SNP sets
187 (**Supplementary Methods**) we observed no evidence of enrichment (**S2 Fig**, $p=0.66$),
188 indicating that immune risk SNPs were not associated with schizophrenia more than expected
189 by chance given the polygenic nature of schizophrenia.

190 Next, we identified potential pleiotropic variants by evaluating the association of
191 individual immune risk variants with schizophrenia. We considered SNPs associated with
192 schizophrenia at $p<8.6\times10^{-5}$ (Bonferroni correction for 581 tests, 563 non-HLA and 18 HLA
193 variants) to have pleiotropic effects. Given the size of the schizophrenia GWAS, we had over
194 80% power to detect pleiotropic SNPs assuming an $OR\geq1.12$ in schizophrenia.

195 Within the MHC region, we observed four HLA risk alleles associated with both immune
196 disease and schizophrenia, particularly in the class II HLA region (**Table 2, S3 Fig**). These HLA
197 risk alleles were the strongest MHC region associations for AA (HLA-DRB1 #37 Asn), CEL
198 (HLA-DQB1 #74 Ala), PSC (HLA-B*08:01), and SJO (HLA-DQB1*02:01). The presence of HLA-
199 DRB1 #37 Asn conferred a protective association in both AA and schizophrenia, but the
200 remaining HLA variants showed the opposite direction of effect in schizophrenia compared to
201 immune disease (**Table 2, S3 Fig**). Notably, none of these four HLA variants were significantly
202 associated with schizophrenia in previous conditional analyses [9, 11], suggesting that their
203 association with schizophrenia may be driven by LD with other causal variants in the region
204 rather than true pleiotropy. Thus, we did not focus additional analyses on these variants.

205 Outside of the MHC region, five immune risk variants showed potential pleiotropic
206 effects, with the risk allele for immune disease also conferring risk for schizophrenia. These
207 variants have been previously implicated in CRO (rs6738825, rs13126505, rs1734907 [34, 35]),
208 MS (rs7132277 [36]), and CEL (rs296547 [37]). To evaluate the pleiotropic potential of these

209 non-HLA variants, we used conditional and joint analysis (COJO) [38] to perform association
210 analyses in the PGC2 schizophrenia GWAS conditioning on each of the five immune risk
211 variants (**S4 Fig**). In the setting of true pleiotropy, no significant associations should remain after
212 conditioning on the immune risk variants (statistically, all $p > 8.6 \times 10^{-5}$). Consistent with pleiotropy,
213 we observed no remaining associations with schizophrenia after conditioning on rs296547 (top
214 SNP after conditioning: rs111530734, $p = 1.19 \times 10^{-3}$), rs1734907 (top SNP after conditioning:
215 rs11768688, $p = 9.79 \times 10^{-4}$), and rs13126505 (top SNP after conditioning: rs112786981,
216 $p = 4.58 \times 10^{-4}$). Significant associations with schizophrenia remained after conditioning on
217 rs6738825 (top SNP after conditioning: rs111744017, $p = 8.03 \times 10^{-6}$) and rs7132277 (top SNP
218 after conditioning: rs74240770, $p = 1.37 \times 10^{-8}$), suggesting there were independent causal
219 variants driving the associations in these regions for schizophrenia and immune disorders.

220 In order to prioritize genes underlying the identified pleiotropic SNPs (rs296547,
221 rs1734907, rs13126505), we performed an integrative analysis of GWAS summary statistics
222 with methylation quantitative trait loci (mQTL) and expression quantitative trait loci (eQTL)
223 studies using SMR and HEIDI [39, 40] (**Materials and Methods**). Notably, rs296547 was not
224 genotyped in the eQTL dataset, and we used rs404339 as a proxy SNP ($r^2 = 0.85$ in 1000
225 Genomes Phase 3 CEU Population [41]) in SMR analyses of gene expression analyses for
226 rs296547. We observed that rs1734907 was an mQTL ($\beta = 0.47$, $P = 2.13 \times 10^{-26}$) and eQTL ($\beta =$
227 -0.24 , $P = 3.54 \times 10^{-10}$) for *EPHB4* in peripheral blood (**S2 Table, Fig 1**). Furthermore, we
228 observed consistent pleiotropic associations for rs1734907 with schizophrenia and *EPHB4*
229 DNAm ($\beta_{\text{SMR}} = -0.14$, $P_{\text{SMR}} = 3.58 \times 10^{-5}$, $P_{\text{HEIDI}} = 0.12$), schizophrenia and *EPHB4* expression
230 ($\beta_{\text{SMR}} = -0.28$, $P_{\text{SMR}} = 2.63 \times 10^{-4}$, $P_{\text{HEIDI}} = 0.17$), and *EPHB4* DNAm and *EPHB4* expression (β_{SMR}
231 $= 1.98$, $P_{\text{SMR}} = 6.56 \times 10^{-8}$, $P_{\text{HEIDI}} = 0.011$). Thus, there was consistent association across
232 molecular phenotypes and schizophrenia at the *EPHB4* locus, suggesting this gene may be
233 driving the association of rs1734907 in schizophrenia (**Fig 1**). Notably, *TRIP6* is also a candidate

234 functional gene underlying the association of rs1734907 with schizophrenia. We observed
235 pleiotropic association for rs1734907 with schizophrenia and *TRIP6* DNAm with inconsistent
236 direction of effect ($\beta_{\text{SMR}} = 0.15$, $P_{\text{SMR}} = 5.00 \times 10^{-5}$, $P_{\text{HEIDI}} = 0.17$ for probe cg18683606; $\beta_{\text{SMR}} = -$
237 0.12 , $P_{\text{SMR}} = 2.32 \times 10^{-5}$, $P_{\text{HEIDI}} = 0.18$ for probe cg27396824), a trend for association with
238 schizophrenia and *TRIP6* expression ($\beta_{\text{SMR}} = -0.33$, $P_{\text{SMR}} = 6.38 \times 10^{-4}$, $P_{\text{HEIDI}} = 0.14$), but no
239 significant association with *TRIP6* DNAm and *TRIP6* expression. The other pleiotropic SNPs
240 (rs296547, rs13126505) did not demonstrate consistent localization to a particular gene across
241 traits and molecular phenotypes (**Table 3, S2 Table**). We observed that rs296547 was an
242 mQTL for *C1orf106* ($\beta = -1.04$, $P < 10^{-30}$), and found pleiotropic associations for rs296547 with
243 schizophrenia and *C1orf106* DNAm but no other phenotypes (**Table 3, S2 Table**). Similarly, we
244 observed that rs13126505 was an mQTL ($\beta = 0.49$, $P = 4.03 \times 10^{-16}$) and eQTL ($\beta = -0.27$, $P =$
245 3.54×10^{-10}) for *SLC39A8*, and found pleiotropic associations for rs13126505 with schizophrenia
246 and *SLC39A8* DNAm along with schizophrenia and *SLC39A8* expression, but not *SLC39A8*
247 DNAm and expression (**Table 3, S2 Table**).
248

249 **Detecting genetic correlations between immune disease and schizophrenia**

250 Our immune risk variant set captured only those variants associated with immune
251 diseases at genome-wide significance in current GWASs. Given the polygenicity of immune-
252 related diseases, there are 100s to 1,000s of additional variants associated with each disease
253 which have not yet been identified [42]. To evaluate sharing of risk alleles between immune
254 diseases and schizophrenia using a broader set of variants, we used PRS [30, 32] and LDSC
255 [16].

256 For each of the 14 immune diseases with available genome-wide summary statistics, we
257 constructed genetic risk scores (GRSs) at a range of p-value thresholds (p_T) as in previous
258 studies [12], and tested for the association of these GRSs with schizophrenia in a refined subset

259 of the PGC2 study (17,000 cases and 20,655 controls) which excluded samples shared with the
260 immune disease GWASs. To benchmark our findings in immune diseases, we also analyzed
261 human height [43] and included previously published PRS results for bipolar disorder [12]. We
262 considered immune diseases with PRS $p < 0.002$ at any p_T to show significant genetic overlap
263 with schizophrenia (Bonferroni correction for 14 immune diseases tested in both sexes,
264 $0.05/(14*2) \approx 0.002$). Commonly used goodness-of-fit estimates obtained from PRS (such as
265 β_{GRS} and Nagelkerke's pseudo- R^2) lack meaningful interpretation, which makes it difficult to
266 compare these estimates across studies [44]. For these reasons we chose to interpret the
267 direction of effect (i.e. positive or negative correlation) obtained from β_{GRS} , but not to interpret or
268 compare the degree of genetic sharing between immune diseases and schizophrenia. For
269 further details of our PRS approach, see **Materials and Methods**. Using PRS, we had over
270 80% power to detect genetic covariance with schizophrenia ranging from 0.02 to 0.03 for most
271 of the immune diseases, although some showed less than 80% power in this range (PSO, SLE,
272 VIT; **S5 Fig**).

273 As previously described, bipolar disorder PRSs were significantly associated with
274 schizophrenia ($p < 1 \times 10^{-50}$ at $p_T < 1$) [12]. Surprisingly, human height PRSs were also significantly
275 associated with schizophrenia ($p = 1 \times 10^{-11}$ at $p_T < 1$, **S3 Table**). Height was analyzed as a
276 negative control based on its previously reported lack of genetic correlation with schizophrenia
277 using LDSC [16]. Using PRS, we observed that genetic liability for increased height protected
278 against schizophrenia ($\beta_{GRS} = -0.11$ at $p_T < 1$). The significant inverse association of height PRSs
279 with schizophrenia case-status we observed may reflect the greater sensitivity of this approach
280 to subtle population stratification, sample sharing, and/or true genetic overlap.

281 Genetic scores including the HLA region were significant for CEL, NAR, PBC, PSO, RA,
282 SLE, SSC, T1D, and UC ($p < 0.002$ at multiple p_T , **S4 Table**). Height was not included in these
283 analyses, given that HLA variants have not been associated with height in previous GWAS [43].

284 With the exception of CEL ($\beta_{GRS} \approx -0.04$ at $p_T < 5 \times 10^{-8}$, 1×10^{-4} , and 1×10^{-3}), all immune diseases
285 exhibited a positively associated PRS with schizophrenia case-status (all $\beta_{GRS} > 0$, **S4 Table**). For
286 CEL, RA, SLE, and SSC only those PRSs constructed using the most stringent p-value cutoffs
287 (5×10^{-8} , 1×10^{-4} , 1×10^{-3}) were significantly associated with schizophrenia. To evaluate whether
288 the HLA region alone was driving the observed genetic sharing, we constructed PRSs excluding
289 this region. After excluding HLA variants, genetic scores for NAR, PBC, PSO, SLE, T1D, and
290 UC remained significantly associated with schizophrenia (**Table 4, S6 Fig**). Because the genetic
291 overlap between these six immune diseases and schizophrenia was not driven by a single HLA
292 variant of large effect, we focused on these findings for the remainder of our analyses.

293 Given the potential sensitivity of PRS to artificial genetic overlap highlighted in our
294 analysis of height, we wanted to assess whether cryptic sample sharing between the immune
295 and schizophrenia GWASs could be driving the shared genetic liability that we observed. To do
296 this, we conducted leave-half-out analyses. If the observed genetic overlap was driven by
297 samples shared between certain schizophrenia cohorts and the immune disease GWASs, the
298 GRS association should not be consistently observed across subsamples leaving out half of the
299 schizophrenia cohorts. Across 1,000 subsamples (N_{cases} ranging from 3,985-13,074) leaving out
300 a randomly selected 14 cohorts, we observed a high proportion of subsamples with GRSs
301 significantly associated with schizophrenia ($p < 0.05$ at $p_T < 1$) for height (0.99), NAR (0.72), PBC
302 (0.95), PSO (0.84), SLE (0.97), T1D (0.95), and UC (0.70) suggesting our findings were not
303 driven by sample sharing.

304 To further validate our finding of genetic overlap between schizophrenia and these six
305 immune-mediated diseases using PRS, we applied an independent method (LDSC) for
306 estimating genome-wide genetic correlation between traits that is robust to sample sharing [16].
307 For LDSC analyses, we used summary statistics from the 49 European-ancestry cohorts in the
308 PGC2 study (31,335 cases and 38,765 controls) [1]. Unlike PRS, LDSC provides an

309 interpretable and comparable estimation of genetic sharing between two traits in the form of
310 genetic correlation (r_g) values. Notably, LDSC is less sensitive than PRS and is not robust when
311 applied to genetic data obtained from specialty chips (e.g. Immunochip) [16]. We did not carry
312 T1D forward for LDSC analysis, due to failure of this dataset on quality control measures
313 (liability scale $h^2 > 1$, likely secondary to inflated effective sample size due to genotyping on
314 Immunochip). Given that this was a secondary analysis, we considered immune diseases with r_g
315 $p < 0.05$ to show significant genetic overlap with schizophrenia.

316 As previously reported [16], our positive control (bipolar disorder) showed significant
317 genetic overlap with schizophrenia ($r_g = 0.75 \pm 0.05$, $p = 8.5 \times 10^{-60}$; **Fig 2, Table 4**). In contrast to our
318 PRS results, but in agreement with previous findings [16], our negative control (height) showed
319 no such overlap using LDSC ($r_g = -0.004 \pm 0.02$, $p = 0.84$; **Fig 2, Table 4**). With respect to immune
320 diseases, LDSC confirmed significant genetic overlap with schizophrenia for PBC, PSO, SLE,
321 and UC ($r_g = 0.10 - 0.18$, **Fig 2, Table 4**) indicating the association of GRSs for these diseases
322 was not driven by shared samples. Notably, genetic correlations for PSO and SLE did not
323 survive correction for the 14 tests performed (**Table 4**). We also observed significant genetic
324 overlap with schizophrenia for NAR using LDSC, with the caveat that this dataset was
325 genotyped using Immunochip and did not survive multiple testing correction (**Fig 2, Table 4**).
326 Overall, LDSC provided consistent results for the immune diseases showing significant genetic
327 sharing with schizophrenia by PRS.

328

329 **Benchmarking genetic correlations between immune disease and schizophrenia with**
330 **epidemiological data**

331 To determine how much of the phenotypic correlation between schizophrenia and
332 immune-mediated diseases was explained by the genetic correlations we observed, we
333 benchmarked significant genetic correlations between schizophrenia and immune-mediated

334 disorders relative to the expected phenotypic correlations from epidemiological data (**Materials**
335 **and Methods**). Using incidence of immune diseases in schizophrenia reported in a large
336 population-based study [3], we estimated phenotypic correlations between schizophrenia and
337 PBC, PSO, SLE, and UC. We were unable to estimate phenotypic correlation for NAR and
338 schizophrenia, given that there were no estimates in the literature of the incidence of NAR in
339 schizophrenia. For PBC, PSO, and SLE we observed small positive genetic correlations with
340 schizophrenia that were consistent with the epidemiological data (PBC: $r_g = 0.131 \pm 0.05$, $r_p =$
341 0.112 ; PSO: $r_g = 0.182 \pm 0.07$, $r_p = 0.130$; SLE: $r_g = 0.130 \pm 0.05$, $r_p = 0.048$). For UC we
342 observed a small positive estimate of genetic correlation ($r_g = 0.106 \pm 0.04$) while there was no
343 strong evidence for any correlation between UC and schizophrenia in the epidemiological data
344 ($r_p = -0.001$). Importantly, while the MHC region contains risk factors for both schizophrenia and
345 immune-mediated diseases, our genetic correlation estimates were obtained considering only
346 SNPs outside of the MHC region due to unusual LD in this region [45].

347

348 **Exploring sex-dependent genetic correlations between immune disease and**
349 **schizophrenia**

350 Given the significant sex bias of autoimmune diseases, with women at greater risk
351 overall [46], we hypothesized that there may be sex-dependent genetic overlap between
352 schizophrenia and some immune-mediated diseases. We therefore performed sex-stratified
353 PRS, testing the association of height and immune disease GRSs with schizophrenia separately
354 in males and females of the PGC2 study. Genetic scores for height showed significant
355 association with schizophrenia in both males and females. Three of the immune diseases (PBC,
356 PSO, T1D) with significant main effects showed sex-dependent effects, with greater signal
357 among males (**S5 Table**). Additionally, although genetic scores for MS were not significantly

358 associated with schizophrenia in the total sample there was significant association among
359 males ($R^2=0.03$, $p=1.26\times 10^{-3}$ at $p_{T}<1$; **S5 Table**).

360 Given the greater statistical power for the male subset of the schizophrenia GWAS, we
361 performed simulations by selecting random subsamples of male cases and controls equal in
362 size to the female sample (5,321 cases and 9,094 controls). If the stronger genetic overlap
363 between schizophrenia and MS, PBC, PSO, and T1D among males was driven by the larger
364 sample size rather than a true sex-dependent effect, there should be no consistent association
365 of GRSs with schizophrenia in these subsamples. Across 1,000 subsamples, the proportion with
366 significant GRSs ($p<0.002$ at $p_{T}<1$) was high for PBC (0.94) and T1D (0.87), suggesting our
367 finding of a greater pleiotropic effect among males for these diseases was not driven solely by
368 lower statistical power among females; this was not the case for PSO (0.59) or MS (0.21).

369 Next, we performed formal statistical tests for an interaction between sex and genetic
370 scores for these four immune diseases. We observed a nominally significant interaction for MS
371 ($p<0.05$ at several p_T ; **S5 Table**), noting that this finding did not survive correction for multiple
372 testing. The remaining immune diseases did not show significant sex interactions, although the
373 direction of effect was consistent with a greater pleiotropic effect in males (**S5 Table**).

374

375 **Discussion**

376 Using a variety of statistical approaches, we provide evidence of shared genetic risk for
377 schizophrenia and several immune diseases. Within the MHC region, we identified four HLA
378 variants showing statistically significant association with schizophrenia. An important caveat is
379 that these four variants were not the top variants in their respective regions of association with
380 schizophrenia, and were not primary drivers of the MHC association in schizophrenia in
381 stepwise conditional analyses [9]. Therefore, the biological significance of these particular HLA
382 variants in schizophrenia is likely limited.

383 Outside of the MHC region, we identified three SNPs with pleiotropic effects - influencing
384 risk for both celiac disease (CEL) (rs296547) or Crohn's disease (CRO) (rs1734907,
385 rs13126505) and schizophrenia. Integration of GWAS, mQTL, and eQTL data implicated
386 *C1orf106*, *SLC39A8*, and *EPHB4* or *TRIP6* as functional candidates driving the pleiotropic
387 association of rs296547, rs13126505, and rs1734907, respectively. Overall, our findings provide
388 the strongest evidence for a model in which genetic variation at rs1734907 (~85kb upstream of
389 *EPHB4*) increases DNA methylation, upregulates *EPHB4* expression, and decreases the risk of
390 schizophrenia. While DNA methylation is classically associated with gene silencing, the effect of
391 methylation on transcription depends on the genomic context [47]; for instance, methylation of
392 silencers or insulators eliminates transcription-blocking activity thereby promoting gene
393 expression [48, 49]. *EPHB4* is a transmembrane tyrosine kinase receptor that coordinates cell
394 movement via bidirectional intercellular signaling at sites of direct cell-to-cell contact [50]. In the
395 brain, ephrin signaling mediates synaptic plasticity by initiating and stabilizing neuronal synapse
396 formation (reviewed by [51]). An analogous role has not yet been discovered in the immune
397 system, possibly due to the much shorter lifespan of immunological synapses between
398 lymphocytes and antigen presenting cells (minutes) as compared to neuronal synapses (years)
399 [52, 53]. Interestingly, ephrin signaling attenuates the migration responses of both neurons and
400 immune cells toward chemoattractants *in vitro* [54, 55]. Thus, disrupted pathfinding may be a
401 shared risk mechanism by which *EPHB4* contributes to immune disease and schizophrenia. The
402 hypotheses raised by our findings require further validation. If the association of rs1734907 with
403 CRO and schizophrenia is robustly replicated in future GWASs, functional studies will be
404 needed to investigate both the genetic mechanism by which rs1734907 (or a causal variant in
405 LD with this SNP) influences *EPHB4* transcription, and the biological mechanism by which
406 increased *EPHB4* expression influences susceptibility to CRO and schizophrenia. With the
407 multi-kinase inhibitor dasatinib already on the market for treatment of chronic myeloid leukemia

408 [56] and other EphB4 inhibitors currently in Phase II trials [57–60], the potential for future drug
409 repurposing makes *EPHB4* an attractive candidate for further investigation.

410 We observed genome-wide sharing of risk variants for schizophrenia and six immune
411 diseases (narcolepsy (NAR), primary biliary cirrhosis (PBC), psoriasis (PSO), systemic lupus
412 erythematosus (SLE), type 1 diabetes (T1D), and ulcerative colitis (UC)) using PRS, all of which
413 have been previously reported to co-occur with schizophrenia in epidemiological studies [3, 5,
414 61]. The strongest evidence of shared genetic risk emerged for PBC, PSO, SLE, and UC, which
415 also showed robust genetic correlation with schizophrenia using LDSC. With the exception of
416 UC, the small positive genetic correlations observed between these immune diseases and
417 schizophrenia ($r_g \sim 0.1$) were consistent with phenotypic correlations observed in
418 epidemiological data. Thus, currently available genetic data suggest that shared genetic risk
419 contributes to the co-occurrence of PBC, PSO, and SLE in schizophrenia. Possible explanations
420 for this sharing of genetic risk include the presence of a subgroup of “autoimmune-like”
421 schizophrenia cases and/or sharing of specific biological pathways between schizophrenia and
422 these particular immune diseases.

423 To our knowledge, this is the first time that sex-dependent genetic correlation with
424 immune diseases has been investigated in schizophrenia. We found nominal evidence of male-
425 specific genetic correlation for multiple sclerosis (MS), and a stronger pleiotropic effect among
426 males for PBC, PSO, and T1D although the latter were not statistically significant. Interestingly,
427 animal studies indicate that sex hormones have opposing effects on predisposition to
428 schizophrenia and autoimmunity; estrogen has been reported to protect against the
429 development of schizophrenia [62], while androgens appear to protect against the development
430 of autoimmune diseases [63, 64]. We emphasize that our sex-dependent findings require
431 validation in independent samples. If replicated, one possibility is that sex hormones modulate
432 pathogenesis among genetically vulnerable individuals, making males more likely to develop
433 schizophrenia and females more likely to develop autoimmune diseases.

434 Our work was subject to several important limitations. Firstly, genome-wide summary
435 statistics were not available for all of the immune diseases, resulting in a more limited analysis
436 of 14 diseases. For five of these diseases (CEL, juvenile idiopathic arthritis (JIA), MS, NAR,
437 T1D) summary statistics were obtained from Immunochip rather than GWAS, providing
438 incomplete coverage of the genome for comparison with schizophrenia and biasing the genetic
439 correlation estimates obtained by LDSC. Secondly, GRSs for human height – analyzed as a
440 negative control – showed stronger association with schizophrenia than any of the immune
441 diseases. An inverse epidemiological relationship between height and schizophrenia has been
442 reported [65, 66], consistent with our PRS findings. The reasons for the discrepancy between
443 PRS and LDSC, which showed no genetic correlation between height and schizophrenia (as
444 previously reported [16]) are unclear. One explanation is that PRS, which uses individual-level
445 genotype data as opposed to summary statistics, is a more sensitive method to detect true
446 genome-wide sharing of risk alleles. If this is the case, it raises a broader question regarding
447 how much genetic overlap is expected across complex traits in general using the PRS
448 approach. Recent work suggests that pleiotropy is pervasive across human diseases, and that
449 this phenomenon is driven at least in part by the polygenic nature of complex traits [21]. If this is
450 the case, the extreme polygenicity of human height (more than 100,000 common variants
451 estimated to exert independent causal effects [67]) may be driving the pleiotropy we observed
452 between height and schizophrenia using PRS. An alternative explanation that must be
453 considered is that PRS may be more vulnerable to confounding by cryptic population
454 stratification, LD, or sample sharing.

455 Despite these limitations, our work adds to a growing body of evidence suggesting that
456 schizophrenia and immune diseases share genetic risk factors. There are conflicting reports in
457 the literature with respect to the specific immune diseases demonstrating genetic overlap with
458 schizophrenia, and the direction of effect (positive or negative genetic correlation). Genetic
459 overlap with schizophrenia has been previously investigated for nine of the 19 immune diseases

460 studied here. Genome-wide genetic correlation with schizophrenia has been previously reported
461 for CRO [23–25, 27], MS [28], PBC [25], PSO [25, 29], rheumatoid arthritis (RA, both positive
462 [23, 24] and negative [31] genetic correlations), SLE [24, 25], T1D [23], and UC [24–27] (see **S1**
463 **Table** for a summary of previous studies). Our results are consistent with previously reported
464 genetic overlap between schizophrenia and PBC [25], PSO [25], SLE [24, 25], T1D [23], and UC
465 [24, 25]. While we did not observe genetic correlation between schizophrenia and MS in the
466 total sample, there was a significant sex-dependent effect with genetic correlation observed
467 among males. We provide new evidence of genetic correlation with NAR (not previously
468 investigated). Notably, we did not find any significant genetic correlation between schizophrenia
469 and RA. Despite the robust inverse epidemiological association between schizophrenia and RA
470 [8], the genetic association is less consistent. Using methods based on summary statistics
471 (including PRS and LDSC), four previous studies reported no evidence of pleiotropy between
472 schizophrenia and RA [8, 16, 25, 30], while two studies reported positive genetic correlation [23,
473 24]. Notably, Lee *et al.* reported an inverse genetic correlation – in keeping with the observed
474 epidemiological effect – using restricted maximum likelihood (GREML), a method utilizing full
475 genotype data which has greater statistical power to detect small pleiotropic effects than PRS or
476 LDSC [31]. Given the modest and potentially sex-dependent genetic correlations observed in
477 the present study, subtle differences in statistical power across studies using different statistical
478 methods and GWAS datasets may explain these discrepant findings. As genetic samples
479 continue to grow, and our understanding of the degree of genetic overlap expected among
480 complex traits evolves, it will be worthwhile to revisit these analyses.

481 Overall, our analyses provide statistical evidence supporting extensive pleiotropy
482 between immune diseases and schizophrenia. Our results highlight *EPHB4*, a transmembrane
483 receptor that coordinates cell migration and has dual roles in immune cell and neuronal
484 pathfinding, as a promising candidate for future functional studies. More broadly, our findings
485 indicate that common genetic variants influencing the risk of immune diseases – in particular

486 NAR, PBC, PSO, SLE, and UC – are also involved in schizophrenia. Studies identifying the cell
487 types and biological pathways that may be driving this genetic overlap are needed, and will
488 hopefully provide further insights into the pathophysiology of schizophrenia. In the meantime,
489 our work supports the emerging hypothesis that pathogenic mechanisms are shared across
490 immune and central nervous system disorders.

491

492 **Materials and Methods**

493 **Samples and quality control**

494 We used either imputed genotype data or summary statistics generated as described in
495 the original GWASs. For sample details, see **Table 1**.

496

497 **Schizophrenia dataset**

498 We used data from the PGC2 study [1]. For analyses of non-HLA genome-wide
499 significant risk variants for immune diseases we used publicly available summary statistics from
500 the total dataset (52 cohorts; 35,476 cases and 46,839 controls) [1]. For PRS analyses we used
501 all 36 European ancestry case-control cohorts with available individual-level genotype data
502 (25,629 cases and 30,976 controls). For analyses including HLA variants we used a further
503 refined 31 European ancestry case-control cohorts (20,253 cases and 25,011 controls) with
504 high-quality coverage of the MHC region, as previously described [11].

505

506 **Immune disease datasets**

507 To estimate the extent of genetic overlap between schizophrenia and immune diseases,
508 we obtained full GWAS or Immunochip summary statistics for 14 of the 19 immune diseases
509 (five immune diseases were not included in PRS analyses due to lack of available summary
510 statistics). We obtained publicly available summary statistics for ten immune diseases (see

511 **URLs**): CEL [68], CRO [69], IBD [69], JIA [70], MS [36], NAR [71], RA [72], SLE [73], T1D
512 [74], and UC [69]. For the following four immune diseases, we obtained summary statistics with
513 permission from the authors: PBC [75], PSO [76], SSC [77], and VIT [78].

514

515 **Testing the association of genome-wide significant risk alleles for 19 immune
516 diseases in schizophrenia**

517 For each of the 19 immune diseases, we defined risk loci outside of the MHC region
518 (chromosome 6: 25-34 Mb) using curated GWAS results from ImmunoBase
519 (<http://www.immunobase.org>; accessed 7 June 2015. For details, see **Supplementary
520 Methods**). Notably, the majority of IBD risk variants were also risk variants for CRO and/or UC.
521 Within the MHC region we considered only the most strongly associated HLA variant (including
522 SNPs, imputed HLA amino acid sites, and classical alleles) for each disease based on
523 univariate analysis in previously published studies (see **Table 2**), because multivariate
524 conditional analyses reporting adjusted effect sizes of independent HLA variants were not
525 available for all immune diseases. In total there were 581 unique variants (563 non-HLA
526 variants and 18 HLA variants) associated with any immune disease at genome-wide
527 significance.

528 First, we tested for shared direction of effect with schizophrenia among SNPs associated
529 with each of the 19 immune diseases using the binomial sign test. Because some immune risk
530 SNPs were associated with multiple diseases with inconsistent direction of effect, we could not
531 evaluate shared direction of effect among the collective set of immune risk SNPs in
532 schizophrenia.

533 Next, we evaluated the collective association of SNPs associated with any immune
534 disease. First we extracted the p-values for a pruned set of 261 LD-independent, non-HLA
535 immune risk SNPs with linkage disequilibrium (LD) Score and minor allele frequency (MAF)

536 information were available in the European LD Score database [16] from the schizophrenia
537 PGC2 GWAS. We then quantified enrichment of these immune risk SNP associations in
538 schizophrenia using the genomic inflation value λ . We obtained an empirical enrichment p-value
539 by comparing this to λ values from 1,000 equal-sized sets of SNPs drawn from the
540 schizophrenia GWAS summary data, and matched to the immune SNP set for MAF and LD
541 score as these parameters are correlated with GWAS test statistics (see **Supplementary**
542 **Methods** for details).

543 Finally, we evaluated the association of each of the 581 variants with schizophrenia
544 using previously published association results for non-HLA [1] and HLA variants [11]. We
545 considered SNPs associated with schizophrenia at $p < 8.6 \times 10^{-5}$ (Bonferroni correction for 581
546 tests, 563 non-HLA and 18 HLA variants) to have pleiotropic effects.

547 To evaluate the pleiotropic potential of immune risk variants significantly associated with
548 schizophrenia, we performed conditional and joint analysis (COJO) using GCTA [79].
549 Specifically, we used COJO to perform association analyses in the PGC2 schizophrenia GWAS
550 conditioning on the immune risk variants of interest (i.e. SNPs that were significantly associated
551 with both an immune disease and schizophrenia). In the setting of true pleiotropy, no significant
552 associations with schizophrenia should remain after conditioning on these immune risk variants
553 (statistically, all $p > 8.6 \times 10^{-5}$). We used the 1000 Genomes Phase 3 European dataset as a
554 reference panel to calculate LD between SNPs.

555 To prioritize genes and regulatory elements driving the pleiotropic GWAS loci we
556 identified (associated with both immune disease and schizophrenia, see **Table 3**), we followed
557 the analytic approach described by Wu *et al.* [40]. This approach integrates summary statistics
558 from independent -omics methylation quantitative trait loci (mQTL) studies, expression
559 quantitative trait loci (eQTL) studies, and GWAS to identify SNPs associated with gene
560 expression, DNA methylation, and disease through shared genetic effects.

561 We obtained mQTL and eQTL data used in Wu *et al.* [40] for genetic regions within a
562 2Mb window of each pleiotropic SNP. These data and the quality control measures applied have
563 been described in detail elsewhere [40]. Briefly, mQTL summary-level SNP data were from a
564 meta-analysis of the Brisbane Systems Genetics Study [80] and Lothian Birth Cohorts of 1921
565 and 1936 [81], which comprised 1,980 individuals with DNA methylation measured in peripheral
566 blood. eQTL summary-level SNP data were from the Consortium for the Architecture of Gene
567 Expression (CAGE) study [82], which comprised 2,765 individuals with gene expression levels
568 measured in peripheral blood. GWAS summary-level SNP data for schizophrenia was from the
569 PGC2 study [1].

570 We applied summary data-based Mendelian randomization (SMR) using GCTA [79] to
571 test for shared associations between the pleiotropic SNPs with DNAm probes and gene
572 expression probes, DNAm probes and schizophrenia, and gene expression probes and
573 schizophrenia. We included DNAm and gene expression probes within 2Mb of the pleiotropic
574 SNPs. We considered significant associations as those with $P_{SMR} < 1.30 \times 10^{-4}$ (0.05/385 tagged
575 genes) for mQTLs and $P_{SMR} < 4.31 \times 10^{-4}$ for eQTLs (0.05/116 tagged genes). Next, we applied
576 the heterogeneity in dependent instruments (HEIDI) test [39] using GCTA [79] to evaluate
577 whether significant shared associations between DNAm, gene expression and schizophrenia
578 were driven by linkage (i.e. separate causal variants in LD exerting genetic effects on DNAm,
579 gene expression, and schizophrenia) or a shared pleiotropic causal variant. We considered
580 genetic effects that passed the HEIDI test ($P_{HEIDI} > 0.01$) to be driven by a single causal variant.
581 We looked for consistent SMR and HEIDI results across GWAS, mQTL, and eQTL studies to
582 prioritize genes for future functional studies.

583

584 **Testing the association of polygenic risk scores for 14 immune diseases in**
585 **schizophrenia**

586 To evaluate whether common variants influencing risk of immune diseases collectively
587 contribute to schizophrenia, we used PRS [30, 32]. To benchmark the amount of genetic
588 overlap between schizophrenia and immune disease, we included previously published results
589 for bipolar disorder as a positive control [12]. We used human height [43] as a negative control
590 because – despite the inverse epidemiological relationship between height and schizophrenia
591 previously reported [65, 66] – a prior study using cross-trait LDSC reported no genetic
592 correlation with schizophrenia [16].

593 For 14 immune diseases with available genome-wide summary statistics we performed
594 PRS at a range of p-value thresholds (p_T) as in previous studies [12]: 5×10^{-8} , 1×10^{-4} , 1×10^{-3} ,
595 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1.0 (which included all LD-independent SNPs, **Table 1**).
596 Due to extensive LD in the HLA region, we performed analyses both including the top HLA
597 variant and excluding the HLA region. At each p_T , we constructed GRSs for each individual i in
598 the schizophrenia cohort for each immune disease h by calculating the sum of risk-allele
599 dosages (g) weighted by their effect sizes (β) for that immune disease:

$$PRS_{i,h} = \sum_M \beta_{M,h} g_{M,i}$$

600 where M iterates over all known risk alleles for disease h , $\beta_{M,h}$ is the effect size (log odds ratio)
601 of M in disease h , and $g_{M,i}$ is the risk-allele dosage of M in individual i . We then performed
602 logistic regression in R [83] using the stats package [83] to evaluate the association between
603 schizophrenia case-status and GRSs for each immune disease. As in previous studies,
604 statistical significance of the GRSs was estimated based on their logistic regression coefficient
605 [12, 30]. Variance in schizophrenia case-status explained by the GRSs was estimated using the
606 deviation in liability-scale R^2 between a null model (including 10 ancestry-informative principal
607 components and study site) and the full model (including GRSs in addition to these covariates),
608 calculated as previously described [44] assuming a population prevalence of schizophrenia of
609 1%. We also estimated Nagelkerke's pseudo- R^2 using the fmsb package [84]. We considered

610 immune diseases with GRS $p < 0.002$ at any p_T to show significant genetic overlap with
611 schizophrenia (Bonferroni correction for 14 immune diseases tested in both sexes,
612 $0.05/(14^2) = 0.002$). As in previous studies [12, 30] we did not use Bonferroni correction for the
613 number of p-value thresholds, as these tests are highly correlated.

614 We excluded eight schizophrenia cohorts using Wellcome Trust Case Control Consortium
615 (WTCCC) controls, due to the use of these samples in the immune disease GWASs. The total
616 schizophrenia sample analyzed by PRS included 37,655 subjects (28 cohorts; 17,000 cases
617 and 20,655 controls). Sex-stratified and formal sex-PRS interaction analyses were performed
618 among the subset of subjects with known sex (9,787 male cases and 9,284 male controls; 5,231
619 female cases and 9,094 female controls). For details of PRS, see **Supplementary Methods**
620 and **Table 1**.

621
622 **Estimating the degree of genetic correlation between schizophrenia and 14 immune**
623 **diseases**

624 To validate our PRS results and obtain genetic correlation (r_g) estimates, we performed a
625 secondary analysis using cross-trait LDSC for immune-mediated diseases with significant PRS
626 associations with schizophrenia [16]. Cross-trait LDSC estimates the genetic correlation
627 between two traits using GWAS summary statistics. Similar to the PRS analyses described
628 above, we benchmarked the genetic correlations observed for immune diseases by analyzing
629 bipolar disorder [85] as a positive control and human height [43] as a negative control.

630 The statistical framework for cross-trait LDSC has been described in detail previously
631 [16]. Briefly, LDSC leverages the relationship between LD and association test statistics to
632 estimate heritability as the slope of the regression of z-scores against LD scores [86]. Cross-trait
633 LDSC is a bivariate extension of this method which estimates genetic covariance as the slope of
634 the regression of the products of z-scores against LD scores using the following equation [16]:

$$E[z_{1j}z_{2j}|\ell_j] = \frac{\sqrt{N_1 N_2} \varrho_g}{M} \ell_j + \frac{\varrho N_s}{\sqrt{N_1 N_2}}$$

635 where z_{ij} denotes the z score for study i and SNP j , ℓ_j is the LD score [86], N_i is the sample size
636 for study i , ϱ_g is the genetic covariance, M is the number of SNPs in the reference panel with
637 MAF between 5% and 50%, N_s is the number of individuals included in both studies, and ϱ is
638 the phenotypic correlation among the N_s overlapping samples. Genetic covariance ϱ_g is
639 estimated by regressing $z_{1j}z_{2j}$ against $\ell_j \sqrt{N_1 N_2}$, and multiplying the resulting slope by M .
640 Statistical significance is assessed using block jackknifing over 200 equally sized blocks of
641 SNPs [16]. Importantly, the MHC region is excluded from LDSC analyses due to its unusual LD
642 structure and genetic architecture [45].

643 Because LDSC is robust to sample sharing across GWAS [16], we used summary
644 statistics from the 49 European-ancestry cohorts in the PGC2 study (31,335 cases and 38,765
645 controls) [1]. We used LD Scores from the “eur_w_ld_chr/” files available from
646 <https://data.broadinstitute.org/alkesgroup/LDSCORE>, computed using 1000 Genomes Project
647 [87] Europeans as a reference panel as previously described [45]. To ensure we were using
648 well-imputed SNPs we filtered all GWAS as previously described [16], including limiting the
649 analysis to HapMap 3 [88] SNPs as implemented in the LDSC script munge_sumstats.py
650 (<https://github.com/bulik/ldsc>). We estimated liability scale h^2 for each trait using previously
651 reported prevalence estimates (**S6 Table**), and removed datasets with $h^2 > 1$. Given that this was
652 a secondary analysis, we considered traits with $r_g p < 0.05$ to have significant genetic correlation
653 with schizophrenia.

654 **Benchmarking with epidemiological data**

655 To determine how much of the phenotypic correlation between schizophrenia and
656 immune-mediated diseases was explained by the genetic correlations we observed, we used
657 the approach previously described by Lee *et al.* [31]. Briefly, we benchmarked our significant

658 genetic correlation estimates between schizophrenia and NAR, PBC, PSO, SLE and UC relative
659 to the expected phenotypic correlations from epidemiological data. We obtained estimates of
660 the population risk of schizophrenia (K_{SCZ}), the population risk of each immune disease
661 (K_{IMMUNE}), and the probability of each immune disease among patients with schizophrenia
662 ($K_{IMMUNE \mid SCZ}$) from the literature as referenced in **S6 Table**. We estimated the phenotypic
663 correlation between schizophrenia and the immune disease of interest ($R_{SCZ-IMMUNE}$) using the
664 following formula, as derived by Lee *et al.* [31] assuming that the phenotypic liabilities of
665 schizophrenia (t_{SCZ}) and immune disease (t_{IMMUNE}) follow a bivariate normal distribution with
666 mean=0 and standard deviation=1:

$$R_{SCZ-IMMUNE} = \frac{i_{SCZ} t_{IMMUNE} - \sqrt{i_{SCZ}^2 t_{IMMUNE}^2 - (t_{IMMUNE \mid SCZ}^2 + i_{SCZ}^2)(t_{IMMUNE}^2 - t_{IMMUNE \mid SCZ}^2)}}{(t_{IMMUNE \mid SCZ}^2 + i_{SCZ}^2)}$$

667 where:

668 t_{SCZ} is the liability threshold for schizophrenia:

669 Z-score of the $(1 - K_{SCZ})^{\text{th}}$ percentile

670 t_{IMMUNE} is the liability threshold for immune disease:

671 Z-score of the $(1 - K_{IMMUNE})^{\text{th}}$ percentile

672 $t_{IMMUNE \mid SCZ}$ is the liability threshold for immune disease in those with schizophrenia:

673 Z-score of the $(1 - K_{IMMUNE \mid SCZ})^{\text{th}}$ percentile

674 d_{SCZ} is the “height” of the normal distribution at the schizophrenia liability threshold:

675 probability density function of t_{SCZ}

676 i_{SCZ} is the mean phenotypic liability of those with schizophrenia:

677 d_{SCZ} / K_{SCZ}

678 Statistical power

679 Power to detect association of individual non-HLA and HLA immune risk variants in
680 schizophrenia was calculated using the Genetic Power Calculator [89] assuming a risk allele

681 frequency (RAF) of 0.05, disease prevalence of 1%, and significance threshold (α) of 8.6×10^{-5} .
682 Power for PRS was evaluated using AVENGEME [90, 91], assuming disease and genetic
683 parameters detailed in **S6 Table**.

684 URLs

685 LD Score database:

686 ftp://atguftp.mgh.harvard.edu/brendan/1k_eur_r2_hm3snps_se_weights.RDS

687

688 GWAS summary statistics:

689 • CEL

690 https://www.immunobase.org/downloads/protected_data/iChip_Data/hg19_gwas_ic_cel_tr
691 ynka_4_19_1.tab.gz

692 • CRO, IBD, UC

693 [ftp://ftp.sanger.ac.uk/pub/consortia/ibdgenetics/iibdgc-trans-ancestry-filtered-summary-](ftp://ftp.sanger.ac.uk/pub/consortia/ibdgenetics/iibdgc-trans-ancestry-filtered-summary-stats.tgz)
694 stats.tgz

695 • JIA

696 https://www.immunobase.org/downloads/protected_data/iChip_Data/hg19_gwas_ic_jia_hin
697 ks_UK_4_19_1.tab.gz

698 • MS

699 https://www.immunobase.org/downloads/protected_data/GWAS_Data/hg19_gwas_ms_im
700 sgc_4_19_1.tab.gz

701 • NAR

702 https://www.immunobase.org/downloads/protected_data/iChip_Data/hg19_gwas_ic_nar_fa
703 raco_4_19_1.tab.gz

704 • RA

705 http://www.broadinstitute.org/ftp/pub/rheumatoid_arthritis/Stahl_etal_2010NG/

706 • SLE

707 https://www.immunobase.org/downloads/protected_data/GWAS_Data/hg19_gwas_sle_be
708 ntham_4_20_0.tab.gz

709 • T1D

710 https://www.immunobase.org/downloads/protected_data/iChip_Data/hg19_gwas_ic_t1d_o

711 nengut_meta_4_19_1.tab.gz

712 Acknowledgements

713 We thank all study participants, and all research staff at the numerous study sites that
714 made this research possible. Computations were performed on the Genetic Cluster Computer
715 (GCC) hosted by SURFsara (www.surfsara.nl). We thank ImmunoBase for curating genetic risk
716 factors for the immune diseases investigated. We thank the Canadian-US PBC Consortium, the
717 Italian PBC Genetics Study Group and the UK-PBC Consortium for sharing their summary data
718 for the PBC GWAS. We thank the International Inflammatory Bowel Disease Genetics
719 Consortium (IIBDGC) for providing publicly available genome-wide summary statistics for CRO,
720 UC, and IBD. We also thank the International Multiple Sclerosis Genetics Consortium (IMSGC)
721 and the investigators leading the GWASs for CEL, JIA, RA, SLE, and T1D for providing
722 genome-wide summary statistics from their studies on ImmunoBase.

723 This research was supported in part by a number of funding sources. This research uses
724 resources provided by the Genetic Association Information Network (GAIN), obtained from the
725 database of Genotypes and Phenotypes (dbGaP) found at <http://www.ncbi.nlm.nih.gov/gap>
726 through dbGaP accession number phs000021.v3.p2; samples and associated phenotype data
727 for this study were provided by the Molecular Genetics of Schizophrenia Collaboration (PI:
728 Pablo V. Gejman, Evanston Northwestern Healthcare (ENH) and Northwestern University,
729 Evanston, IL, USA). JG Pouget is supported by Fulbright Canada, the Weston Foundation, and
730 Brain Canada through the Canada Brain Research Fund - a public-private partnership
731 established by the Government of Canada. B Han is supported by the National Research
732 Foundation of Korea (NRF) (grant 2016R1C1B2013126) and the Bio & Medical Technology
733 Development Program of the NRF (grant 2017M3A9B6061852) funded by the Korean
734 government, Ministry of Science and ICT (MSIT). HM Ollila is supported by the Finnish Cultural
735 Foundation and Academy of Finland (grant 309643). J Martin is supported by grants SAF2015-
736 66761-P from the Spanish Ministry of Economy and Competitiveness and P12-BIO-1395 from

737 from Consejería de Innovación, Ciencia y Tecnología, Junta de Andalucía (Spain). Y Jin, SA
738 Santorico, and R Spritz are supported by the U.S. National Institutes of Health (NIH) grants
739 R01AR045584, R01AR056292, X01HG007484, and P30AR057212 and by institutional
740 research funding IUT20-46 from the Estonian Ministry of Education and Research. MD Mayes is
741 supported by the U.S. NIH grants N01AR02251 and R01AR05528. S Raychaudhuri is
742 supported by the U.S. NIH grants 1R01AR063759, 1R01AR062886, 1UH2AR067677-01, and
743 U19AI111224-01 and Doris Duke Charitable Foundation grant 2013097. J Knight is the Joanne
744 Murphy Professor in Behavioural Science. Funding for the GAIN schizophrenia sample was
745 provided by the U.S. NIH grants R01 MH67257, R01 MH59588, R01 MH59571, R01 MH59565,
746 R01 MH59587, R01 MH60870, R01 MH59566, R01 MH59586, R01 MH61675, R01 MH60879,
747 R01 MH81800, U01 MH46276, U01 MH46289 U01 MH46318, U01 MH79469, and U01
748 MH79470 and the genotyping of samples was provided through GAIN. The funding sources did
749 not influence the study design, data analysis, or writing of this manuscript.

750 References

- 751 1. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights
752 from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-7.
- 753 2. Chan MK, Krebs MO, Cox D, Guest PC, Yolken RH, Rahmoune H, et al. Development of a
754 blood-based molecular biomarker test for identification of schizophrenia before disease
755 onset. *Transl Psychiatry*. 2015;5:e601.
- 756 3. Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB.
757 Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year
758 population-based register study. *Am J Psychiatry*. 2011;168(12):1303-10.
- 759 4. Chen SJ, Chao YL, Chen CY, Chang CM, Wu EC, Wu CS, et al. Prevalence of
760 autoimmune diseases in in-patients with schizophrenia: nationwide population-based
761 study. *Br J Psychiatry*. 2012;200(5):374-80.
- 762 5. Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB. A
763 nationwide study on the risk of autoimmune diseases in individuals with a personal or a
764 family history of schizophrenia and related psychosis. *Am J Psychiatry*. 2014;171(2):218-
765 26.
- 766 6. Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, et al. Association of
767 schizophrenia and autoimmune diseases: linkage of Danish national registers. *Am J
768 Psychiatry*. 2006;163(3):521-8.
- 769 7. Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar
770 disorder, and non-affective psychosis. *Bipolar Disord*. 2010;12(6):638-46.
- 771 8. Euesden J, Breen G, Farmer A, McGuffin P, Lewis CM. The relationship between
772 schizophrenia and rheumatoid arthritis revisited: genetic and epidemiological analyses.
773 *Am J Med Genet B Neuropsychiatr Genet*. 2015;168B(2):81-8.
- 774 9. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia
775 risk from complex variation of complement component 4. *Nature*. 2016;530(7589):177-83.
- 776 10. Yih Chen J, Ling Wu Y, Yin Mok M, Jan Wu YJ, Lintner KE, Wang CM, et al. Effects of
777 complement C4 gene copy number variations, size dichotomy, and C4A deficiency on
778 genetic risk and clinical presentation of systemic lupus erythematosus in East Asian
779 populations. *Arthritis Rheumatol*. 2016;68(6):1442-53.
- 780 11. Pouget JG, Goncalves VF, Spain SL, Finucane HK, Raychaudhuri S, Kennedy JL, et al.
781 Genome-wide association studies suggest limited immune gene enrichment in
782 schizophrenia compared to 5 autoimmune diseases. *Schizophr Bull*. 2016;42(5):1176-84.
- 783 12. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci
784 with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet*.
785 2013;381:1371-9.
- 786 13. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship
787 between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*.
788 2013;45(9):984-94.
- 789 14. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al.
790 Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation
791 study. *Lancet*. 2012;380(9841):572-80.
- 792 15. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, et al. Common variants
793 associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet*.
794 2013;45(11):1345-52.
- 795 16. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al. An atlas of
796 genetic correlations across human diseases and traits. *Nat Genet*. 2015;47(11):1236-41.

797 17. Ellinghaus D, Jostins L, Spain SL, Cortes A, Bethune J, Han B, et al. Analysis of five
798 chronic inflammatory diseases identifies 27 new associations and highlights disease-
799 specific patterns at shared loci. *Nat Genet.* 2016;48(5):510-8.

800 18. Brainstorm Consortium, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, et al.
801 Analysis of shared heritability in common disorders of the brain. *Science.* 2018;360(6395)

802 19. Chesmore K, Bartlett J, Williams SM. The ubiquity of pleiotropy in human disease. *Hum
803 Genet.* 2018;137(1):39-44.

804 20. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in
805 causal relationships inferred from Mendelian randomization between complex traits and
806 diseases. *Nat Genet.* 2018;50(5):693-8.

807 21. Jordan DM, Verbanck M, Do R. The landscape of pervasive horizontal pleiotropy in human
808 genetic variation is driven by extreme polygenicity of human traits and diseases. *bioRxiv.*
809 2018;doi: <https://doi.org/10.1101/416545>

810 22. Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C, et al. Shared
811 molecular neuropathology across major psychiatric disorders parallels polygenic overlap.
812 *Science.* 2018;359(6376):693-7.

813 23. Stringer S, Kahn RS, de Witte LD, Ophoff RA, Derkx EM. Genetic liability for
814 schizophrenia predicts risk of immune disorders. *Schizophr Res.* 2014;159:347-52.

815 24. Wang Q, Yang C, Gelernter J, Zhao H. Pervasive pleiotropy between psychiatric disorders
816 and immune disorders revealed by integrative analysis of multiple GWAS. *Hum Genet.*
817 2015;134(11-12):1195-209.

818 25. Tylee DS, Sun J, Hess JL, Tahir MA, Sharma E, Malik R, et al. Genetic correlations
819 among psychiatric and immune-related phenotypes based on genome-wide association
820 data. *Am J Med Genet B Neuropsychiatr Genet.* 2018;177(7):641-57.

821 26. Duncan LE, Shen H, Ballon JS, Hardy KV, Noordsy DL, Levinson DF. Genetic correlation
822 profile of schizophrenia mirrors epidemiological results and suggests link between
823 polygenic and rare variant (22q11.2) cases of schizophrenia. *Schizophr Bull.*
824 2018;44(6):1350-61.

825 27. Pickrell JK, Berisa T, Liu JZ, Segurel L, Tung JY, Hinds DA. Detection and interpretation of
826 shared genetic influences on 42 human traits. *Nat Genet.* 2016;48(7):709-17.

827 28. Andreassen OA, Harbo HF, Wang Y, Thompson WK, Schork AJ, Mattingdal M, et al.
828 Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder:
829 differential involvement of immune-related gene loci. *Mol Psychiatry.* 2015;20:207-14.

830 29. Yin X, Wineinger NE, Wang K, Yue W, Norgren N, Wang L, et al. Common susceptibility
831 variants are shared between schizophrenia and psoriasis in the Han Chinese population. *J
832 Psychiatry Neurosci.* 2016;41(6):413-21.

833 30. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al.
834 Common polygenic variation contributes to risk of schizophrenia and bipolar disorder.
835 *Nature.* 2009;460(7256):748-52.

836 31. Lee SH, Byrne EM, Hultman CM, Kahler A, Vinkhuyzen AA, Ripke S, et al. New data and
837 an old puzzle: the negative association between schizophrenia and rheumatoid arthritis.
838 *Int J Epidemiol.* 2015;44(5):1706-21.

839 32. Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk to disease from
840 genome-wide association studies. *Genome Res.* 2007;17(10):1520-8.

841 33. Fernando MM, Stevens CR, Walsh EC, De Jager PL, Goyette P, Plenge RM, et al.
842 Defining the role of the MHC in autoimmunity: a review and pooled analysis. *PLoS Genet.*
843 2008;4:e1000024.

844 34. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al.
845 Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease
846 susceptibility loci. *Nat Genet.* 2010;42(12):1118-25.

847 35. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe
848 interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*.
849 2012;491(7422):119-24.

850 36. Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kemppinen A, Cotsapas C, et al.
851 Analysis of immune-related loci identifies 48 new susceptibility variants for multiple
852 sclerosis. *Nat Genet*. 2013;45(11):1353-60.

853 37. Dubois PC, Trynka G, Franke L, Hunt KA, Romanos J, Curtotti A, et al. Multiple common
854 variants for celiac disease influencing immune gene expression. *Nat Genet*.
855 2010;42(4):295-302.

856 38. Yang J, Ferreira T, Morris AP, Medland SE, Genetic IOANTGIANTC, DIAbetes GRAM-
857 aDIAGRAMC, et al. Conditional and joint multiple-SNP analysis of GWAS summary
858 statistics identifies additional variants influencing complex traits. *Nat Genet*.
859 2012;44(4):369-75, S1.

860 39. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, et al. Integration of summary
861 data from GWAS and eQTL studies predicts complex trait gene targets. *Nat Genet*.
862 2016;48(5):481-7.

863 40. Wu Y, Zeng J, Zhang F, Zhu Z, Qi T, Zheng Z, et al. Integrative analysis of omics
864 summary data reveals putative mechanisms underlying complex traits. *Nat Commun*.
865 2018;9(1):918.

866 41. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang
867 HM, et al. A global reference for human genetic variation. *Nature*. 2015;526(7571):68-74.

868 42. Stahl EA, Wegmann D, Trynka G, Gutierrez-Achury J, Do R, Voight BF, et al. Bayesian
869 inference analyses of the polygenic architecture of rheumatoid arthritis. *Nat Genet*.
870 2012;44(5):483-9.

871 43. Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, et al. Defining the role of
872 common variation in the genomic and biological architecture of adult human height. *Nat
873 Genet*. 2014;46(11):1173-86.

874 44. Lee SH, Goddard ME, Wray NR, Visscher PM. A better coefficient of determination for
875 genetic profile analysis. *Genet Epidemiol*. 2012;36(3):214-24.

876 45. Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh PR, et al. Partitioning
877 heritability by functional annotation using genome-wide association summary statistics.
878 *Nat Genet*. 2015;47(11):1228-35.

879 46. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from
880 a pathological perspective. *Am J Pathol*. 2008;173(3):600-9.

881 47. Jones PA. Functions of DNA methylation: islands, start sites, gene bodies and beyond.
882 *Nat Rev Genet*. 2012;13(7):484-92.

883 48. Bell AC, Felsenfeld G. Methylation of a CTCF-dependent boundary controls imprinted
884 expression of the Igf2 gene. *Nature*. 2000;405(6785):482-5.

885 49. Eden S, Constancia M, Hashimshony T, Dean W, Goldstein B, Johnson AC, et al. An
886 upstream repressor element plays a role in Igf2 imprinting. *EMBO J*. 2001;20(13):3518-25.

887 50. Davis S, Gale NW, Aldrich TH, Maisonpierre PC, Lhotak V, Pawson T, et al. Ligands for
888 EPH-related receptor tyrosine kinases that require membrane attachment or clustering for
889 activity. *Science*. 1994;266(5186):816-9.

890 51. Hruska M, Dalva MB. Ephrin regulation of synapse formation, function and plasticity. *Mol
891 Cell Neurosci*. 2012;50(1):35-44.

892 52. Dustin ML. Signaling at neuro/immune synapses. *J Clin Invest*. 2012;122(4):1149-55.

893 53. Basu R, Huse M. Mechanical communication at the immunological synapse. *Trends Cell
894 Biol*. 2017;27(4):241-54.

895 54. Sharfe N, Freywald A, Toro A, Dadi H, Roifman C. Ephrin stimulation modulates T cell
896 chemotaxis. *Eur J Immunol*. 2002;32(12):3745-55.

897 55. Lu Q, Sun EE, Klein RS, Flanagan JG. Ephrin-B reverse signaling is mediated by a novel
898 PDZ-RGS protein and selectively inhibits G protein-coupled chemoattraction. *Cell*.
899 2001;105(1):69-79.

900 56. U.S. Food and Drug Administration, Centre for Drug Evaluation and Research. Sprycel
901 (dasatinib) NDA 21986/22072 approval letter, 2006 June 28. Retrieved 2018 November 4,
902 from
903 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021986s000_Sprycel_APPR_OV.pdf.

904 57. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016
905 March 23. Identifier: NCT02717156, Combination therapy with Pembrolizumab and
906 sEphB4-HSA in previously treated urothelial carcinoma. Available from:
907 <https://clinicaltrials.gov/ct2/show/NCT02717156>.

908 58. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 June
909 15. Identifier NCT02799485, EphB4-HSA in treating patients with Kaposi sarcoma.
910 Available from: <https://clinicaltrials.gov/ct2/show/NCT02799485>.

911 59. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 May
912 10. Identifier NCT03146871, Recombinant EphB4-HSA fusion protein and Azacitidine or
913 Decitabine in treating patients with relapsed or refractory myelodysplastic syndrome,
914 chronic myelomonocytic leukemia, or acute myeloid leukemia previously treated with a
915 hypomethylating agent. Available from: <https://clinicaltrials.gov/ct2/show/NCT03146871>.

916 60. ClinicalTrials.gov [Internet] C. Bethesda (MD): National Library of Medicine (US). 2017
917 February 10. Identifier: NCT03049618, Recombinant EphB4-HSA fusion protein and
918 Pembrolizumab in treating patients with locally advanced or metastatic non-small cell lung
919 cancer or locally recurrent or metastatic head and neck squamous cell cancer. Available
920 from: <https://clinicaltrials.gov/ct2/show/NCT03049618>.

921 61. Canellas F, Lin L, Julia MR, Clemente A, Vives-Bauza C, Ollila HM, et al. Dual cases of
922 type 1 narcolepsy with schizophrenia and other psychotic disorders. *J Clin Sleep Med*.
923 2014;10(9):1011-8.

924 62. Arad M, Weiner I. Disruption of latent inhibition induced by ovariectomy can be reversed
925 by estradiol and clozapine as well as by co-administration of haloperidol with estradiol but
926 not by haloperidol alone. *Psychopharmacology (Berl)*. 2009;206(4):731-40.

927 63. Zhu ML, Bakhru P, Conley B, Nelson JS, Free M, Martin A, et al. Sex bias in CNS
928 autoimmune disease mediated by androgen control of autoimmune regulator. *Nat
929 Commun*. 2016;7:11350.

930 64. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, et al.
931 Sex differences in the gut microbiome drive hormone-dependent regulation of
932 autoimmunity. *Science*. 2013;339(6123):1084-8.

933 65. Zammit S, Rasmussen F, Farahmand B, Gunnell D, Lewis G, Tynelius P, et al. Height and
934 body mass index in young adulthood and risk of schizophrenia: a longitudinal study of 1
935 347 520 Swedish men. *Acta Psychiatr Scand*. 2007;116(5):378-85.

936 66. Takayanagi Y, Petersen L, Laursen TM, Cascella NG, Sawa A, Mortensen PB, et al. Risk
937 of schizophrenia spectrum and affective disorders associated with small for gestational
938 age birth and height in adulthood. *Schizophr Res*. 2014;160(1-3):230-2.

939 67. Boyle EA, Li YI, Pritchard JK. An expanded view of complex traits: from polygenic to
940 omnigenic. *Cell*. 2017;169(7):1177-86.

941 68. Trynka G, Hunt KA, Bockett NA, Romanos J, Mistry V, Szperl A, et al. Dense genotyping
942 identifies and localizes multiple common and rare variant association signals in celiac
943 disease. *Nat Genet*. 2011;43(12):1193-201.

944 69. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, et al. Association
945 analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared
946 genetic risk across populations. *Nat Genet*. 2015;47(9):979-86.

947

948 70. Hinks A, Cobb J, Marion MC, Prahalad S, Sudman M, Bowes J, et al. Dense genotyping of
949 immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic
950 arthritis. *Nat Genet.* 2013;45(6):664-9.

951 71. Faraco J, Lin L, Kornum BR, Kenny EE, Trynka G, Einen M, et al. ImmunoChip study
952 implicates antigen presentation to T cells in narcolepsy. *PLoS Genet.* 2013;9(2):e1003270.

953 72. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eye S, Thomson BP, et al. Genome-
954 wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci.
955 *Nat Genet.* 2010;42(6):508-14.

956 73. Bentham J, Morris DL, Cunningham Graham DS, Pinder CL, Tombleson P, Behrens TW,
957 et al. Genetic association analyses implicate aberrant regulation of innate and adaptive
958 immunity genes in the pathogenesis of systemic lupus erythematosus. *Nat Genet.*
959 2015;47(12):1457-64.

960 74. Onengut-Gumuscu S, Chen WM, Burren O, Cooper NJ, Quinlan AR, Mychaleckyj JC, et
961 al. Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of
962 causal variants with lymphoid gene enhancers. *Nat Genet.* 2015;47(4):381-6.

963 75. Cordell HJ, Han Y, Mellis GF, Li Y, Hirschfield GM, Greene CS, et al. International
964 genome-wide meta-analysis identifies new primary biliary cirrhosis risk loci and targetable
965 pathogenic pathways. *Nat Commun.* 2015;6:8019.

966 76. Strange A, Capon F, Spencer CC, Knight J, Weale ME, Allen MH, et al. A genome-wide
967 association study identifies new psoriasis susceptibility loci and an interaction between
968 HLA-C and ERAP1. *Nat Genet.* 2010;42(11):985-90.

969 77. Radstake TR, Gorlova O, Rueda B, Martin JE, Alizadeh BZ, Palomino-Morales R, et al.
970 Genome-wide association study of systemic sclerosis identifies CD247 as a new
971 susceptibility locus. *Nat Genet.* 2010;42(5):426-9.

972 78. Jin Y, Andersen G, Yorgov D, Ferrara TM, Ben S, Brownson KM, et al. Genome-wide
973 association studies of autoimmune vitiligo identify 23 new risk loci and highlight key
974 pathways and regulatory variants. *Nat Genet.* 2016;48(11):1418-24.

975 79. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait
976 analysis. *Am J Hum Genet.* 2011;88(1):76-82.

977 80. Powell JE, Henders AK, McRae AF, Caracella A, Smith S, Wright MJ, et al. The Brisbane
978 Systems Genetics Study: genetical genomics meets complex trait genetics. *PLoS One.*
979 2012;7(4):e35430.

980 81. Chen BH, Marioni RE, Colicino E, Peters MJ, Ward-Caviness CK, Tsai PC, et al. DNA
981 methylation-based measures of biological age: meta-analysis predicting time to death.
982 *Aging (Albany NY).* 2016;8(9):1844-65.

983 82. Lloyd-Jones LR, Holloway A, McRae A, Yang J, Small K, Zhao J, et al. The genetic
984 architecture of gene expression in peripheral blood. *Am J Hum Genet.* 2017;100(2):371.

985 83. R Core Team. R: A language and environment for statistical computing. R Foundation for
986 Statistical Computing. 2012;Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org/>.

986 84. Nakazawa M. fmsb: Functions for medical statistics book with some demographic data. R
987 package version 051. 2014 <http://CRAN.R-project.org/package=fmsb>.

988 85. Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide
989 association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4.
990 *Nat Genet.* 2011;43(10):977-83.

991 86. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N, et al. LD Score
992 regression distinguishes confounding from polygenicity in genome-wide association
993 studies. *Nat Genet.* 2015;47(3):291-5.

994 87. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, et al. An
995 integrated map of genetic variation from 1,092 human genomes. *Nature.*
996 2012;491(7422):56-65.

997

998

999 88. International HapMap 3 Consortium, Altshuler DM, Gibbs RA, Peltonen L, Altshuler DM,
1000 Gibbs RA, et al. Integrating common and rare genetic variation in diverse human
1001 populations. *Nature*. 2010;467(7311):52-8.

1002 89. Purcell S, Cherny SS, Sham PC. Genetic Power Calculator: design of linkage and
1003 association genetic mapping studies of complex traits. *Bioinformatics*. 2003;19(1):149-50.

1004 90. Palla L, Dudbridge F. A fast method that uses polygenic scores to estimate the variance
1005 explained by genome-wide marker panels and the proportion of variants affecting a trait.
1006 *Am J Hum Genet*. 2015;97(2):250-9.

1007 91. Dudbridge F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet*.
1008 2013;9(3):e1003348.

1009 92. Betz RC, Petukhova L, Ripke S, Huang H, Menelaou A, Redler S, et al. Genome-wide
1010 meta-analysis in alopecia areata resolves HLA associations and reveals two new
1011 susceptibility loci. *Nat Commun*. 2015;6:5966.

1012 93. Cortes A, Hadler J, Pointon JP, Robinson PC, Karaderi T, Leo P, et al. Identification of
1013 multiple risk variants for ankylosing spondylitis through high-density genotyping of
1014 immune-related loci. *Nat Genet*. 2013;45(7):730-8.

1015 94. Chu X, Pan CM, Zhao SX, Liang J, Gao GQ, Zhang XM, et al. A genome-wide association
1016 study identifies two new risk loci for Graves' disease. *Nat Genet*. 2011;43(9):897-901.

1017 95. Gutierrez-Achury J, Zhernakova A, Pilit SL, Trynka G, Hunt KA, Romanos J, et al. Fine
1018 mapping in the MHC region accounts for 18% additional genetic risk for celiac disease.
1019 *Nat Genet*. 2015;47(6):577-8.

1020 96. Goyette P, Boucher G, Mallon D, Ellinghaus E, Jostins L, Huang H, et al. High-density
1021 mapping of the MHC identifies a shared role for HLA-DRB1*01:03 in inflammatory bowel
1022 diseases and heterozygous advantage in ulcerative colitis. *Nat Genet*. 2015;47(2):172-9.

1023 97. Patsopoulos NA, Barcellos LF, Hintzen RQ, Schaefer C, van Duijn CM, Noble JA, et al.
1024 Fine-mapping the genetic association of the major histocompatibility complex in multiple
1025 sclerosis: HLA and non-HLA effects. *PLoS Genet*. 2013;9(11):e1003926.

1026 98. Tafti M, Hor H, Dauvilliers Y, Lammers GJ, Overeem S, Mayer G, et al. DQB1 locus alone
1027 explains most of the risk and protection in narcolepsy with cataplexy in Europe. *Sleep*.
1028 2014;37(1):19-25.

1029 99. Liu JZ, Almarri MA, Gaffney DJ, Mells GF, Jostins L, Cordell HJ, et al. Dense fine-mapping
1030 study identifies new susceptibility loci for primary biliary cirrhosis. *Nat Genet*.
1031 2012;44(10):1137-41.

1032 100. Liu JZ, Hov JR, Folseraas T, Ellinghaus E, Rushbrook SM, Doncheva NT, et al. Dense
1033 genotyping of immune-related disease regions identifies nine new risk loci for primary
1034 sclerosing cholangitis. *Nat Genet*. 2013;45(6):670-5.

1035 101. Okada Y, Han B, Tsoi LC, Stuart PE, Ellinghaus E, Tejasvi T, et al. Fine mapping major
1036 histocompatibility complex associations in psoriasis and its clinical subtypes. *Am J Hum
1037 Genet*. 2014;95(2):162-72.

1038 102. Raychaudhuri S, Sandor C, Stahl EA, Freudenberg J, Lee HS, Jia X, et al. Five amino
1039 acids in three HLA proteins explain most of the association between MHC and
1040 seropositive rheumatoid arthritis. *Nat Genet*. 2012;44(3):291-6.

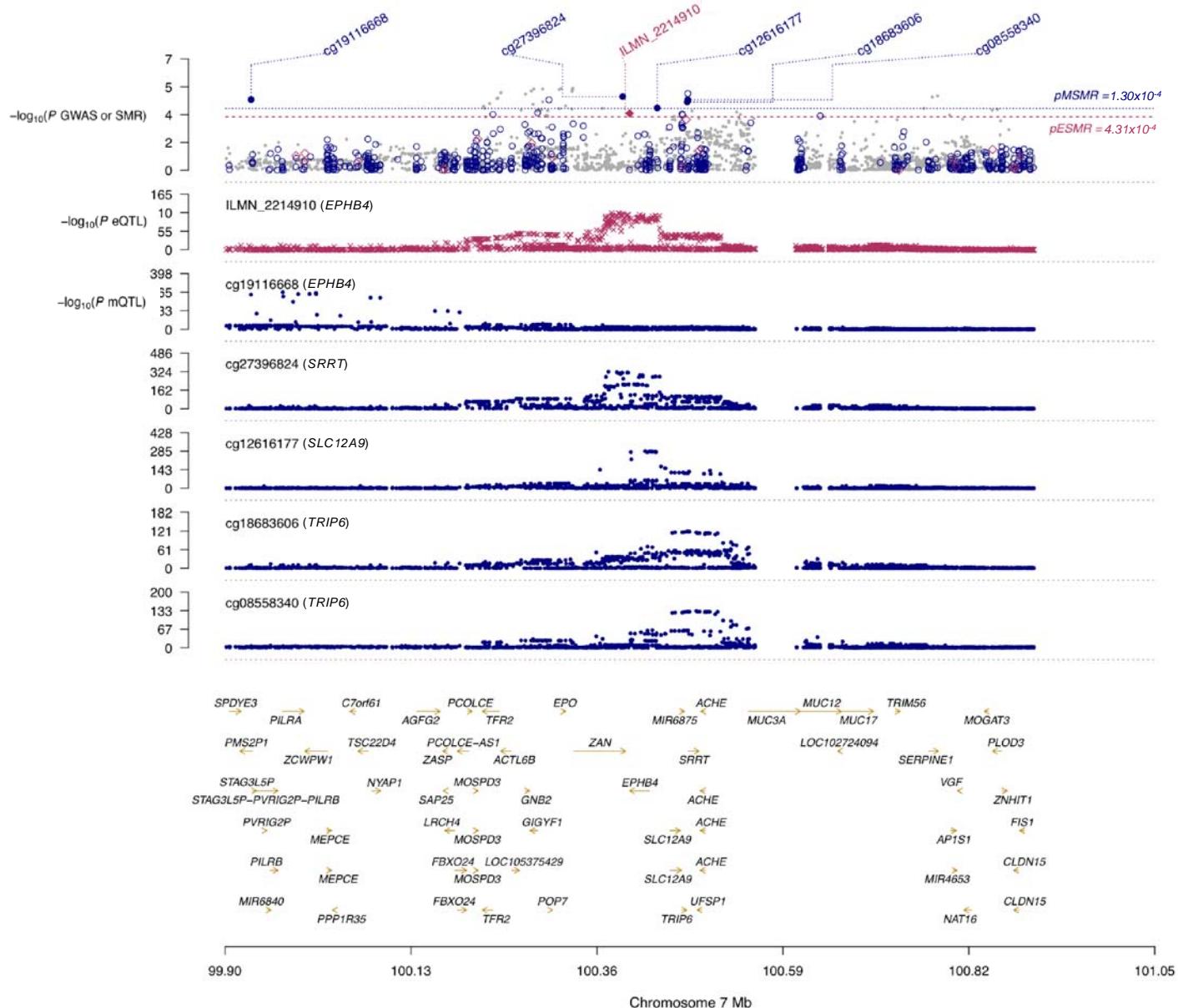
1041 103. Lessard CJ, Li H, Adrianto I, Ice JA, Rasmussen A, Grundahl KM, et al. Variants at
1042 multiple loci implicated in both innate and adaptive immune responses are associated with
1043 Sjogren's syndrome. *Nat Genet*. 2013;45(11):1284-92.

1044 104. Kim K, Bang SY, Lee HS, Okada Y, Han B, Saw WY, et al. The HLA-DRbeta1 amino acid
1045 positions 11-13-26 explain the majority of SLE-MHC associations. *Nat Commun*.
1046 2014;5:5902.

1047 105. Mayes MD, Bossini-Castillo L, Gorlova O, Martin JE, Zhou X, Chen WV, et al. Immunochip
1048 analysis identifies multiple susceptibility loci for systemic sclerosis. *Am J Hum Genet*.
1049 2014;94(1):47-61.

1050 106. Hu X, Deutsch AJ, Lenz TL, Onengut-Gumuscu S, Han B, Chen WM, et al. Additive and
1051 interaction effects at three amino acid positions in HLA-DQ and HLA-DR molecules drive
1052 type 1 diabetes risk. *Nat Genet.* 2015;47(8):898-905.
1053

1054 **Figure Legends**



1055 **Fig 1. Prioritizing genes driving the pleiotropic association of rs1734907 in**

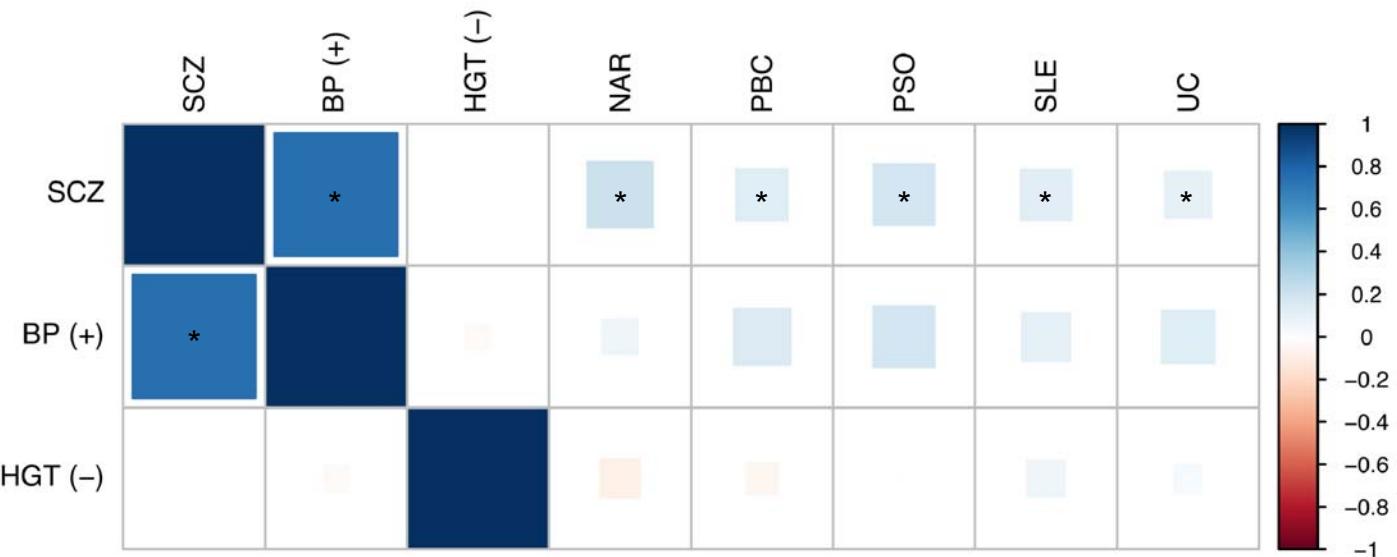
1056 **Crohn's disease and schizophrenia**

1057 Associations for SNP and SMR analyses across GWAS, eQTL, and mQTL datasets. Top plot

1058 gray circles illustrate SNP association ($-\log_{10}$ p-value) with schizophrenia in the PGC-2 GWAS,

1059 while pink diamonds and blue circles indicate results of SMR tests ($-\log_{10}$ p-value) for

1060 association of gene expression and DNA methylation with schizophrenia, respectively, with solid shading
1061 indicating probes passing the HEIDI test. Middle plot illustrates SNP association ($-\log_{10}$ p-value)
1062 with gene expression from peripheral blood eQTL dataset. Lower plots illustrate SNP
1063 association ($-\log_{10}$ p-value) with gene methylation from peripheral blood mQTL dataset.



1064 **Fig 2. Genetic correlation between schizophrenia and other traits**

1065 Genetic correlation between schizophrenia, bipolar disorder, height, and 14 immune diseases
1066 was estimated using cross-trait LDSC [16]. Colour of square indicates strength of genetic
1067 correlation (red, negative correlation; blue, positive correlation). Size of square indicates
1068 statistical significance (larger, more significant p -value). Asterisks indicate genetic correlations
1069 that are statistically significant at $p < 0.05$ threshold. BP, bipolar disorder; CEL, celiac disease;
1070 CRO, Crohn's disease; HGT, height; IBD, inflammatory bowel disease; JIA, juvenile idiopathic
1071 arthritis; MS, multiple sclerosis; NAR, narcolepsy; PBC, primary biliary cirrhosis; PSO, psoriasis,
1072 RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSC, systemic sclerosis; T1D,
1073 type 1 diabetes; UC, ulcerative colitis; VIT, vitiligo.

1074 **Tables**

1075 **Table 1. Description of datasets analyzed**

								Total number of SNPs
	Abr	Genome-wide significant SNPs ^a	Polygenic risk scoring ^b	Cases	Controls	Full GWAS	Merged with SCZ ^c	Pruned ^d
Schizophrenia	SCZ	-	Target [1]	35,476	46,839	-	-	-
Height	HGT	-	Negative control [43]	253,288	-	2,085,602	2,035,446	124,888
Alopecia areata	AA	11	-	-	-	-	-	-
Ankylosing spondylitis	AS	23	-	-	-	-	-	-
Autoimmune thyroid disease	ATD	7	-	-	-	-	-	-
Celiac disease	CEL	38	Training [68]	12,041	12,228	133,352 ^f	90,922	19,698
Crohn's disease	CRO	119	Training [69]	5,956	14,927	12,276,506	4,990,991	114,950
Inflammatory bowel disease	IBD	145	Training [69]	12,882	21,770	12,716,150	5,095,448	116,346
Juvenile idiopathic arthritis	JIA	22	Training [70]	772 ^e	8,530 ^e	122,330 ^f	98,477	20,337
Multiple sclerosis	MS	103	Training [36]	14,498	24,091	155,756 ^f	108,118	21,818
Narcolepsy	NAR	3	Training [71]	1,886	10,421	109,768 ^f	92,859	19,866
Primary biliary cirrhosis	PBC	19	Training [75]	2,764	10,475	1,038,537	1,041,977	97,806
Primary sclerosing cholangitis	PSC	12	-	-	-	-	-	-
Psoriasis	PSO	34	Training [76]	2,178	5,175	7,586,779	3,701,354	107,002
Rheumatoid arthritis	RA	77	Training [72]	5,539	20,169	2,090,825	2,087,383	126,049
Sjögren's syndrome	SJO	6	-	-	-	-	-	-
Systemic lupus erythematosus	SLE	19	Training [73]	4,036	6,959	7,915,251	6,539,217	264,374
Systemic sclerosis	SSC	4	Training [77]	1,486 ^g	3,477 ^g	253,179 ^f	251,441	66,402
Type 1 diabetes	T1D	56	Training [74]	9,340 ^h	12,835	123,081 ^f	98,418	20,835
Ulcerative colitis	UC	96	Training [69]	6,968	20,464	12,255,263	5,167,266	120,720
Vitiligo	VIT	16	Training [78]	1,381	14,518	8,790,155	6,223,502	257,654

1076 ^aWe obtained lists of genome-wide significant SNPs for each autoimmune disease from ImmunoBase, and processed them as described in
 1077 **Supplementary Methods**; ^bThe following columns provide details for datasets used in the polygenic risk scoring analysis. We used effect sizes

1078 obtained from the height (negative control) and autoimmune disease GWASs (training datasets) to construct polygenic risk scores in the
1079 schizophrenia sample (target dataset). Because genome-wide summary statistics were required for this analysis, we were unable to perform
1080 polygenic risk scoring for five autoimmune diseases for which these data were not available (AA, AS, ATD, PSC, SJO); ^cPrior to merging the
1081 training dataset SNP set with the target schizophrenia dataset SNP set, the following quality control steps were performed: SNPs on non-
1082 autosomal chromosomes (X, Y, M) were removed, SNPs with MAF<0.01 were removed if MAF was available in the training dataset, SNPs with
1083 INFO<0.90 were removed if INFO was available in the training dataset, SNPs with missing p-value or OR were removed, symmetrical SNPs were
1084 removed; ^dPruning was performed by clumping using PLINK to retain SNPs with $r^2<0.1$ within 1,000 kb windows, while filtering for the highest
1085 significance levels within LD blocks (using options --clump-p1 1 --clump-p2 1 --clump-r2 0.1 --clump-kb 1000); ^eonly the UK cohort from this study
1086 was available for analysis; ^fthis sample was genotyped using a specialty chip (Immunochip); ^gonly the US cohort from this study was available for
1087 analysis; ^hincludes cases from 2,601 affected sibling pairs and 69 trios, which were analyzed using the Generalized Disequilibrium Test (GDT)
1088 method and combined with case-control results by meta-analysis; Abr, abbreviation; -, not analyzed.

1089 **Table 2. Association of top HLA variants for immune diseases in schizophrenia**

Disease	HLA variant	Autoimmune		Schizophrenia		r^2 with top SCZ SNP ^a
		<i>p</i>	OR	<i>p</i>	OR	
AA [92]	HLA-DRB1#37Asn	4.99x10⁻⁷³	0.42	4.85x10⁻⁹	0.91	0.04
AS [93]	HLA-B*27	<1x10 ⁻¹⁰⁰	46	0.13	1.05	0
ATD [94]	rs2281388 (tags HLA-DPB1*05:01)	1.50x10 ⁻⁶⁵	1.64	0.39	1.04 ^b	0
CEL [95]	HLA-DQB1#74Ala	n.r.	2.14	2.16x10⁻¹²	0.89	0.11
CRO [96]	HLA-DRB1*01:03	3.00x10 ⁻⁶²	2.51	0.61	0.96	0
IBD [96]	HLA-DRB1*01:03	1.93x10 ⁻¹¹²	3.01	0.61	0.96	0
JIA [70]	rs7775055	3.14x10 ⁻¹⁷⁴	6.01	0.12	0.94	0
MS [97]	HLA-DRB1*15:01	1.40x10 ⁻²³⁴	2.92	5.10x10 ⁻³	1.06	0
NAR [98]	HLA-DQB1*06:02	1.04x10 ⁻¹²⁰	251	7.30x10 ⁻³	1.06	0
PBC [99]	HLA-DQA1*04:01	5.90x10 ⁻⁴⁵	3.06	0.20	0.95	0
PSC [100]	HLA-B*08:01	3.70x10⁻²⁴⁶	2.82	5.65x10⁻¹⁶	0.84	0.2
PSO [101]	HLA-C*06:02	2.10x10 ⁻²⁰¹	3.26	0.55	0.99	0
RA [102]	HLA-DRB1#11Val	<1x10 ⁻⁵⁸¹	3.80	2.68x10 ⁻⁴	1.07	0
SJO [103]	HLA-DQB1*02:01	1.38x10⁻⁹⁵	3.36	3.84x10⁻¹⁵	0.85	0.11
SLE [104]	HLA-DRB1#13Arg	7.99x10 ⁻¹⁰	1.55 ^c	5.81x10 ⁻⁴	1.07	0
SSC [105]	rs17500468 (TAP2)	5.87x10 ⁻⁶²	2.87	6.76x10 ⁻⁴	1.07	0
T1D [106]	HLA-DQB1#57Ala	<1x10 ⁻¹⁰⁰⁰	5.17	7.80x10 ⁻⁴	0.95	0.06
UC [96]	rs6927022	8.00x10 ⁻¹⁵⁴	1.49	3.37x10 ⁻⁴	1.06	0.03
VIT [78]	rs9271597 (4.7kb upstream of HLA-DQA1)	3.15x10 ⁻⁸⁹	1.77	0.01	1.04	0

1090 ^a r^2 with rs1233578, the top HLA variant in schizophrenia, was obtained from the GAIN schizophrenia cohort (mgs2); ^bEffect size estimate is for
 1091 HLA-DPB1*05:01; ^cEffect size estimate obtained from Asian sample. n.r., not reported; Disease abbreviations as defined in **Table 1**. Bold font
 1092 indicates statistically significant association with schizophrenia.

1093 **Table 3. Immune disease risk SNPs showing pleiotropic effect in schizophrenia**

SNP (chr:bp)	Immune Disease	Risk Allele/ Non-Risk Allele	Immune OR (95% CI); p ^a	Schizophrenia OR (95% CI); p	Nearby Genes	eQTL ^b	mQTL ^c	Genomic associations co-localizing ^d to this gene ^e
rs296547 ^e (chr1:200892137)	CEL [37]	G/A	1.12 (1.09-1.16); 4.11x10 ⁻⁹	1.04 (1.02-1.07); 6.17x10 ⁻⁵	CAMSAP2 C1orf106 KIF21B CACNA1S ASCL5	n.s.	C1orf106, decreased methylation	SCZ-mQTL
rs13126505 (chr4:102865304)	CRO ^f [35]	A/G	1.17 (1.10-1.25); 2.33x10 ⁻¹⁰	1.14 (1.10-1.19); 1.19x10 ⁻⁸	BANK1 SLC39A8 NFKB1	SLC39A8, decreased expression	SLC39A8, increased methylation	SCZ-eQTL, SCZ-mQTL
rs1734907 (chr7:100315517)	CRO ^f [35]	A/G	1.16 (1.11-1.21); 1.67x10 ⁻¹³	1.07 (1.04-1.10); 7.55x10 ⁻⁶	TFR2 ACTL6B GNB2 GIGYF1 POP7 EPO ZAN EPHB4 SLC12A9	EPHB4, decreased expression	EPHB4, increased methylation	SCZ-eQTL, SCZ-mQTL, eQTL-mQTL

1094 ^aEffect sizes and p-values reported based on Immunobase curation, which reports statistics from meta-analysis of discovery and replication
1095 datasets where available; ^beQTL data was obtained from the CAGE study [82] which measured gene expression in peripheral blood. Effect on
1096 expression (increased/decreased) corresponds to the risk allele; ^cmQTL data was obtained from a meta-analysis of the Brisbane Systems
1097 Genetics Study [80] and Lothian Birth Cohorts of 1921 and 1936 [81], which measured DNA methylation in peripheral blood. Effect on expression
1098 (increased/decreased) corresponds to the risk allele; ^dSignificant SMR and HEIDI [39, 40] results indicating co-localization of genomic associations
1099 with the gene of interest in schizophrenia-eQTL (SCZ-eQTL), schizophrenia-mQTL (SCZ-mQTL), and eQTL-mQTL (eQTL-mQTL) datasets; ^eeQTL
1100 data were unavailable for rs296547, and rs404339 was used as a proxy SNP ($r^2=0.85$ in 1000 Genomes Phase 3 CEU Population [41]; ^fAlso
1101 associated with inflammatory bowel disease; n.s., no statistically significant findings; Disease abbreviations as defined in **Table 1**.

1102

Table 4. Estimated phenotypic and genome-wide genetic correlations between schizophrenia and other traits

Trait	$h^2 \pm SE^a$	r_p	PRS			LDSC		
			best p_T	$\beta_{GRS} \pm SE$	$R^2(\%)$	p	$r_g \pm SE$	p
BPD (+) ^b	0.26 ± 0.01		1	n.a.	2.1	<10 ⁻⁵⁰	0.75 ± 0.05	4.02x10 ⁻⁵⁷
HGT (-)	0.34 ± 0.19		1	-0.11 ± 0.02	0.064	1.22x10 ⁻¹¹	7.47x10 ⁻⁵ ± 0.02	0.99
NAR	0.31 ± 0.09	n.a.	1	0.04 ± 0.01	0.017	4.07x10 ⁻⁴	0.213 ± 0.10	0.03
PBC	0.46 ± 0.08	0.11	0.3	0.07 ± 0.01	0.053	8.05x10 ⁻¹⁰	0.131 ± 0.05	4.00x10 ⁻³
PSO	0.27 ± 0.09	0.13	0.3	0.04 ± 0.01	0.025	2.26x10 ⁻⁵	0.182 ± 0.07	7.80x10 ⁻³
SLE	0.15 ± 0.02	0.05	0.5	0.07 ± 0.01	0.047	1.50x10 ⁻⁸	0.127 ± 0.045	4.60x10 ⁻³
UC	0.23 ± 0.03	-0.001	0.4	0.04 ± 0.01	0.018	3.74x10 ⁻⁴	0.106 ± 0.04	4.00x10 ⁻³

1103
1104
1105
1106

R^2 and h^2 are reported on the liability scale for all diseases; ^a h^2 was estimated using LDSC; ^bresults reported are from previously published analyses by the Cross-Disorder Working Group of the Psychiatric Genomics Consortium [12]; (+), positive control; (-), negative control; n.a., not available; SE, standard error; r_g , genetic correlation; r_p , expected phenotypic correlation based on epidemiological data (see **Materials and Methods** for details of r_p estimation).