Title: Genetic correlations among neuro-behavioral and immune-related phenotypes based on genome-wide association data.

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Abstract

Evidence of elevated autoimmune comorbidity and altered immune signaling has been observed in samples of individuals affected by neuropsychiatric disorders. It remains unclear whether these altered immunological states have a genetic basis. The present study sought to use existing summary-level data generated from previous genome-wide association studies (GWASs) in order to explore whether common variant genetic risk factors (*i.e.*, SNPs) are shared between a set of neuro-behavioral phenotypes and a set of immune-inflammatory phenotypes. For each phenotype, we calculated the estimated heritability and examined pair-wise genetic correlations using the LD score regression method. We observed significant positive genetic correlations between bipolar disorder and each of: celiac disease ($rg = 0.31 \pm 0.09$, uncorrected $p = 4.0\text{x}10^{-4}$), Crohn's disease ($rg = 0.21 \pm 0.05$, uncorrected $p = 3.7\text{x}10^{-5}$), and ulcerative colitis ($rg = 0.23 \pm 0.06$, uncorrected $p = 2.0\text{x}10^{-4}$). We observed significant positive correlations between schizophrenia and each of: Crohn's disease ($rg = 0.12 \pm 0.03$, uncorrected $p = 3.0\text{x}10^{-4}$), ulcerative colitis ($rg = 0.13 \pm 0.04$, uncorrected $p = 4.0\text{x}10^{-4}$), primary biliary cirrhosis ($rg = 0.15 \pm 0.05$, uncorrected $p = 0.0012$), and systemic lupus erythematous ($rg = 0.14 \pm 0.04$, uncorrected $p = 0.0013$). We also found significant positive correlations between major depression and hypothyroidism ($rg = 0.33 \pm 0.09$, uncorrected $p = 5\text{x}10^{-4}$) and between Tourette syndrome and allergy ($rg = 0.24 \pm 0.06$, uncorrected $p = 2.7\text{x}10^{-5}$). We highlight genes mapping near the top single nucleotide polymorphisms (SNPs) that may contribute to these behavior-immune correlations. We also observed many significant genetic correlations amongst the immune-inflammatory phenotypes that survived testing for multiple correction. We discuss these results in the context of clinical epidemiologic literature and other genomic approaches and discuss important limitations and caveats of the LD score regression approach we utilized. These results shed new light on the immunogenetics of psychiatric disorders and suggest that similarities in a polygenic diathesis may contribute to increased comorbidity between psychiatric and immune-related disorders.

Keywords: autoimmune disorder, autoimmune thyroiditis, bipolar disorder, celiac disease, genetic correlation, major depression, Tourette syndrome, ulcerative colitis.

Introduction

The biological bases of major psychiatric and neurodevelopmental disorders have been studied for decades, yet they remain largely unresolved for the majority affected by apparently idiopathic disease. Evidence from both clinical and biomedical literature has demonstrated that individuals with these conditions show differences in circulating immunologic markers, functional capacities of isolated immune cells, and atypical prevalence of clinical immune-related phenotypes, compared to individuals not affected by psychiatric or neurodevelopmental disorders (Dowlati et al., 2010; Eaton et al., 2006; Fineberg & Ellman, 2013; Gesundheit et al., 2013; Gibney & Drexhage, 2013; K. A. Jones & Thomsen, 2013; Masi et al., 2015; Modabbernia et al., 2013; Rege & Hodgkinson, 2013). It remains unclear what roles (if any) altered immunologic functions may play in the major psychiatric phenotypes, though plausible mechanisms linking altered immune functions with neurobiological changes during early brain development and in fully developed adults have been identified (Deverman & Patterson, 2009; Felger & Lotrich, 2013; Meyer, 2014; Miller et al., 2013; Oskvig et al., 2012; Sekar et al., 2016; Shatz, 2009; Smith et al., 2007). While some studies have already suggested potential genetic bases for the immune dysregulation observed in a subset of psychiatric patients (Jung, Kohane, & Wall, 2011; Stringer et al., 2014; The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium, 2015; Q. Wang et al., 2015), the extent to which co-occurrence or segregation of clinical phenotypes may be influenced by similarities in genome-wide genetic risk signals warrants further examination. Genome-wide association studies (GWASs) and meta-analyses can shed light on the regions of the genome that tend to associate with a clinical phenotype, quantitative trait, or biomarker; this is accomplished through tagging and association testing of single nucleotide polymorphisms (SNPs) that vary within the population. The recently developed the LD score regression method allows direct comparison of GWAS summary statistics for two different phenotypes, allowing for a quantitative assessment of genetic correlation.

In the present study, we leveraged existing data to examine the genetic associations of a set of medical phenotypes that are enriched with immune and inflammatory processes; these included allergic

conditions, classic autoimmune diseases, and diseases with a known or suspected inflammatory etiopathology. We sought to cross-correlate the genetic associations of these phenotypes with the associations obtained from studies of a set of neuropsychiatric behavioral phenotypes. We anticipated that this approach would shed light on immunogenetic intermediate phenotypes that may contribute to risk for common psychiatric disorders. We hypothesized that some phenotype pairs with evidence for increased clinical comorbidity might also share similarities in their genome-wide association profile, which would be reflected in our analyses as significant positive correlations. Additionally, in light of literature suggesting shared genetic risk among some immune and inflammatory disorders, we sought to assess genetic correlations within this set of phenotypes using the LD score regression method. This latter analysis also provided an important framework for identifying and quantifying shared polygenic diatheses among immune-related disorders.

Materials and Methods

Literature Search

We searched the published literature (Pubmed, SCOPUS), data repositories (dbGaP and immunobase.org), and the downloads page of the Psychiatric Genomics Consortium (PGC) website (https://www.med.unc.edu/pgc/downloads) to identify phenotypes with potentially usable GWAS and GWAS meta-analysis summary statistics. In order to facilitate cross-study comparison, we utilized studies that reported samples of European ancestry, broadly defined to include Central, Southern and Eastern Europe, Scandinavia, and Western Russia. One exception to this was the PGC-II schizophrenia summary data, which reflects a meta-analysis of 46 European cohorts and 3 cohorts of East Asian ancestry (Ripke et al., 2014). When multiple studies were identified for a given phenotype, we first pursued the study with the largest effective sample size. In several instances, data from the largest existing study could not be shared or reflected a mixed-ancestry meta-analysis. In these cases, we deferred to the next largest study. We chose to examine only phenotypes whose datasets contained an effective sample size greater than 5000 individuals, in keeping with a previously recommended minimum

sample size in order to reduce to error (B. Bulik-Sullivan et al., 2015). For studies identified in the published literature, we contacted corresponding authors to request summary statistics. The full list of phenotypes identified in the search and retained for analyses is shown in Supplementary Tables I and II, along with identification of the study cohorts and consortia that generated these data, full citations of the respective publications, and indications of sample size, information regarding genomic inflation, and estimated SNP heritability.

GWAS Phenotypes Obtained and Retained for Genetic Correlation

For our brain- and behavior-related phenotypes, we obtained summary data reflecting studies of Alzheimer's disease (Lambert et al., 2013), angry temperament (Mick et al., 2014), anxiety-spectrum disorders (Otowa et al., 2016), attention deficit-hyperactivity disorder (ADHD; Neale et al., 2010), autism (PGC Autism Working Group, 2016), borderline personality disorder (Lubke et al., 2014), bipolar disorder (PGC Bipolar Disorder Working Group, 2011), epilepsy (partial seizures; Kasperaviciūte et al., 2010), major depression (Ripke et al., 2013), obsessive-compulsive disorder (OCD; personal communication from PGC Working Group), Parkinson's disease (Pickrell et al., 2016), cigarette smoking (ever-smoked status and cigarettes per day; The Tobacco and Genetics Consortium, 2010), schizophrenia (Ripke et al., 2014), and Tourette Syndrome (personal communication from PGC Working Group). Collectively, these phenotypes were treated as a set and are subsequently referred to as the neuro-behavioral phenotypes.

We obtained GWAS data for a variety of phenotypes that are known or suspected to involve alterations to immune cells and/or inflammatory signaling. These included allergy (any, self-reported; Hinds et al., 2013; Pickrell et al., 2016), asthma (self-reported; Pickrell et al., 2016), atopic dermatitis (EAGLE Eczema and Australian Asthma Genetics Consortia 2015), autoimmune hepatitis (De Boer et al., 2014), childhood ear infection (self-reported; Pickrell et al., 2016), celiac disease (Dubois et al., 2010), serum C-reactive protein (CRP; Dehghan et al., 2011), Crohn's disease (Franke et al., 2010), type 1 diabetes (Bradfield et al., 2011), eosinophilic esophagitis (Sleiman et al., 2014), hypothyroidism (self-reported; Pickrell et al., 2016), multiple sclerosis (Sawcer et al., 2012), primary biliary cirrhosis (Cordell

et al., 2015), psoriasis (Tsoi et al., 2015), rheumatoid arthritis (Okada et al., 2014), systemic sclerosis (Radstake et al., 2010), systemic lupus erythematosus (Bentham et al., 2015), susceptibility to pulmonary tuberculosis (Curtis et al., 2015), and ulcerative colitis (Anderson et al., 2011). These phenotypes were treated as a set in subsequent analyses and are referred to collectively as immune-inflammatory phenotypes.

Data Pre-Processing and Analysis

All data pre-processing and analyses were performed using tools supplied within the LD Score Regression software suite (LDSC; https://github.com/bulik/ldsc; B. Bulik-Sullivan et al., 2015; B. K. Bulik-Sullivan et al., 2015). Briefly, this set of tools can be used with existing GWAS summary data in order to distinguish polygenicity from confounding caused by uncontrolled population stratification or cryptic relatedness among samples (B. K. Bulik-Sullivan et al., 2015), to estimate the heritability of a given phenotype (B. Bulik-Sullivan et al., 2015), and to estimate the genetic correlation between two phenotypes based on two separate or related sets of summary statistics (B. Bulik-Sullivan et al., 2015). In the latter application, the minimal requirements for each set of summary statistics include columns of data indicating SNP ID, the identities of reference and non-reference allele, association *p*-value, effect size test statistic (*e.g.*, odds ratio, regression β, or Z-score), and sample size (per SNP or for all SNPs). For each pair of phenotypes, this tool compares the strength and direction of association signal at each locus while correcting for the correlation that would be expected based on genetic linkage alone, and it provides an estimate of the genetic correlation between phenotypes. This method relies on adjustment for the linkage between SNPs (*i.e.*, covariance caused by genomic proximity); for our analyses, we used the set of LD scores provided by the software's creators, based on the 1000 Genomes Project's European sample (file = eur_w_ld_chr, URL = https://data.broadinstitute.org/alkesgroup/LDSCORE). Because minor allele frequencies and imputation quality scores were not available for all the obtained sets of GWAS results, we filtered the GWAS results to retain only SNPs that were included within the HapMap3 panel and had a minor allele frequency $\geq$ 5 % within the 1000 Genomes Project Phase 3 European samples (B. Bulik-Sullivan et al., 2015);); this ensured equitable treatment of all data-sets. Additional SNP quality control

(QC) routines followed those implemented by the GWAS authors and the defaults employed with the LDSC *munge_sumstats.py* function; this function checks alleles to ensure that the supplied alleles match those in the HapMap3 reference panel. For each dataset, we estimated the phenotype's heritability using the *ldsc.py* function. The results of this analysis, along with features of each GWAS dataset (sample size, number of QC-positive SNPs, genomic inflation factor, *etc.*), are shown in Supplementary Tables I and II. All phenotypes with estimated heritability greater than the error of the estimate were retained for correlational analysis (indicated in Supplementary Tables I and II).

Pair-wise genetic correlations were assessed between all retained phenotypes based on the intersection of QC-positive SNPs, and heatmaps were constructed to depict these relationships. For correlation coefficients returned within the bounds of the LDSC software, *p*-values were corrected using the Benjamini-Hochberg (BH) method for the total number of unique tests depicted in each correlation matrix. Within the main text, we describe only correlations that survived family-wise multiple test correction. Correlations are reported as the coefficient $\pm$ standard error, with the SNP-based heritabilities for these phenotypes shown in Table I.

The extended major histocompatibility complex (MHC) region contains high amounts of long-range LD, making it challenging to accurately map association signals in this region. For this reason, and following the work of others (B. Bulik-Sullivan et al., 2015; Zheng et al., 2016), we repeated our analyses under conditions that excluded and included this region (chromosome 6, base positions $25x10^6$ to $35x10^6$). In the main text and figures, we report genetic correlations observed under conditions of MHC exclusion, though most of these correlations remained unchanged with MHC inclusion (reported in full detail in Supplementary Figures 1 and 2 and Supplementary Tables III and IV). Estimated heritability and features of each GWAS dataset under MHC inclusion are shown in Supplementary Table II.

Characterization of Psychiatric-Immunologic Pleiotropic Tag SNPs

For select behavior-immune phenotype pairs showing significant genetic correlations after BH correction for multiple testing, we examined the SNPs with the potential to contribute to the genetic correlation (attaining association *p*-values < 0.005 for both phenotypes, MHC excluded). For positive

genetic correlations, we identified shared SNPs with matched direction of effect and ranked the lists of SNPs based on average effect size across the two phenotypes, and then reported the top 10 LD-independent signals ($r^2 < 0.2$ in 1000 Genomes Phase 3 European sample). We further identified nearby genes for each SNP (within 100 kb) and report SNP positions based on the GRCh37 human genome build.

Results

Correlations between Neuro-Behavioral and Immune-Inflammatory Phenotypes

We first examined relationships between the set of neuro-behavioral phenotypes and the set of immune-inflammatory phenotypes. The GWAS signals for angry temperament did not show significant correlations with any of the immune and inflammatory phenotypes investigated, so they were omitted from the following set of analyses. Pair-wise genetic correlations between neuro-behavioral and immune-inflammatory phenotypes are shown in Figure 1 and detailed results are provided in Supplementary Table III. These same genetic correlations, repeated in the presence of the extended MHC region, are described in Supplementary Figure 1 and Supplementary Table IV. Notably, eleven correlations survived Benjamini-Hochberg (BH) multiple-test correction, most of which maintained this threshold of significance with MHC inclusion. Significant positive relationships were observed between bipolar disorder and celiac disease ($rg = 0.31 \pm 0.09$, uncorrected $p = 4.0\text{x}10^{-4}$), bipolar disorder and ulcerative colitis ($rg = 0.23 \pm 0.06$, uncorrected $p = 2.0\text{x}10^{-4}$), and bipolar disorder and Crohn's disease ($rg = 0.21 \pm 0.05$, uncorrected $p = 3.7\text{x}10^{-5}$). Schizophrenia had a positive genetic correlation with primary biliary cirrhosis ($rg = 0.15 \pm 0.05$, uncorrected $p = 1.2 \text{ x } 10^{-3}$), systemic lupus erythematous ($rg = 0.14 \pm 0.04$, uncorrected $p = 1.3\text{x}10^{-3}$), ulcerative colitis ($rg = 0.13 \pm 0.04$, uncorrected $p = 4.0\text{x}10^{-4}$), and Crohn's disease ($rg = 0.12 \pm 0.03$, uncorrected $p = 3.0\text{x}10^{-4}$). We observed a positive genetic correlation between major depression and hypothyroidism ($rg = 0.33 \pm 0.09$, uncorrected $p = 5\text{x}10^{-4}$), and one between Tourette syndrome and allergy ($rg = 0.24 \pm 0.06$, uncorrected $p = 2.7\text{x}10^{-5}$). We also observed positive genetic correlations between CRP and cigarettes per day ($rg = 0.37 \pm 0.09$, uncorrected $p = 5.0\text{x}10^{-5}$) and

ever-smoked status (*rg* = 0.31 ± 0.07, uncorrected p = $3.6x10^{-5}$). Estimated SNP-based heritability and sample size for these phenotypes are shown in Table I. Notably, the schizophrenia-systemic lupus erythematous correlation was not observed when the MHC region was included. Under MHC inclusion, an additional correlation between bipolar disorder and psoriasis was observed (*rg* = 0.22 ± 0.07, uncorrected *p* = $1.8x10^{-3}$). The remaining correlations depicted in Figure 1 did not survive BH correction for multiple testing.

Correlations among Immune-Inflammatory Phenotypes

In addition to correlations between behavioral-psychiatric phenotypes and autoimmune-inflammatory phenotypes, we also examined the correlations among the set of immune and inflammatory phenotypes, which has not previously been performed by LD score regression. We observed several highly significant correlations, which are depicted in Figure 2, with full summary statistics in Supplementary Tables V (MHC excluded) and VI (MHC included). Specifically, thirty-six correlations survived family-wise BH correction. Among these, celiac disease was positively correlated with Crohn's disease (*rg* = 0.27 ± 0.08, uncorrected *p* = $8.0x10^{-4}$), type 1 diabetes (*rg* = 0.32 ± 0.09, uncorrected *p* = $6.0x10^{-4}$), rheumatoid arthritis (*rg* = 0.24 ± 0.08, uncorrected *p* = $2.2x10^{-3}$), psoriasis (*rg* = 0.23 ± 0.09, uncorrected *p* = 0.01), allergy (*rg* = 0.19 ± 0.07, uncorrected *p* = $6.8x10^{-3}$), and hypothyroidism (*rg* = 0.38 ± 0.09, uncorrected *p* = $2.0x10^{-5}$). Ulcerative colitis was positively correlated with Crohn's disease (*rg* = 0.71 ± 0.06, uncorrected *p* = $3.5x10^{-36}$), primary biliary cirrhosis (*rg* = 0.32 ± 0.09, uncorrected *p* = $4.0x10^{-4}$), multiple sclerosis (*rg* = 0.64 ± 0.20, uncorrected *p* = $1.5x10^{-3}$), and psoriasis (*rg* = 0.39 ± 0.08, uncorrected *p* = $1.6x10^{-6}$). Rheumatoid arthritis was positively correlated with systemic sclerosis (*rg* = 0.43 ± 0.17, uncorrected *p* = 0.01), type 1 diabetes (*rg* = 0.41 ± 0.14, uncorrected *p* = $2.1x10^{-3}$), hypothyroidism (*rg* = 0.34 ± 0.07, uncorrected *p* = $7.4x10^{-6}$), multiple sclerosis (*rg* = 0.44 ± 0.16, uncorrected *p* = $5.3x10^{-3}$), primary biliary cirrhosis (*rg* = 0.27 ± 0.08, uncorrected *p* = $1.4x10^{-3}$), systemic lupus erythematous (*rg* = 0.46 ± 0.06, uncorrected *p* = $1.8x10^{-13}$), and autoimmune hepatitis (*rg* = 0.58 ± 0.21, uncorrected *p* = $6.4x10^{-3}$). Furthermore, systemic lupus sclerosis was positively correlated with

multiple sclerosis (*rg* = 0.69 ± 0.24, uncorrected $p = 3.7x10^{-3}$) and systemic sclerosis (*rg* = 0.72 ± 0.25, uncorrected $p = 3.6x10^{-3}$).

Allergy was positively related to asthma (*rg* = 0.79 ± 0.04, uncorrected $p = 2.0x10^{-107}$), atopic dermatitis (*rg* = 0.25 ± 0.07, uncorrected $p = 2.0x10^{-4}$), childhood ear infections (*rg* = 0.22 ± 0.05, uncorrected $p = 2.9x10^{-6}$), CRP (0.13 ± 0.05, uncorrected $p = 5.4x10^{-3}$), tuberculosis susceptibility (*rg* = 0.22 ± 0.08, uncorrected $p = 8.1x10^{-3}$), and hypothyroidism (*rg* = 0.20 ± 0.05, uncorrected $p = 4.0x10^{-5}$). Primary biliary cirrhosis was positively correlated with psoriasis (*rg* = 0.27 ± 0.10, uncorrected $p = 5.4x10^{-3}$), systemic lupus erythematous (*rg* = 0.62 ± 0.08, uncorrected $p = 2.2x10^{-13}$), Crohn's disease (*rg* = 0.24 ±0.08, uncorrected $p = 1.6x10^{-3}$), hypothyroidism (*rg* = 0.24 ± 0.09, uncorrected $p = 7.6x10^{-3}$), and systemic sclerosis (*rg* = >0.95 ± 0.31, uncorrected $p = 5.0x10^{-4}$). Asthma was positively related to childhood ear infection (*rg* = 0.15 ± 0.04, uncorrected $p = 3.0x10^{-4}$), atopic dermatitis (*rg* = 0.39 ± 0.07, uncorrected $p = 1.5x10^{-7}$) and CRP (*rg* = 0.17 ± 0.05, uncorrected $p = 6.0x10^{-4}$). Hypothyroidism was also positively correlated with childhood ear infections (*rg* = 0.14 ± 0.05, uncorrected $p = 5.4x10^{-3}$) and type 1 diabetes (*rg* = 0.40 ± 0.10, uncorrected $p = 4.6x10^{-5}$). Finally, psoriasis was positively correlated with Crohn's disease (*rg* = 0.34 ± 0.07, uncorrected $p = 2.3x10^{-7}$). The remaining correlations depicted in Figure 2 did not survive BH correction for multiple testing.

When analyzed with inclusion of the MHC region (Supplementary Figure 2, Supplementary Table VI), a total of twenty-four correlations reached a corrected threshold of significance; twenty-three of these had reached the same threshold under MHC exclusion. One new positive correlation was observed between autoimmune hepatitis and type 1 diabetes was only under MHC inclusion (*rg* = 0.55 ± 0.19, uncorrected $p = 4.2x10^{-3}$). The following positive correlations no longer reached a corrected significance threshold upon MHC inclusion: celiac disease and psoriasis, ulcerative colitis and multiple sclerosis, ulcerative colitis and psoriasis, rheumatoid arthritis and type 1 diabetes, rheumatoid arthritis and multiple sclerosis, rheumatoid arthritis and systemic lupus erythematous, rheumatoid arthritis and autoimmune hepatitis, allergy and tuberculosis infection susceptibility, primary biliary cirrhosis and psoriasis, primary biliary cirrhosis and systemic lupus erythematous, primary biliary cirrhosis and

hypothyroidism, systemic lupus sclerosis and multiple sclerosis, and hypothyroidism and childhood ear infections. Estimated SNP-based heritability and sample size for all phenotypes are shown in Table I.

Characterization of Psychiatric-Immunologic Pleiotropic Tag SNPs

We sought to explore the top SNPs shared by select behavior-immune phenotype pairs that demonstrated a BH-corrected significant genetic correlation (bipolar-celiac, bipolar-ulcerative colitis, bipolar-Crohn's, bipolar-psoriasis, schizophrenia-systemic lupus erythematous, schizophrenia-ulcerative colitis, schizophrenia-Crohn's, schizophrenia-primary biliary cirrhosis, depression-hypothyroidism, and Tourette syndrome-allergy). Note that although the CRP-ever smoked and CRP-cigarettes per day correlations were highly significant in our analyses, we did not explore them further in this study due to potential confounding effects; the CRP GWAS was not controlled for smoking status. For each of the remaining phenotype pairs, we highlight the number of QC positive "risk" SNPs for each phenotype of the pair, the number of shared QC positive SNPs at a *p*-value threshold of 0.005, and the top 10 linkage disequilibrium (LD)-independent ($r^2 < 0.2$) SNPs based on the magnitude of the average effect size across the two phenotypes, as well the genes located nearby. These top 10 SNPs are also highlighted in yellow in corresponding Supplementary Tables VII through XVI. Data from additional phenotype pairs can be provided upon request to the corresponding author.

At an uncorrected association *p*-value < 0.005, we observed 44 SNPs that were associated with both bipolar disorder and celiac disease, 33 of which shared the same directionality of effect for both phenotypes (Table II and Supplementary Table VII). Bipolar disorder and ulcerative colitis shared 425 SNPs (318 with shared direction of effect for both phenotypes; Table II and Supplementary Table VIII). Bipolar disorder and Crohn's Disease shared 349 SNPs (263 with the same direction of effect; Table II and Supplementary Table IX), and bipolar disorder and psoriasis shared 394 SNPs (305 with the same direction of effect; Supplementary Table XVI). Schizophrenia and ulcerative colitis shared 3391 SNPs, of which 2324 had the same direction of effect (Table II and Supplementary Table X). Schizophrenia shared 6166 SNPs with Crohn's disease (4894 with same directionality; Table II and Supplementary Table XI). Notably, there is significant overlap in SNPs shared by bipolar disorder, schizophrenia, ulcerative colitis,

and Crohn's disease (40 SNPs). Two SNPs are furthermore shared between both bipolar disorder and schizophrenia and all three inflammatory gut disorders (including celiac disease) at an uncorrected $p < 0.005$ threshold, namely: rs2297909 and rs296547 (linked SNPs mapping near *KIF21B*).

At an uncorrected p-value < 0.005, we furthermore observed 857 SNPs shared between schizophrenia and primary biliary cirrhosis (574 with the same direction of effect; Table II and Supplementary Table XII) and 5913 SNPs shared between schizophrenia and systemic lupus erythematous (4256 with the same direction of effect; Table II and Supplementary Table XIII). We observed 79 SNPs that were associated with both major depression and hypothyroidism, among which 58 had the same direction of effect for both phenotypes (Table II; Supplementary Table XIV). At an uncorrected association p-value < 0.005, we observed 2231 SNPs that were associated with both Tourette syndrome and allergy; among these 1,519 shared the same direction of effect for both phenotypes (Table II; Supplementary Table XV). For each list of SNPs shared by a behavioral/immune phenotype pair, SNPs that have been previously identified as genome-wide significant associations for any autoimmune disease within immunobase.org are noted in Supplementary Tables VII through XVI).

Discussion

In this study, we examined the genetic relationships between and within sets of psychiatric-behavioral and immune-inflammatory phenotypes using the LD score regression method. In doing so, we advanced the existing epidemiologic literature in several ways. First, we obtained data from both publicly available and privately held sources, which enabled us to have more comprehensive representation of immune-related GWAS phenotypes; this reflects a significant expansion of scope compared with previous studies (*e.g.*, Wang et al., 2015) and compared to genetic correlation results currently available in the public domain (http://ldsc.broadinstitute.org/). Additionally, our study reflects the first application of the LD score regression method for many of these psychiatric-immune phenotype pairs. We identified several positive genetic correlations between psychiatric and immune-related phenotypes that were robust to multiple testing and we followed up with qualitative examination of associated SNPs for each phenotype pair. We focus our discussion here on these correlations, comparing our findings with those of

previous cross-phenotype genetic studies, as well as relevant clinical epidemiological literature. More generally, however, our results suggest that a common polygenic diathesis might be shared amongst a cluster of psychiatric (*i.e*. bipolar disorder, and to a lesser extent, schizophrenia) and immune-related phenotypes (*i.e*. celiac disease, Crohn's disease, primary biliary cirrhosis, and ulcerative colitis).

Quantitative SNP-based genetic relationships between phenotypes have been explored previously using other statistical approaches, including restricted maximum likelihood (REML) co-heritability, polygenic risk scores, genetic analysis incorporating pleiotropy and annotations, and other permutation-based methods (Cross-Disorder Group of the PGC, 2013; Lee et al., 2013; Pouget et al., 2016; Q. Wang et al., 2015). While other methods are better suited to characterizing the specific loci contributing to shared genetic risk (Cotsapas et al., 2011; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Pouget et al., 2016; Q. Wang et al., 2015), the approach taken here attempts to quantitate similarities and differences in association signals across the entire genome. Some of the phenotype pairs assessed here have been examined previously using the LD score regression method and we compare our findings when possible (Anttila et al., 2016; B. K. Bulik-Sullivan et al., 2015; Zheng et al., 2016).

Prominent among our findings was a cluster of positive genetic correlations between bipolar disorder, schizophrenia, and conditions involving altered gut immunologic function (celiac disease (bipolar only), ulcerative colitis, and Crohn's disease). These relationships have been corroborated by previous clinical findings. Specifically, one study found that a history of celiac disease or ulcerative colitis appears to significantly increase the subsequent risk for mood disorders, including bipolar disorder (Benros et al., 2013). Patients ascertained for bipolar disorder have demonstrated differences in serologic markers associated with gluten sensitivity, suggesting interplay with celiac disease (Dickerson et al., 2011; Sidhom et al., 2012). A different study reported a positive association between ulcerative colitis (as well as Crohn's disease) and risk for a concurrent diagnosis of bipolar disorder (Eaton et al., 2010). Finally, Stringer et al. (2014) reported a positive association between schizophrenia and Crohn's disease using polygenic risk score analysis, and Cucino & Sonnenberg (2001) found schizophrenia to be a statistically significant comorbidity in ulcerative colitis patients. One important limitation of the available

clinical epidemiological literature is that affected individuals are often lumped together to create a combined risk-exposed group (e.g., the presence of any autoimmune disorder) in order to examine the incidence of a different phenotype (e.g., a specific psychiatric disorder or any psychiatric disorder). This approach is taken in order to increase sample size, but it may fail to capture specific relationships between clusters of disorders that may share pathophysiologic mechanisms.

Notably, however, that there are also studies that do not support our observations. A previous study implementing a REML-based approach did not find significant SNP-based co-heritabilities between Crohn's disease and the major psychiatric phenotypes (Lee et al., 2013), and a study from West et al. (2006) found no clinical association between the schizophrenia and any of the inflammatory gut disorders. The first study implementing the LD score regression method (B. Bulik-Sullivan et al., 2015) used a dataset reflecting 27,432 subjects analyzed in Jostins et al., (2012) and reported no significant correlation ($rg = 0.08 \pm 0.08$, uncorrected $p = 0.33$) between bipolar disorder and ulcerative colitis, and a similar non-correlation is also reported in LD-Hub (http://ldsc.broadinstitute.org/), using what appears to be the same datasets as the initial report (27,432 subjects, referencing Liu et al., 2015). The present study also used the same GWAS summary data for both phenotypes, but we restricted our analysis to SNPs with a minor allele frequency $\geq$ 5% in the 1000 Genomes Project Phase 3 European samples. These findings suggest that dataset selection and preprocessing can have a considerable effect on the result of the LD score regression analysis.

Notably, our results show that the above-mentioned inflammatory gut disorders are positively correlated with both bipolar disorder and (more modestly with) schizophrenia. This is unsurprising, as previous studies from the Cross-Disorder Group of the PGC (2013) and Anttila et al. (2016; using LD score regression) have reported a genetic link between the two psychiatric phenotypes. Furthermore, when we compared the lists of nominally associated SNPs (uncorrected $p < 0.005$) in the present study, we found 40 SNPs that were common to all four of bipolar disorder, schizophrenia, Crohn's disease, and ulcerative colitis. Interestingly, when we further included celiac disease in the comparison, only 2 common SNPs were retained amongst the five phenotypes. Both of these SNPs are linked to *KIF21B*,

which encodes Kinesin Family Member 21B. Remarkably, multiple autoimmune phenotypes have yielded genome-wide significant association signals mapping near this gene (Danoy et al., 2010; Goris et al., 2010; Harada et al., 2007; Kreft et al., 2014; Labonté et al., 2013; Y. Liu et al., 2013; Marszalek et al., 1999; McCauley & Hussman, 2010; Robinson et al., 2015; Yang et al., 2015). *KIF21B* encodes a neuronal motor protein implicated in $GABA_A$ receptor trafficking (Labonte, Thies, & Kneussel, 2014). With regards to its role spanning both psychiatric and immune-related phenotypes, it is possible that dysregulation of this protein can lead to altered GABA signaling in neurons in both the brain and enteric nervous system. *KIF21B* is additionally found in several lymphocyte subtypes, and may thus have a role in mediating inflammatory signaling in these phenotypes (Goris et al, 2010). Another SNP (rs716501) was nominally associated with bipolar disorder, celiac disease, Crohn's disease, and ulcerative colitis in the present data; this particular SNP is located in the 4q27 region, which contains the *IL2* and *IL21* genes. This region has been shown to be a susceptibility locus for several autoimmune diseases (Diaz-Gallo et al., 2013; C. Garner et al., 2014; C. P. Garner et al., 2009; Glas et al., 2009; Hughes et al., 2011; Márquez et al., 2009; Plagnol et al., 2011; Srivastava et al., 2012; Stallhofer et al., 2011).

However, certain caveats should be taken with respect to our SNP-identification approach, which is highly anecdotal in nature. Indeed, it is plausible that two shared risk SNPs could be identified among 5 unrelated phenotypes by chance alone. In order to make more confident (quantitative) conclusions about the functions of genes enriched among the SNPs that mediate a significant genetic correlation, existing analysis methods must be adapted and validated. For example, summary-level GWAS data could be consolidated across two phenotypes *via* meta-analysis and analyzed as a single dataset, but the specificity of this approach to SNPs mediating a positive genetic correlation is yet unclear, and the approach is not as easily generalized to examine the SNPs mediating a negative genetic correlation. Alternatively, enrichment analysis could be performed separately and consolidated at the pathway level, but this approach also lacks specificity. Future studies should employ optimized methods to investigate and characterize the genes and functions implicated by brain-immune genetic correlations identified using well-powered data sets.

Our study also found positive genetic correlations between schizophrenia and two more autoimmune phenotypes: primary biliary cirrhosis and systemic lupus erythematous. To the best of the authors' knowledge, there are no prior clinical or genetic studies that support a link between schizophrenia and primary biliary cirrhosis, but one epidemiological study from Tiosano et al. (2016) has previously reported a positive clinical association between schizophrenia and systemic lupus erythematous. We also observed a modest but significant positive correlation between Tourette syndrome and allergy ($rg = 0.23 \pm 0.06$, uncorrected $p = 2.7\text{x}10^{-5}$), which is consistent with evidence of increased comorbidity between these phenotypes (Chang et al., 2011; Yuce et al., 2014). Among the SNPs shared between phenotypes in this correlation were many that reached a genome-wide threshold of association with allergy, some of which also show associations with multiple sclerosis in previous studies (shown in Supplementary Table XI). Note that allergy GWAS data was obtained through 23andMe, Inc., along with data for asthma, childhood ear infection, hypothyroidism, and Parkinson's disease. The sample sizes for these datasets are an order of magnitude larger than the other datasets, allowing for a relatively small error in the estimation of heritability and better power for the detection of genetic correlations. However, the phenotype data used to perform these studies are based on self-report, and thus may be more susceptible to bias stemming from misdiagnosis or misreporting.

The above-mentioned caveat also applies to the genetic correlation observed between major depression and self-reported hypothyroidism ($rg = 0.33 \pm 0.09$, uncorrected $p = 5\text{x}10^{-4}$). This correlation is consistent with general clinical observation. It is important to consider that depressive-like symptoms can be a manifestation of hypothyroidism, which could increase the frequency of cross-contamination between these phenotypes and bias data toward a positive correlation. However, the majority of cases of hypothyroidism in developed countries are attributed to autoimmune causes (Garber et al., 2012), and as such we expected the 23andMe data to predominantly reflect the signature of autoimmune thyroiditis. This is compatible with the observed positive correlations between hypothyroidism and other autoimmune phenotypes, including primary biliary cirrhosis ($rg = 0.24 \pm 0.09$, uncorrected $p = 0.008$), celiac disease ($rg = 0.38 \pm 0.09$, uncorrected $p = 2.0\text{x}10^{-5}$), rheumatoid arthritis ($rg = 0.34 \pm 0.07$,

uncorrected $p = 7.4\text{x}10^{-6}$), allergy ($rg = 0.20 \pm 0.05$, uncorrected $p = 4.0\text{x}10^{-5}$), and type 1 diabetes ($rg = 0.40 \pm 0.10$, uncorrected $p = 4.6\text{x}10^{-5}$).

Along this note, genetic relationships between different autoimmune/inflammatory phenotypes are well-supported by the observation that the same loci were identified as genome-wide hits for multiple autoimmune/inflammatory disorders (immunobase.org), as well as a multitude of epidemiologic studies. Clinical co-segregation within individuals and families have been demonstrated for many autoimmune disease pairs: for example, Crohn's disease is correlated with ulcerative colitis (Baumgart et al., 2012; Eaton et al., 2007); the inflammatory bowel disorders with celiac disease (Cooper, Bynum, & Somers, 2009; Eaton et al., 2007) and type 1 diabetes (Cárdenas-Roldán, Rojas-Villarraga, & Anaya, 2013; Cooper et al., 2009); and rheumatoid arthritis with type 1 diabetes (Cárdenas-Roldán et al., 2013; Cooper et al., 2009). To the best of the authors' knowledge, genetic relationships between many of the immune/inflammatory phenotypes analyzed in our study have not previously been quantified elsewhere using the LD score regression method. Quantitative comparative genetic studies employing alternative methods to ours have been performed which also suggested considerable genetic pleiotropy (Cotsapas et al., 2011; Ellinghaus et al., 2016) and genetic correlation between these phenotypes (Li et al., 2015). Notably, we would reasonably expect the extended MHC region (chromosome six) to be the source of much of the observed genetic overlap between autoimmune phenotypes, at it is enriched with genes subserving immunologic functions and harbors important association signals for many of the best-studied autoimmune and inflammatory phenotypes (Fernando et al., 2008; Gough & Simmonds, 2007). However, most of the highly significant correlations identified in the present study were unaffected by the presence/absence of the MHC region (Table I and Table II), which underscores a distributed polygenic nature of SNP-mediated risk for these phenotypes.

It bears mentioning in this discussion that different approaches to examining cross-phenotype genetic relationships appear somewhat prone to arriving at different conclusions. Using several approaches that were not dependent on the directionality of a given SNP's effect, Wang et al., (2015) concluded that many (24 of 35) pairs of psychiatric and immune-related phenotypes shared a statistically

significant proportion of risk-associated loci; among these findings was a significant genetic correlation between bipolar disorder (as well as schizophrenia) and ulcerative colitis. However, many of the other relationships identified by Wang and colleagues were not significant in the present study. A recent study by Pouget and colleagues furthermore demonstrated that polygenic risk scores reflecting additive risk for several autoimmune diseases can explain a small proportion of variance in schizophrenia case-control status, yet the genome-wide significant SNPs from the autoimmune GWASs were not over-represented among schizophrenia's genome-wide significant hits when permutation-based analysis was performed (Pouget et al., 2016). The apparent disagreement between different approaches for assessing shared genetic liability thus underscores the value of examining the consensus across studies and methods (Pouget et al., 2016).

SNP-based genetic correlations such as used in the present study are complex and may arise from a wide variety of underlying factors. Potential pitfalls to interpretation include the possibility that the relationship between a phenotype pair is partially mediated by behavioral or cultural factors, or influenced by a heritable but unexamined underlying trait that confers risk to both phenotypes (Anttila et al., 2016; B. Bulik-Sullivan et al., 2015). A relevant example within the present data might include the robust positive correlations observed between smoking behavior and immune/inflammatory conditions thought to be caused or exacerbated by smoking (*e.g.*, susceptibility to tuberculosis, rheumatoid arthritis). These observations suggest that the GWAS signals of some immune or inflammatory diseases may actually be biased, with GWAS signal reflecting propensity toward smoking behavior. Statistical control or *post-hoc* adjustment of results may help distinguish these two effects. Other factors that could contribute to genetic correlations include effects mediated by parental genotypes and their influence on parental behaviors that impact the offspring (Coop & Pickrell, 2016). For example, in simulations, assortative mating over generations can induce a genetic correlation between two traits designed to be genetically independent (Coop & Pickrell, 2016). Additionally, GWAS studies of psychiatric phenotypes typically do not screen affected cases based on general medical conditions, and studies of immune-related phenotypes may not exclude individuals with psychiatric comorbidity. Over-representation of a given immune-related

phenotype in a psychiatric sample and vice-versa could bias the data toward the detection of a genetic correlation. Alternatively, it is unclear the extent to which explicit exclusion of individuals from a control group could bias the estimated genetic correlation in certain circumstances (*e.g.*, the exclusion of individuals with type 2 diabetes from the control group of a study of type 1 diabetes). Finally, estimates of genetic similarities could be influenced by misdiagnosed cases (Wray, Lee, & Kendler, 2012).

Further caveats to the interpretation of our particular study include the lack of clearly identified positive and negative control comparisons. Additionally, for extremely well-powered datasets such as those obtained from 23andMe, it is yet unclear whether small magnitude genetic correlations are clinically meaningful. This could be clarified by examining whether genetic correlation strength is predictive of the magnitude of cross-disorder epidemiologic risk across many pairs of phenotypes, which would additionally help shed light on the sensitivity and specificity of the LD score regression method. Other general limitations of this method (in comparison with other approaches) have been discussed previously elsewhere and will not be covered here (Anttila et al., 2016; B. Bulik-Sullivan et al., 2015). Further work considering expression quantitative trait loci, differentially expressed or methylated genes, or enriched ontological and functional terms may provide a broader context for assessing biological similarities between phenotypes.

Despite the limitations of our method, many of the nominally significant correlations implicating relationships of psychiatric phenotypes with immune-inflammatory phenotypes are intriguing and warrant further examination. Future studies should seek to repeat these analyses with GWAS data derived from larger samples in order to reduce the error associated with heritability and genetic correlation. Furthermore, the incorporation of GWAS data reflecting continuously measured immunologic parameters (*e.g.*, circulating immune cell subtype abundances or circulating cytokine levels; Lambert et al., 2013; Orrù et al., 2013) may provide additional contexts for understanding immunogenetic diatheses related to human health and diseases. The recent launch of a web-based platform (http://ldsc.broadinstitute.org/; Zheng et al., 2016) for performing LD score regression analyses and sharing GWAS summary-level data enables investigators to perform their own analyses for phenotypes of interest with relative ease.

A growing body of literature suggests that the cells and signaling molecules of the immune system may influence early neural development as well as brain plasticity and function in fully developed organisms. Plausible mechanisms linking altered immune functions with neurobiological changes have been identified in model systems, and research efforts to evaluate modulation of immune and inflammatory signaling as a treatment target in psychiatry are currently well underway. Therefore, it stands to reason that genetic variation that impacts immune functioning may have the potential to influence brain development and function in ways that dispose individuals toward mental illness; such a mechanism could help explain the genetic correlations observed presently. The identification of genetic similarities between psychiatric phenotypes and well-studied autoimmune phenotypess may help accelerate our understanding of psychiatric pathophysiology and guide the search for treatment targets and potentially therapeutic compounds. The results of the present study, as well as its predecessors (Anttila et al., 2016; B. Bulik-Sullivan et al., 2015; Zheng et al., 2016), and other approaches for cross-phenotype GWAS integration (Burstyn et al., 2011; Cotsapas et al., 2011; Himmelstein & Baranzini, 2015; L. Wang et al., 2015) underscore an impetus for open sharing of GWAS results in order to accelerate the discovery of previously undetected genetic relationships that extend across medical disciplines and to support the identification and prioritization of multi-disease-associated loci.

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Legends for Tables and Supplementary Tables

Table I Legend. Full publication references, consortia names, and links to web resources are provided in Supplementary Tables I and II. GWAS *N* denoted with * indicates the median *N* for all SNPs. Abbreviations: Attention deficit-hyperactivity disorder (ADHD), C-reactive protein (CRP), major histocompatibility complex (MHC), obsessive-compulsive disorder (OCD), Psychiatric Genomics Consortium (PGC), quality control (QC), single nucleotide polymorphism (SNP).

Table II Legend: Summary of quality control positive (QC) SNPs associated with each phenotype and phenotype pair at $p < 0.005$, and details of the top 10 linkage disequilibrium-independent SNPs associated with each phenotype pair, ranked by average magnitude of effect. SNP base positions listed refer to human genome build version GRCh37. These SNPs are also highlighted yellow in corresponding Supplementary Tables VII through XVI.

Supplementary Table I. GWAS Sample Information and Single Phenotype Statistics, MHC Excluded.

Supplementary Table II. GWAS Sample Information and Single Phenotype Statistics, MHC Included

Supplementary Table III. Neuro-Behavioral vs. Immune-Inflammatory Correlations, MHC Excluded.

Supplementary Table IV. Neuro-Behavioral vs. Immune-Inflammatory Correlations, MHC Included.

Supplementary Table V. Correlations among Immune-Inflammatory Phenotypes, MHC Excluded.

Supplementary Table VI. Correlations among Immune-Inflammatory Phenotypes, MHC Included.

Supplementary Table VII. Bipolar Disorder and Celiac Disease SNP Intersection.

Supplementary Table VIII. Bipolar Disorder and Ulcerative Colitis SNP Intersection.

Supplementary Table IX. Bipolar Disorder and Crohn's Disease SNP Intersection.

Supplementary Table X. Schizophrenia and Ulcerative Colitis SNP Intersection.

Supplementary Table XI. Schizophrenia and Crohn's Disease SNP Intersection.

Supplementary Table XII. Schizophrenia and Primary Biliary Cirrhosis SNP Intersection.

Supplementary Table XIII. Schizophrenia and Systemic Lupus Erythematous SNP Intersection.

Supplementary Table XIV. Major Depression and Hypothyroid SNP Intersection.

Supplementary Table XV. Tourette Syndrome and Allergy SNP Intersection.

Supplementary Table XVI. Bipolar Disorder and Psoriasis SNP Intersection

Figure Legends.

Figure 1 Legend. Genetic correlations between psychiatric-behavioral and autoimmune-inflammatory phenotypes under MHC exclusion are depicted using a heatmap such that red reflects more positive correlation coefficients while blue reflects more negative coefficients. Genetic correlation coefficients are provided within each cell, with full details provided in Supplementary Table III (MHC exclusion) and Supplementary Table IV (MHC inclusion). Correlations reaching trend-level significance ($0.05 <$ uncorrected $p < 0.10$) are depicted as colored panels, while relationships surpassing uncorrected $p < 0.05$ are additionally denoted with *, and relationships surpassing BH-$p < 0.05$ (for the total number of tests depicted in the figure) are denoted with **. The ordering of each phenotype within the rows and columns of each heatmap were based on hierarchical clustering of the correlation coefficients. Abbreviations: Attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD).

Figure 2 Legend. Genetic correlations between autoimmune-inflammatory phenotypes under MHC exclusion are depicted using a heatmap such that red reflects more positive correlation coefficients while blue reflects more negative coefficients. Genetic correlation coefficients are provided within each cell, with full details provided in Supplementary Table V (MHC exclusion) and Supplementary Table VI (MHC inclusion). Correlations reaching trend-level significance ($0.05 <$ uncorrected $p < 0.10$) are depicted as colored panels, while relationships surpassing uncorrected $p < 0.05$ are additionally denoted with *, and relationships surpassing BH-$p < 0.05$ (for the total number of tests depicted in the figure) are denoted with **. The ordering of each phenotype within the rows and columns of each heatmap were based on hierarchical clustering of the correlation coefficients.

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Manuscript Abbreviations

Attention deficit-hyperactivity disorder (ADHD), Benjamini-Hochberg (BH), C-reactive protein (CRP) genome-wide association study (GWAS), linkage disequilibrium (LD), major histocompatibility (MHC), obsessive compulsive disorder (OCD), Psychiatric Genomics Consortium (PGC), quality control (QC), restricted maximum likelihood (REML), single nucleotide polymorphism (SNP)

Table I. Sample Characteristics for Phenotypes Involved in Significant Correlations

Phenotype	**Data Source**	**Estimated SNP Heritability ± Error (MHC Included / MHC Excluded)**	**GWAS *N***	**QC-Positive SNPS (MHC Included / MHC Excluded)**
ADHD	Neale *et al*. (2010)	0.23 ± 0.10 / 0.23 ± 0.10	5,422	968,316 / 965,717
Allergy (Any, Self-Report)	The 23andMe Research Team	0.08 ± 0.01 / 0.08 ± 0.01	181,000	1,063,433 / 1,060,611
Asthma (Self-Report)	The 23andMe Research Team	0.07 ± 0.01 / 0.07 ± 0.01	157,000	1,063,434 / 1,060,612
Anxiety-Spectrum Disorder	Otowa *et al.* (2016)	0.08 ± 0.03 / 0.07 ± 0.03	17,310*	977,187 / 974,672
Atopic Dermatitis	EAGLE Consortium	0.08 ± 0.02 / 0.08 ± 0.02	40,835	1,058,814 / 1,056,034
Autism	PGC Autism Working Group	0.39 ± 0.06 / 0.39 ± 0.06	10,263	1,064,887 / 1,062,056
Bipolar Disorder	PGC Bipolar Working Group	0.45 ± 0.04 / 0.44 ± 0.04	16,731	967,291 / 964,863
Childhood Ear Infection	The 23andMe Research Team	0.07 ± 0.01 / 0.07 ± 0.01	122,000	1,063,434 / 1,060,612
Celiac Disease	Dubois *et al.*, (2010)	0.30 ± 0.05 / 0.30 ± 0.05	15,283	271,764 / 271,764
Cigarettes per Day	Tobacco and Genetics Consortium	0.03 ± 0.01 / 0.03 ± 0.01	68,028	965,918 / 963,495
Cigarettes (Ever-Smoked)	Tobacco and Genetics Consortium	0.07 ± 0.01 / 0.07 ± 0.01	74,035	965,778 / 963,355
Crohn's Disease	Liu *et al.* (2015)	0.47 ± 0.06 / 0.47 ± 0.06	21,389	1,064, 906 / 1,062, 075
C-Reactive Protein	Dehghan *et al.* (2011)	0.13 + 0.02 / 0.13 + 0.02	66,185	968,285 / 965,855
Hypothyroidism (Self-Report)	The 23andMe Research Team	0.05 + 0.01 / 0.05 + 0.01	135,000	1,063,434 / 1,060,612
Major Depression	PGC Depression Working Group	0.15 ± 0.03 / 0.14 ± 0.03	18,759	970,136 / 967,534
OCD	PGC OCD/TS Working Group	0.30 ± 0.05 / 0.29 ± 0.05	10,215*	1,057,568 / 1,054,746
Parkinson's Disease (Self-Report)	The 23andMe Research Team	0.03 ± 0.00 / 0.03 ± 0.00	335,000	1,063,435 / 1,060,613
Primary Biliary Cirrhosis	Cordell *et al.*, (2015)	0.41 + 0.08 / 0.37 + 0.06	13,239	943,294 / 940,715
Psoriasis	Tsoi *et al.*, (2015)	>0.95 ± 0.51 / 0.82 ± 0.13	5,116*	1,040,081 / 1,037,355
Rheumatoid Arthritis	Okada *et al.* (2014)	0.21 ± 0.07 / 0.14 + 0.02	58,284	1,054,583 / 1,051,805
Schizophrenia	PGC Schizophrenia Working Group	0.48 ± 0.02 / 0.47 ± 0.02	77,096	1,064,360 / 1,061,529
Systemic Sclerosis	Radstake *et al.* (2010)	0.22 + 0.08 / 0.20 + 0.09	7,444	232,449 / 231,820
Tourette Syndrome	PGC OCD/TS Working Group	0.35 ± 0.05 / 0.35 ± 0.04	13,341*	1,044,499 / 1,041, 689
Type 1 Diabetes	Bradfield *et al.* (2011)	0.29 ± 0.12 / 0.18 + 0.03	26,890*	856,183 / 854,164
Ulcerative Colitis	Liu *et al.* (2015)	0.26 ± 0.03 / 0.25 ± 0.03	27,432	1,064,925 / 1,062,094

Table II. Top 10 LD-Independent SNPs Involved in Behavior-Immune Genetic Correlations

Bipolar Disorder – Celiac Disease

Bipolar Disorder		**Celiac Disease**		**Bipolar-Celiac**	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction
964863	21946	271764	2728	44	0.75

SNP ID	**Chromosome; Base Position**	**Nearby Gene Symbol**	**Corresponding Gene Names**
rs4810480	chr20; 44554686	*ACOT8, CTSA, MMP9, NEURL2, PCIF1, PLTP, SLC12A5, SNX21, SPATA25, TNNC2, ZNF335, ZSWIM1, ZSWIM3*	Acyl-CoA Thioesterase 8, Cathepsin A, Matrix Metallopeptidase 9, Neuralized E3 Ubiquitin Protein Ligase 2, PDX1 C-Terminal Inhibiting Factor 1, Phospholipid Transfer Protein, Solute Carrier Family 12 Member 5, Sorting Nexin Family Member 21, Spermatogenesis Associated 25, Troponin C2 Fast Skeletal Type, Zinc Finger Protein 335, Zinc Finger SWIM-Type Containing 1
rs10495392	chr1; 237422989	*RYR2*	Ryanodine Receptor 2
rs1354329	chr11; 16485301	*SOX6*	SRY-Box 6
rs7767017	chr6; 109519922	*CCDC162P, CEP57L1, LLOC100996634*	Coiled-Coil Domain Containing 162 Pseudogene, Centrosomal Protein 57 Like 1, Transmembrane Protein FLJ37396
rs7002268	chr8; 142277340	*DENND3, GPR20, LINC01300, SLC45A4*	DENN Domain Containing 3, G Protein-Coupled Receptor 20, Long Intergenic Non-Protein Coding RNA 1300, Solute Carrier Family 45 Member 4
rs676388	chr 19; 49211969	*BCAT2, CA11, DBP, FAM83E, FGF21, FUT1, FUT2, IZUMO1, MAMSTR, NTN5, RASIP1, RPL18, SEC1P, SPHK2*	Branched Chain Amino Acid Transaminase 2, Carbonic Anhydrase 11, D-Box Binding PAR BZIP Transcription Factor, Family With Sequence Similarity 83 Member E, Fibroblast Growth Factor 21, Fucosyltransferase 1 (H Blood Group)/2, Izumo Sperm-Egg Fusion 1, MEF2 Activating Motif And SAP Domain Containing Transcriptional Regulator, Netrin 5, Ras Interacting Protein 1, Ribosomal Protein L18, Secretory Blood Group 1, Pseudogene, Sphingosine Kinase 2
rs4077924	chr2; 181991389	*UBE2E3*	Ubiquitin Conjugating Enzyme E2 E3

rs1250576	chr10; 80964796	*ZMIZ1*	Zinc Finger MIZ-Type Containing 1
rs4464229	chr2; 28038080	*BRE, BRE-AS1, MRPL33, RBKS*	Brain And Reproductive Organ-Expressed (TNFRSF1A Modulator), BRE Antisense RNA 1, Mitochondrial Ribosomal Protein L33, Ribokinase
rs1262774	chr13; 51068896	*DLEU1*	Deleted In Lymphocytic Leukemia 1

Bipolar Disorder – Ulcerative Colitis

Bipolar Disorder		**Ulcerative Colitis**		**Bipolar-Ulcerative Colitis**	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction
964863	21946	1062094	65745	425	0.75

SNP ID	**Chromosome; Base Position**	**Nearby Gene Symbol**	**Corresponding Gene Names**
rs6947314	chr7; 3086311	--	--
rs7479562	chr11; 36664702	*RAG2, RAG1, C11orf74*	Recombination Activating 2, Recombination Activating 1, Chromosome 11 Open Reading Frame 74
rs9567446	chr13; 32800426	*FRY, BRCA2, ZAR1L*	FRY Microtubule Binding Protein, BRCA2 DNA Repair Associated, Zygote Arrest 1-Like
rs2132158	chr15; 38987322	*C15orf53*	Chromosome 15 Open Reading Frame 53
rs6427852	chr1; 200676208	*CAMSAP2, DDX59, KIF14*	Calmodulin Regulated Spectrin Associated Protein Family Member 2, DEAD-box Helicase 59, Kinesin Family Member 14
rs9528205	chr13; 61309043	--	--
rs10494819	chr1; 200704754	*KIF14, DDX59*	Kinesin Family Member 14, DEAD-box Helicase 59
rs373747	chr22; 20155192	*MIR3618, DGCR8, TANGO2, RANBP1, MIR1306, LINC00896, TRMT2A, MIR1286, RTN4R,*	MicroRNA 3618, Microprocessor Complex Subunit, Transport and Golgi Organization 2 Homolog, RNA Binding Protein 1, MicroRNA 1306, Long Intergenic Non-protein Coding RNA 896, TRNA

		LOC284865	Methyltransferase 2 Homolog A, MicroRNA1286, Reticulon 4 Receptor, (Uncharacterized)
rs10858499	chr12; 87230678	*MGAT4C*	Alpha-1,3-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase C
rs2305929	chr2; 28113911	*MRPL33, MIR4263, RBKS, BRE*	Mitochondrial Ribosomal Protein L33, MicroRNA 4263, Ribokinase, BRCA1-A complex subunit BRE

Bipolar Disorder – Crohn's Disease

Bipolar Disorder		**Crohn's Disease**		**Bipolar-Crohn's**	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction
964863	21946	1062075	76917	349	0.75

SNP ID	**Chromosome; Base Position**	**Nearby Gene Symbol**	**Corresponding Gene Names**
rs3852070	chr3; 52212661	*TWF2, PPM1M, WDR82, POC1A, MIR135A1, MIRLET7G, LINC00696, GLYCTK, TLR9*	Twinfillin Actin Binding Protein 2, Protein Phosphatase, Mg2+/Mn2+ Dependent 1M, WD Repeat Domain 82, POC1 Centriolar Protein A, MicroRNA 135a-1, MicroRNA Let-7g, Long Intergenic Non-Protein Coding RNA 696, Glycerate Kinase, Toll Like Receptor 9
rs804541	chr20; 22140724	*LINC01432*	Long Intergenic Non-Protein Coding RNA 1432
rs16853589	chr3; 107254203	*BBX*	HMG Box Transcription Factor/Bobby Sox Homolog
rs2628618	chr15; 25808244	*ATP10A*	ATPase Phospholipid Transporting 10A (putative)
rs11753417	chr6; 37696596	*ZFAND3, MDGA1*	Zinc Finger AN1-Type Containing 3, MAM Domain Containing Glycosylphosphatidylinositol Anchor 1
rs17391694	chr1; 78623626	*MGC27382, GIPC2*	(uncharacterized), PDZ Domain Containing Family Member 2
rs11617551	chr13; 44443977	*ENOX1, CCDC122*	Ecto-NOX Disulfide-Thiol Exchanger 1, Coiled-Coil Domain Containing 122

rs9851055	chr3; 107295008	*BBX*	HMG Box Transcription Factor/Bobby Sox Homolog
rs6561150	chr13; 44460470	*LACC1, ENOX1*	Laccase Domain Containing 1, Ecto-NOX Disulfide-Thiol Exchanger 1
rs174528	chr11; 61543499	*MYRF, FADS1, MIR1908, DAGLA, FADS2, FADS3*	Myelin Regulatory Factor, Fatty Acid Desaturase 1, MicroRNA 1908, Diacylglycerol Lipase Alpha, Fatty Acid Desaturase 2, Fatty Acid Desaturase 3

Schizophrenia – Ulcerative Colitis

Schizophrenia		**Ulcerative Colitis**		**Schizophrenia-Ulcerative Colitis**	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction
1061529	221482	1062094	65745	6535	0.69

SNP ID	**Chromosome; Base Position**	**Nearby Gene Symbol**	**Corresponding Gene Names**
rs149382991	chr3; 52161508	*PPM1M, TLR9, ALAS1, POC1A, DUSP7, TWF2, LINC00696*	Protein Phosphatase (Mg2+/Mn2+ Dependent 1M), Toll Like Receptor 9, 5'-Aminolevulinate Synthase 1, POC1 Centriolar Protein A, Dual Specificity Phosphatase 7, Twinfillin Actin Binding Protein 2, Long Intergenic Non-Protein Coding RNA 696
rs34861250	chr7; 110922528	*IMMP2L*	Inner Mitochondrial Membrane Peptidase Subunit 2
rs76736116	chr1; 200899781	*GPR25, CACNA1S, CAMSAP2, KIF21B*	G-Protein Coupled Receptor 25, Calcium Voltage-Gated Channel Subunit Alpha 1S, Calmodulin-Regulated Spectrin Associated Protein Family Member 2, Kinesin Family Member 21 B
rs113265714	chr3; 52309169	*DNAH1, TLR9, WDR82, PPM1M, ALAS1, TWF2*	Dynein Axonemal Heavy Chain 1, Toll Like Receptor 9, WD Repeat Domain 82, Protein Phosphatase (Mg2+/Mn2+ Dependent 1M), 5'-Aminolevulinate Synthase 1, Twinfillin Actin Binding Protein 2
rs79262028	chr12; 93770053	*LOC643339, NUDT4, UBE2N, MRPL42*	(uncharacterized), Nudix Hydrolase 4, Ubiquitin Conjugating Enzyme E2 N, Mitochondrial Ribosomal Protein L42
rs1836847	chr15; 40176196	*FSIP1, GPR176, EIF2AK4*	Fibrous Sheath Interacting Protein 1, G-Protein Couple Receptor 176,

			Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4
rs55793914	chr3; 51593842	*DCAF1, TEX264, RAD54L2*	DDB1 and CUL4 Associated Factor 1, Testis Expression 264, RAD54 Like 2
rs4729626	chr7; 100537280	*EPHB4, SLC12A9, ACHE, SRRT, TRIP6, UFSP1, MUC12*	EPH Receptor B4, Solute Carrier Family 12 Member 9, Acetylcholinesterase, Serrate RNA Effector Molecule, Thyroid Hormone Receptor Interactor 6, UFM1 Specific Peptidase 1, Mucin 12 (Cell Surface Associated)
rs74872710	chr9; 115248347	*KIAA1958*	Uncharacterized KIAA1958 Protein
rs12545036	chr8; 66147690	*LINC00251*	Long Intergenic Non-Protein Coding RNA 251

Schizophrenia – Crohn's Disease

Schizophrenia		**Crohn's Disease**		**Schizophrenia-Crohn's**	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction
1061529	221482	1062075	76917	6166	0.79

SNP ID	**Chromosome; Base Position**	**Nearby Gene Symbol**	**Corresponding Gene Names**
rs1813006	chr4; 103001649	--	--
rs34861250	chr7; 110922528	*IMMP2L*	Inner Mitochondrial Membrane Peptidase Subunit 2
rs36064566	chr7; 100731184	*MOGAT3, SERPINE1, MIR4653, MUC12, NAT16, VGF, AP1S1, PLOD3, MUC17*	Monoacylglycerol O-Acyltransferase 3, Serpin Family E Member 1, MicroRNA 4653, Mucin 12 Cell Surface Associated, N-acetyltransferase 16 (putative), VGF Nerve Growth Factor Inducible, Adaptor Related Protein Complex 1 Sigma 1 Subunit, Procollagen-Lysine 2-oxoglutarate 5-dioxygenase 3, Mucin 17 Cell Surface Associated
rs13101632	chr4; 103034391	*BANK1*	B-Cell Scaffold Protein with Ankyrin Repeats 1

rs8056611	chr16 ; 50767647	*SNX20, NKD1*	Sorting Nexin 20, Naked Cuticle Homolog 1
rs13125328	chr4; 102855110	*BANK1*	B-Cell Scaffold Protein with Ankyrin Repeats 1
rs13114461	chr4; 103284697	--	--
rs9360631	chr6; 73789481	*KCNQ5-AS1, MIR4282, KCNQ5*	Potassium Voltage-Gated Channel Subfamily KQT Member 5 Antisense RNA, MicroRNA 4282, Potassium Voltage-Gated Channel Subfamily KQT Member 5
rs61978021	chr14; 30186991	*PRKD1*	Protein Kinase D1
rs35665782	chr1; 177789483	*SEC16B*	SEC16 Homolog B, Endoplasmic Reticulum Export Factor

Schizophrenia – Primary Biliary Cirrhosis

Schizophrenia		**Primary Biliary Cirrhosis**		**Schizophrenia-Primary Biliary Cirrhosis**	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction
1061529	221482	940715	10001	857	0.67

SNP ID	**Chromosome; Base Position**	**Nearby Gene Symbol**	**Corresponding Gene Names**
rs2697246	chr2; 198037641	*ANKRD44*	Ankyrin Repeat Domain 44
rs4820378	chr22; 39869209	*LOC100506472, RPS19BP1, CACNA1I, SYNGR1, TAB1, MIEF1, MGAT3, ATF4*	(uncharacterized), Ribosomal Protein S19 Binding Protein 1, Calcium Voltage-Gated Channel Subunit Alpha 1 I, Synaptogyrin 1, TGF-Beta Activated Kinase 1 (MAP3K7) Binding Protein 1, Mitochondrial Elongation Factor 1, Mannosyl (Beta-1,4-)-Glycoprotein Beta-1,4-N-Acetylglucosaminyltransferase, Activating Transcription Factor 4
rs4348501	chr8; 8712895	*MFHAS1*	Malignant Fibrous Histiocytoma Amplified Sequence 1

rs3748816	chr1; 2526746	*PLCH2, LOC115110, TNFRSF14, PANK4, TTC34, HES5, MMEL1*	Phospholipase C Eta 2, TNF Receptor Superfamily Member 14 Antisense RNA 1, TNF Receptor Superfamily Member 14, Pantothenate Kinase 4, Tetratricopeptide Repeat Domain 34, Hes Family BHLH Transcription Factor 5, Membrane Metalloendopeptidase Like 1
rs7694724	chr4; 103962532	*CENPE, SLC9B1, BDH2, SLC9B2*	Centromere Protein E, Solute Carrier Family 9 Member B1, 3-Hydroxybutyrate Dehydrogenase 2, Solute Carrier Family 9 Member B2
rs4752926	chr11; 46692870	*CKAP5, SNORD67, MIR5582, ZNF408, ATG13, F2, HARBI1, AMBRA1*	Cytoskeleton Associated Protein 5, Small Nucleolar RNA C/D Box 67, MicroRNA 5582, Zinc Finger Protein 48, Autophagy Related 13, Coagulation Factor II/Thrombin, Harbinger Transposase Derived 1, Autophagy and Beclin 1 Regulator 1
rs2245730	chr21; 44125328	*PDE9A*	Phosphodiesterase 9A
rs731707	chr16; 85980968	*IRF8*	Interferon Regulatory Factor 8
rs9539890	chr13; 34739632	--	--
rs986110	chr8 ; 31450133	*NRG1*	Neuregulin 1

Schizophrenia – Systemic Lupus Erythematous

Schizophrenia		**Systemic Lupus Erythematous**		**Schizophrenia-Systemic Lupus Erythematous**	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction
1061529	221482	1056783	69964	5913	0.72

SNP ID	**Chromosome; Base Position**	**Nearby Gene Symbol**	**Corresponding Gene Names**
rs77053654	chr2; 228646873	*CCL20, SLC19A3, DAW1*	C-C Motif Chemokine Ligand 20, Solute Carrier Family 19 Member 3, Dynein Assembly Factor with WD Repeats 1

rs2910024	chr5; 152528762	--	--
rs12648748	chr4; 162383297	*FSTL5*	Follistatin Like 5
rs4729626	chr7; 100537280	*ACHE, EPHB4, MUC12, TRIP6, SLC12A9, SRRT, UFSP1*	Acetylcholinesterase, EPH Receptor B4, Mucin 12 Cell Surface Associated, Thyroid Hormone Receptor Interactor 6, Solute Carrier Family 12 Member 9, Serrate RNA Effector Molecule, UFM1 Specific Peptidase 1 (Inactive)
rs11227283	chr11; 65499022	*MAP3K11, MIR4690, RELA, AP5B1, MIR4489, OVOL1, PCNX3, SNX32, SIPA1*	Mitogen-Activated Protein Kinase Kinase Kinase 11, MicroRNA 4690, RELA Proto-Oncogene NF-KB Subunit, Adaptor Related Protein Complex 5 Beta 1 Subunit, MicroRNA 4489, Ovo Like Transcriptional Repressor 1, Pecanex-Like Protein 3, Sorting-Nexin 32, Signal-Induced Proliferation-Associated Protein 1
rs55860742	chr8; 11358156	*BLK, FAM167A, LINC00208, FAM167A-AS1*	BLK Proto-Oncogene Src Family Tyrosine Kinase, Family With Sequence Similarity 167 Member A, Long Intergenic Non-Protein Coding RNA 208, Family With Sequence Similarity 167 Member A Antisense RNA
rs10481445	chr8; 11136604	*FAM167A-AS1, TDH, SLC35G5, XKR6*	Family With Sequence Similarity 167 Member A Antisense RNA, L-Threonine Dehydrogenase, Solute Carrier Family 35 Member G5, XK-Related 6
rs907183	chr8; 8729761	*MFHAS1*	Malignant Fibrous Histiocytoma Amplified Sequence 1
rs2921073	chr8; 8307643	*PRAG1*	PEAK1 Related Kinase Activating Pseudokinase 1
rs10821949	chr10; 63811678	*MIR548AV, ARID5B*	MicroRNA 548av, AT-Rich Interaction Domain 5B

Major Depressive Disorder – Hypothyroidism

Major Depressive Disorder		**Hypothyroidism**		**Depression-Hypothyroidism**	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction
967534	7229	1060612	60590	79	0.73

SNP ID	Chromosome; Base Position	Nearby Gene Symbol	Corresponding Gene Names
rs17119564	chr2; 97384728	*CNNM3, CNNM4, FER1L5, KANSL3, LMAN2L, MIR3127*	Cyclin And CBS Domain Divalent Metal Cation Transport Mediator 3/4/5, Fer-1 Like Family Member 5, KAT8 Regulatory NSL Complex Subunit 3, Lectin, Mannose Binding 2 Like, MicroRNA 3127
rs3924194	chr4; 69971092	*UGT2B7, UGT2B11*	UDP Glucuronosyltransferase Family 2 Member B7/B11
rs11683997	chr2; 31290374	*GALNT14*	Polypeptide N-Acetylgalactosaminyltransferase 14
rs2443744	chr5; 118983414	*FAM170A*	Family With Sequence Similarity 170 Member A
rs6584555	chr10; 105299611	*CALHM1, CALHM2, CALHM3, NEURL1, PDCD11, SH3PXD2A*	Calcium Homeostasis Modulator 1/2/3, Neuralized E3 Ubiquitin Protein Ligase 1, Programmed Cell Death 11, SH3 And PX Domains 2A
rs644198	chr1; 226710870	*C1orf95 (STUM1)*	Stum, Mechanosensory Transduction Mediator Homolog
rs7912645	chr10; 116522225	*ABLIM1, FAM160B1*	Actin Binding LIM Protein 1, Family With Sequence Similarity 160 Member B1
rs6476722	chr9; 3866849	*GLIS3, GLIS3-AS1*	GLIS Family Zinc Finger 3, GLIS3 Antisense Transcript 1
rs12938083	chr17; 71270468	*C17orf80, CDC42EP4, COG1, CPSF4L, FAM104A, SDK2*	Chromosome 17 Open Reading Frame 80, CDC42 Effector Protein 4, Component Of Oligomeric Golgi Complex 1, Cleavage And Polyadenylation Specific Factor 4 Like, Family With Sequence Similarity 104 Member A, Sidekick Cell Adhesion Molecule 2
rs1034780	chr7; 82573523	*PCLO*	Piccolo Presynaptic Cytomatrix Protein

Tourette Syndrome - Allergy

Tourette Syndrome		Allergy		Tourette-Allergy	
Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Total QC positive SNPs	QC positive SNPs, $p < 0.005$	Common QC positive SNPs, $p < 0.005$	Proportion with same direction

1041689	45153	1060611	99398	2231	0.68

SNP ID	Chromosome; Base Position	Nearby Gene Symbol	Corresponding Gene Names
rs114341981	chr5; 80564403	*ACOT12, CKMT2, CKMT2-AS1, RASGRF2, RNU5E-1, ZCCHC9*	Acyl-CoA Thioesterase 12, Creatine Kinase, Mitochondrial 2, CKMT2 Antisense RNA 1, Ras Protein Specific Guanine Nucleotide Releasing Factor 2, RNA, U5E Small Nuclear 1, Zinc Finger CCHC-Type Containing 9
rs4552281	chr22; 41714622	CHADL, L3MBTL2, RANGAP1, TEF, ZC3H7B	Chondroadherin Like, L3MBTL2 Polycomb Repressive Complex 1 Subunit, Ran GTPase Activating Protein 1, TEF Transcription Factor, Zinc Finger CCCH-Type Containing 7B
rs10914465	chr1; 32147673	*ADGRB2, COL16A1, HCRTR1, MIR4254, PEF1, TINAGL1*	Adhesion G Protein-Coupled Receptor B2, Collagen Type XVI Alpha 1 Chain, Hypocretin Receptor 1, MicroRNA 4254, Penta-EF-Hand Domain Containing 1, Tubulointerstitial Nephritis Antigen Like 1
rs73231956	chr12; 123791649	*C12orf65, CDK2AP1, KMT5A, MPHOSPH9, SBNO1*	Chromosome 12 Open Reading Frame 65, Cyclin Dependent Kinase 2 Associated Protein 1, Lysine Methyltransferase 5A, M-Phase Phosphoprotein 9, Strawberry Notch Homolog 1
rs115172926	chr1; 190503420	*BRINP3, LOC440704*	BMP/Retinoic Acid Inducible Neural Specific 3, Uncharacterized LOC440704
rs71358686	chr18; 63407371	*CDH7*	Cadherin 7
rs146264265	ch17; 47321968	*ABI3, B4GALNT2, FLJ40194, GNGT2, PHOSPHO1, ZNF652*	ABI Family Member 3, Beta-1,4-N-Acetyl-Galactosaminyltransferase 2, Uncharacterized FLJ40194, G Protein Subunit Gamma Transducin 2, Phosphoethanolamine/Phosphocholine Phosphatase, Zinc Finger Protein 652
rs1109934	chr16; 79037784	*WWOX*	WW Domain Containing Oxidoreductase
rs13217636	chr6; 149205163	*UST, UST-AS1*	Uronyl 2-Sulfotransferase, UST Antisense RNA 1
rs17155933	chr11; 611802	*CDHR5, DEAF1, DRD4, EPS8L2, HRAS, IRF7, LMNTD2, LOC143666, LRRC56, MIR210, MIR210HG, PHRF1, RASSF7,*	Cadherin Related Family Member 5, DEAF1, Transcription Factor, Dopamine Receptor D4, EPS8 Like 2, HRas Proto-Oncogene, GTPase, Interferon Regulatory Factor 7, Lamin Tail Domain Containing 2, Uncharacterized LOC143666, Leucine Rich Repeat

	SCT, TMEM80	Containing 56, MicroRNA 210/HostGene, PHD And Ring Finger Domains 1, Ras Association Domain Family Member 7, Secretin, Transmembrane Protein 80

Figure 1

	System Lupus Erythematous	Tuberculosis Susceptability	C-Reative Protein	Autoimmune Hepatitis	Type 1 Diabetes	Rheumatoid Arthrtitis	Eosinophilic Esophagitis	Atopic Dermatitis	Multiple Sclerosis	Childhood Ear Infection	Allergy (Any)	Asthma	Systemic Sclerosis	Hypothyroidism	Celiac Disease	Crohn's Disease	Psoriasis	Primary Biliary Cirrhosis	Ulcerative Colitis
Cigarettes per Day	0.02	0.51*	0.37**	−0.08	0.06	0.13	0.05	0.25	0.32	0.01	0.04	−0.06	0.02	0.05	0.04	0.19*	0.21	0.14	0.09
Cigarettes (Ever−Smoked)	0.1	0.28*	0.31**	0.35	−0.04	0.17**	0.2	−0.02	−0.06	0.11	−0.01	0.01	0.17	0.13*	−0.09	−0.02	0.1	0.1	0
Major Depression	0.08	0.07	0.21*	−0.29	−0.09	−0.07	−0.01	0.04	0.12	0.17*	0.09	0.15	0.46	0.33**	0.2	−0.01	0.01	−0.02	0.16
Autism	−0.26*	−0.05	−0.01	0.46	0.16	−0.09	−0.19	−0.01	−0.28	0.12	0.01	−0.04	0.02	0.16	−0.03	−0.07	−0.08	−0.06	0.01
Bipolar Disorder	0.06	−0.06	0.01	0.03	−0.06	−0.15*	−0.06	0.04	0.13	0.1	−0.11*	0.01	−0.11	0.11	0.31**	0.21**	0.24*	0.19*	0.23**
Schizophrenia	0.14**	0.19*	−0.05	−0.07	−0.02	−0.01	0.11	0.03	0.05	0.04	0.03	0.06	0.12	0.08	0.09	0.12**	0.1*	0.15**	0.13**
OCD	−0.04	−0.04	−0.18*	−0.05	−0.32*	−0.16*	−0.09	−0.01	−0.2	0.03	−0.08	0.02	−0.31	−0.14	0.43*	0.06	0.02	0.15	0.18
Anxiety−Spectrum	0.09	0.11	−0.07	0.67	0.17	0.07	0.07	0.04	0.19	0.2	0.23	0.25	−0.21	0.3*	0.11	0.09	0.07	0.17	0.17
Tourette Syndrome	0.12	0.13	0.03	0.02	−0.05	0.08	0.08	−0.08	0.2	0	0.24**	0.12	0.08	0.08	0.02	0.03	0.25*	0.08	0.04
ADHD	0.12	0.24	0.34*	0.27	0.09	−0.02	−0.06	0.13	−0.4	0.18	−0.05	0	−0.24	0.11	−0.14	0.14	0.1	0	0.2
Alzhimer's Disease	0.01	0.1	0.06	−0.23	−0.08	−0.13	0.33	0.11	−0.12	−0.09	−0.18*	−0.07	0.44	−0.11	0.02	−0.09	−0.02	−0.21	−0.15
Parkinson's Disease	−0.06	0.03	−0.06	−0.34	0.09	−0.04	−0.24*	−0.04	−0.02	−0.01	−0.06	−0.09	−0.08	−0.09	0.13	−0.02	−0.09	0.04	−0.02
Epilepsy (Partial)	0.72*	−0.24	0.15	−0.58	−0.13	0.21	−0.58	0.42	0.35	0.15	−0.09	0.11	0.47	−0.04	−0.39	0.38	0.36	0.52	0.39

Magnitude of Correlation

-1 0 1

Figure 2

	System Lupus Erythematous	Rheumatoid Arthrtitis	Primary Biliary Cirrhosis	Systemic Sclerosis	Multiple Sclerosis	Crohn's Disease	Ulcerative Colitis	Autoimmune Hepatitis	Hypothyroidism	Type 1 Diabetes	Celiac Disease	Asthma	Allergy (Any)	Atopic Dermatitis	Eosinophilic Esophagitis	Childhood Ear Infection	C−Reative Protein	Tuberculosis Susceptability	Psoriasis
Psoriasis	0.14	0.17*	0.27**	0.1	0.23	0.34**	0.39**	0.3	0.13	0.12	0.23**	−0.05	−0.01	0.05	0.21	0.01	0.21*	0	
Tuberculosis Susceptability	0.14	0.18	0.26	0.11	0.01	0.23*	0.34*	−0.32	0.17	0.04	0.11	0.06	0.22**	0.1	0.18	−0.11	−0.1		0
C−Reative Protein	0.05	−0.03	0.14	−0.07	0.24	0.11	−0.12	0.31	0	−0.03	0.01	0.17**	0.13**	0.23*	0.12	0.06		−0.1	0.21*
Childhood Ear Infection	0	0.07	0.02	0.01	0.07	0.03	0	−0.16	0.14**	0.02	0.16*	0.15**	0.22**	0.02	−0.02		0.06	−0.11	0.01
Eosinophilic Esophagitis	0.02	−0.03	0.07	−0.49	0.21	−0.13	−0.07	0.7	0.2	−0.13	0.1	−0.01	−0.22*	−0.01		−0.02	0.12	0.18	0.21
Atopic Dermatitis	−0.02	−0.06	0.05	0.02	0.16	0.19*	0.08	−0.03	−0.16	−0.21	0.22	0.39**	0.25**		−0.01	0.02	0.23*	0.1	0.05
Allergy (Any)	−0.01	0.04	0.05	−0.07	0.12	0.06	0.04	−0.05	0.2**	0.02	0.19**	0.79**		0.25**	−0.22*	0.22**	0.13**	0.22**	−0.01
Asthma	−0.09	−0.05	0.04	0.04	0.13	−0.02	−0.03	−0.04	0.07	−0.01	0.15		0.79**	0.39**	−0.01	0.15**	0.17**	0.06	−0.05
Celiac Disease	0.21*	0.24**	0.03	0.39*	−0.09	0.27**	0.23*	0.27	0.38**	0.32**		0.15	0.19**	0.22	0.1	0.16*	0.01	0.11	0.23**
Type 1 Diabetes	0.25	0.41**	0.11	0.07	0.12	−0.02	0.19*	0.44*	0.4**		0.32**	−0.01	0.02	−0.21	−0.13	0.02	−0.03	0.04	0.12
Hypothyroidism	0.12	0.34**	0.24**	0.03	−0.09	−0.01	0.07	0.11		0.4**	0.38**	0.07	0.2**	−0.16	0.2	0.14**	0	0.17	0.13
Autoimmune Hepatitis	0.23	0.58**	0.64*	0.08	0.74	−0.01	0.26		0.11	0.44*	0.27	−0.04	−0.05	−0.03	0.7	−0.16	0.31	−0.32	0.3
Ulcerative Colitis	0.14	0.13*	0.32**	0.17	0.64**	0.71**		0.26	0.07	0.19*	0.23*	−0.03	0.04	0.08	−0.07	0	−0.12	0.34*	0.39**
Crohn's Disease	0.12	0.09	0.24**	−0.13	0.32*		0.71**	−0.01	−0.01	−0.02	0.27**	−0.02	0.06	0.19*	−0.13	0.03	0.11	0.23*	0.34**
Multiple Sclerosis	0.69**	0.44**	0.58**	0.14		0.32*	0.64**	0.74	−0.09	0.12	−0.09	0.13	0.12	0.16	0.21	0.07	0.24	0.01	0.23
Systemic Sclerosis	0.72**	0.43**	>0.95**		0.14	−0.13	0.17	0.08	0.03	0.07	0.39*	0.04	−0.07	0.02	−0.49	0.01	−0.07	0.11	0.1
Primary Biliary Cirrhosis	0.62**	0.27**		>0.95**	0.58**	0.24**	0.32**	0.64*	0.24**	0.11	0.03	0.04	0.05	0.05	0.07	0.02	0.14	0.26	0.27**
Rheumatoid Arthrtitis	0.46**		0.27**	0.43**	0.44**	0.09	0.13*	0.58**	0.34**	0.41**	0.24**	−0.05	0.04	−0.06	−0.03	0.07	−0.03	0.18	0.17*
System Lupus Erythematous		0.46**	0.62**	0.72**	0.69**	0.12	0.14	0.23	0.12	0.25	0.21*	−0.09	−0.01	−0.02	0.02	0	0.05	0.14	0.14

Magnitude of Correlation

-1 0 1