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Genome-wide Pleiotropy Between Parkinson Disease and Autoimmune Diseases

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IMPORTANCE Recent genome-wide association studies (GWAS) and pathway analyses supported long-standing observations of an association between immune-mediated diseases and Parkinson disease (PD). The post-GWAS era provides an opportunity for cross-phenotype analyses between different complex phenotypes.

OBJECTIVES To test the hypothesis that there are common genetic risk variants conveying risk of both PD and autoimmune diseases (ie, pleiotropy) and to identify new shared genetic variants and their pathways by applying a novel statistical framework in a genome-wide approach.

DESIGN, SETTING, AND PARTICIPANTS Using the conjunction false discovery rate method, this study analyzed GWAS data from a selection of archetypal autoimmune diseases among 138 511 individuals of European ancestry and systemically investigated pleiotropy between PD and type 1 diabetes, Crohn disease, ulcerative colitis, rheumatoid arthritis, celiac disease, psoriasis, and multiple sclerosis. NeuroX data (6927 PD cases and 6108 controls) were used for replication. The study investigated the biological correlation between the top loci through protein-protein interaction and changes in the gene expression and methylation levels. The dates of the analysis were June 10, 2015, to March 4, 2017.

MAIN OUTCOMES AND MEASURES The primary outcome was a list of novel loci and their pathways involved in PD and autoimmune diseases.

RESULTS Genome-wide conjunctional analysis identified 17 novel loci at false discovery rate less than 0.05 with overlap between PD and autoimmune diseases, including known PD loci adjacent to *GAK*, *HLA-DRB5*, *LRRK2*, and *MAPT* for rheumatoid arthritis, ulcerative colitis and Crohn disease. Replication confirmed the involvement of *HLA*, *LRRK2*, *MAPT*, *TRIM10*, and SE*TD1A* in PD. Among the novel genes discovered, *WNT3*, *KANSL1*, *CRHR1*, *BOLA2*, and *GUCY1A3* are within a protein-protein interaction network with known PD genes. A subset of novel loci was significantly associated with changes in methylation or expression levels of adjacent genes.

CONCLUSIONS AND RELEVANCE The study findings provide novel mechanistic insights into PD and autoimmune diseases and identify a common genetic pathway between these phenotypes. The results may have implications for future therapeutic trials involving anti-inflammatory agents.

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Supplemental content

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Emerging evidence suggests a substantial genetic component underlying Parkinson disease (PD).[1,2] Linkage analysis and genome-wide association studies (GWAS) confirmed the role of genes involved in familial and sporadic forms of PD.[3,4] Genome-wide association studies are able to identify variants with strong genetic effects; however, true polygenic risk alleles with weaker evidence for association may be overlooked.[5,6] The estimated heritability in PD GWAS substantially increases when weak effect loci are also considered,[2] further emphasizing the involvement of a large proportion of genetic risk variants below standard genome-wide significance thresholds. Moreover, these studies[2,5] nominate novel loci that have not been implicated in disease pathogenesis.

The association between inflammation and neurodegenerative diseases has long been observed in Alzheimer disease (AD),[7,8] amyotrophic lateral sclerosis, and, highlighted in this work, PD.[9-11] In an epidemiological study[12] in Sweden, 6 of 33 studied types of autoimmune disorders were identified with an increased risk of developing PD, including amyotrophic lateral sclerosis, hyperthyroidism, hypothyroidism, multiple sclerosis, pernicious anemia, and polymyalgia rheumatica, although this finding was not observed in a population-based case-control study[13] from Denmark. The association between PD and MS has been confirmed in other studies.[14-16] Furthermore, in clinical studies,[17,18] regular users of nonsteroidal anti-inflammatory drugs were found to have lowered risk of PD. It is still not clear whether immune dysfunction has an important role in early stages of PD or is simply the end product of a neuronal degeneration process.[19]

The occurrence of PD in patients with autoimmune diseases, or vice versa, could reflect genetically determined factors influencing both lipid metabolism and immune disorders that cannot be elucidated by epidemiological and clinical studies alone.[19] Genome-wide–based pathway analyses in PD supported the association between PD and autoimmune diseases.[5] Early independent studies showed that at least one gene, *LRRK2*, is statistically significant in both PD[20] and Crohn disease.[21] The results of a recently published study[22] suggested that, along with known PD loci *USP25*, *HLA-DRA*, and *LRRK2,* additional genetic factors are present that contribute to genetic comorbidity shared by PD and CD. A systematic study is needed to decipher whether shared polygenetic risk variants (ie, genetic pleiotropy) exist between PD and autoimmune diseases and whether particular molecular biological pathways are involved.

An approach combining GWAS data from 2 disorders with shared pathways can significantly increase the power to discover novel loci and partly reveal the missing heritability in GWAS. Our group recently developed a novel statistical framework to identify single-nucleotide polymorphisms (SNPs) exhibiting genetic pleiotropy between multiple phenotypes and applied it to identify pleiotropy between AD and autoimmune diseases.[23] This approach also identified novel loci between schizophrenia and cardiovascular diseases,[24] psychiatric disorders,[25] and neurological diseases.[26]

Herein, we applied this approach to investigate the potentially shared genetic basis for PD and autoimmune diseases. Autoimmune diseases were selected based on available large GWAS, including PD, type 1 diabetes, CD, ulcerative colitis, rheumatoid arthritis celiac disease, psoriasis, and multiple sclerosis.[27-33] We used conditional and conjunction false discovery rate analyses to define SNPs associated with both groups of phenotypes (pleiotropic SNPs).

Key Points

Question Are there genome-wide genetic risk factors for Parkinson disease that are shared with pathways of autoimmune diseases?

Findings In this study of combined genome-wide association data with control replication, we identified 17 novel genetic loci shared between Parkinson disease and type 1 diabetes, Crohn disease, ulcerative colitis, rheumatoid arthritis, celiac disease, psoriasis, and multiple sclerosis.

Meaning Our findings identify a common genetic pathway between Parkinson disease and autoimmune diseases and suggest that the immune system influences Parkinson disease pathogenesis.

Methods

Participant Samples

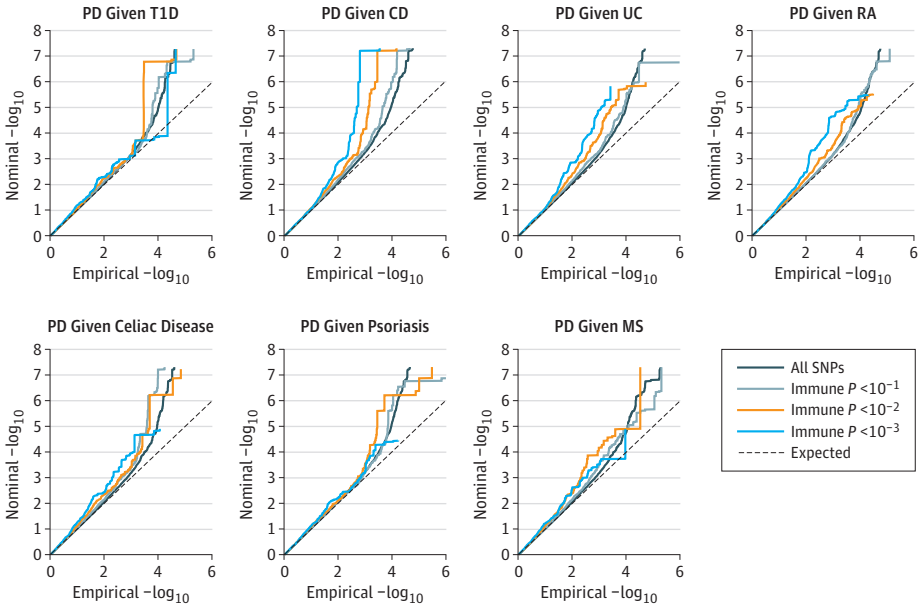
Using the conjunction false discovery rate method, this study analyzed GWAS data from a selection of archetypal autoimmune diseases among 138 511 individuals of European ancestry and systemically investigated pleiotropy between PD and type 1 diabetes, Crohn disease, ulcerative colitis, RA, celiac disease, psoriasis, and multiple sclerosis. Genome-wide association studies summary statistic *P* values and *z* scores were obtained from the studies of PD,[4] CD,[27] ulcerative colitis,[28] RA,[29] type 1 diabetes,[30] celiac disease,[31] psoriasis,[32] and multiple sclerosis[33] (eTable 1 in the Supplement). Details of the inclusion criteria and phenotype characteristics of the GWAS are described in the original publications. The relevant institutional review boards or ethics committees approved the research protocol of the individual GWAS used in the present analysis, and all participants gave written informed consent. The dates of the analysis were June 10, 2015, to March 4, 2017. All *P* values were corrected for inflation using a genomic control procedure.[24,25]

Statistical Analysis

Conditional Quantile-Quantile Plots

The quantitative estimates of true associations and statistical enrichment were calculated from the distributions of summary statistics.[34,35] We plotted conditional quantile-quantile (Q-Q) plots for a primary phenotype by filtering SNPs based on their level of association with a secondary phenotype. Pleiotropic enrichment between PD and an autoimmune disorder was evident if the degree of deflection of PD *P* values from the expected null line produced successive leftward deflection when conditioned on an autoimmune disease.[24,25,36] To control for linkage disequilibrium (LD), we performed a random pruning procedure.[37]

Figure 1. Pleiotropic Enrichment of Parkinson Disease (PD) Conditioned on Association *P* Values of Autoimmune Diseases



Conditional quantile-quantile plots (nominal vs empirical $-\log_{10}$ *P* values) are calculated from single-nucleotide polymorphism (SNP) populations of varying degrees of association with autoimmune diseases. Each population is composed of SNPs that pass certain significance of association (type 1 diabetes [T1D], Crohn disease [CD], ulcerative colitis [UC], rheumatoid arthritis [RA], celiac disease, psoriasis, and multiple sclerosis [MS]) at $P \leq 1$ (All SNPs), $P < 10^{-1}$, $P < 10^{-2}$, and $P < 10^{-3}$. All *P* values have been corrected for genomic inflation. Dotted lines indicate the expected line under the null hypothesis, and leftward deflection shows increasing degrees of enrichment.

Conditional and Conjunction False Discovery Rate

We defined conditional false discovery rate, denoted by $FDR_{trait1|trait2}$, as the posterior probability that a given SNP is null for the first trait given that the *P* values in both traits are smaller than their observed *P* values.[24,25] We defined conjunction false discovery rate, denoted by $FDR_{trait1\&trait2}$, as the posterior probability that a given SNP is null for both phenotypes simultaneously given that the *P* values for both traits are as small or smaller than the observed *P* values. We obtained a conservative estimate of conjunction false discovery rate by taking the minimum of $FDR_{trait1|trait2}$ and $FDR_{trait2|trait1}$. To control for LD, we applied a random pruning procedure.[37] Detailed information on the methods can be found in prior studies.[24,25]

NeuroX Data

We replicated the top conjunction false discovery rate loci, highly associated with both PD and autoimmune disorders, in a second independent PD data set. The data set was generated with the NeuroX exome array,[3,38] including 6927 PD cases and 6108 controls. Variants passing standard quality control (Hardy-Weinberg equilibrium $P > 1 \times 10^{-6}$ and maximum missingness rate of 5%) were tested for association with PD with a logistic model correcting for the first 4 multidimensional scaling components and sex.

Gene Expression and Methylation Changes

We determined the regional methylation and expression patterns within ±1 megabases of 103 SNPs of interest. We investigated frontal cortex and cerebellum microarray data from the North American Brain Expression Consortium (NABEC)[39] and the United Kingdom Brain Expression Consortium (UKBEC)[40] of 396 European samples without neuropathological evidence of disease. We also accessed a second expression quantitative trait loci (eQTL) data set based on cap analysis gene expression profiling technique of the frontal cortex of 119 NABEC samples.[41] A total of 98 variants (3 not testable) and 83 variants (20 not testable) were studied for the microarray-based and cap analysis gene expression–based data sets, respectively. For details of these procedures, see the eMethods in the Supplement.

Genetic Correlations Among Implicated Loci

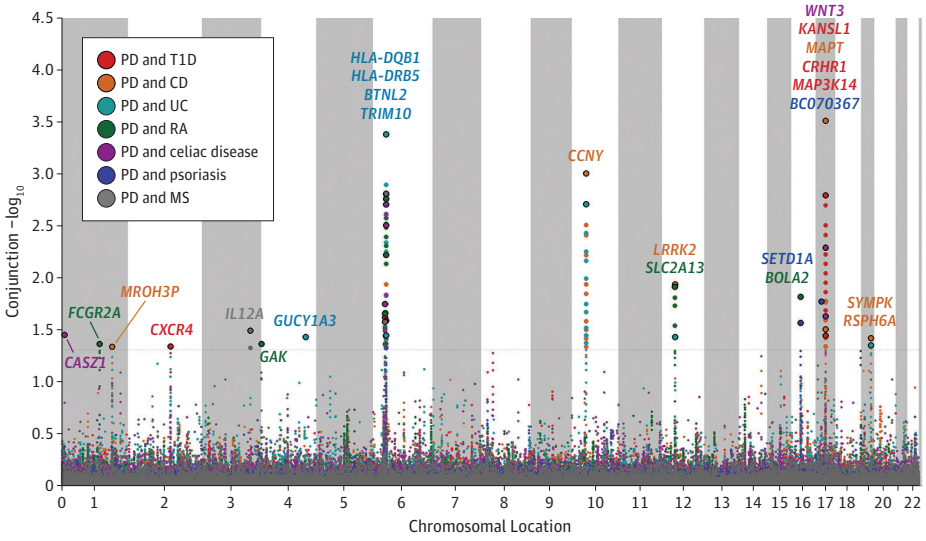
To investigate the genetic relatedness among implicated SNPs, we performed protein-protein interaction analyses using STRING version 10.[42] The input consisted of novel loci as identified in pleiotropic analyses. We considered total scores above 0.400 (medium confidence) that correspond to the combination of the following 4 different scores: coexpression, experimental, knowledge, and text mining.

Results

Significant Genetic Overlap Between PD and Autoimmune Diseases

Conditional Q-Q plots for PD conditioned on association *P* values of autoimmune diseases showed strong enrichment for Crohn disease (**Figure 1**). Successive leftward shifts for decreasing nominal PD *P* values indicated that the proportion of non-null SNPs in PD increased considerably with higher levels of association with an autoimmune phenotype. For example, when conditioned on CD, the proportion of SNPs reaching a significance of PD $P < 10^{-5}$ in the category Crohn disease $P < 10^{-3}$ is 20 times greater than when all SNPs were examined (Figure 1 and eFigure 1 in the Supplement). Similar enrichment was found with ulcerative colitis and RA, and weaker

Figure 2. Conjunctional False Discovery Rate Manhattan Plot of $-\log_{10}$ Values for the Associated Autoimmune Phenotypes



All single-nucleotide polymorphisms without pruning are plotted: enlarged points represent significant single-nucleotide polymorphisms with conjunction false discovery rate less than 0.05, and small points represent the nonsignificant single-nucleotide polymorphisms. The most significant single-nucleotide polymorphism in each linkage disequilibrium block is marked with black circles and annotated with its closest gene, showing the localization of 17 common loci (some loci may have multiple genes) between Parkinson disease and autoimmune diseases listed in Table 1. CD indicates Crohn disease; MS, multiple sclerosis; RA, rheumatoid arthritis; T1D, type 1 diabetes; and UC, ulcerative colitis.

enrichment was found with celiac disease and multiple sclerosis. The enrichment remained after removing the major histocompatibility complex and *MAPT* regions (eFigure 2 in the Supplement).

Shared Susceptibility Loci for PD and Autoimmune Disorders

We performed a conjunction false discovery rate analysis and visualized the pleiotropic loci between PD and autoimmune diseases in a Manhattan plot (**Figure 2**). Based on conjunction false discovery rate less than 0.05, we detected 17 independent pleiotropic loci for the 7 autoimmune diseases (**Table 1**). Nine loci remained after excluding the major histocompatibility complex and *MAPT* regions (eTable 2 in the Supplement). Of the 17 loci, the directions of PD effect given by *z* scores were mostly the same with Crohn disease, ulcerative colitis, and celiac disease and opposite with rheumatoid arthritisand psoriasis (Table 1 and eTable 3 in the Supplement). The conjunction false discovery rate analyses over multiple autoimmune phenotypes showed overlapping susceptibility loci between Crohn disease and ulcerative colitis and demonstrated some overlap between ulcerative colitis, RA, celiac disease, and multiple sclerosis (eFigure 3 in the Supplement). We were able to replicate 5 loci in our in-house independent NeuroX data at $P < .05$ (Table 1). In addition to the previously published *HLA*, *LRRK2*, and *MAPT* associations,[4] we also identified 2 new loci adjacently located to *TRIM10* and SE*TD1A*.

Functional Interpretation of Shared Susceptibility Loci

A total of 103 associated variants resulting from conditional false discovery rate less than 0.01 and conjunction false discovery rate less than 0.05 were tested for being a methylation QTL (methQTL) or an eQTL. **Table 2** summarizes the significant methQTL and eQTL in the brain in which the affected gene is implied by the literature (see the Discussion section) to have a function in the immune system. As expected, most hits are for variants located in the *HLA* locus and *MAPT* locus, both of which have been implicated in PD.[3,37,43-45] Within the NABEC data set, 31 of the 103 variants were shown to have a significant effect on the methylation status of 16 genes (eTable 4 in the Supplement). Likewise, 29 variants were significantly associated with changes in expression of 14 genes in the NABEC, UKBEC, or in-house eQTL data set (eTable 5 in the Supplement).

In addition to the exploration for methQTL and eQTL within the described data sets, we compared a recent elaborate eQTL study[46] of multiple immune cell types (B cells, CD4 T cells, CD8 T cells, monocytes, and neutrophils) in patients with inflammatory bowel disease and healthy controls. Our 103 candidate SNPs intersected with those authors' significant (false discovery rate <0.05) eQTL results. eTable 6 in the Supplement lists significant eQTL for 10 variants influencing the expression of 8 genes, 5 of which (*DGKQ*, *IDUA*, *BST1*, *CD38*, and *SNCA*) have previously been discussed in the context of PD.[4] These SNPs could contribute to PD risk through immune mechanisms by regulating the gene expression of these PD-related genes in these immune-specific cells. Six immune eQTL that regulate the expression of 2 genes (*DGKQ* and *DMPK*) were also observed in the brain eQTL and methQTL data, affirming the immune-related involvement of these genes in PD.

Shared Biological Pathways Between Significant Risk Loci

Using functional gene networks and protein interaction networks, the connectivity among the loci in the combined network increased considerably compared with the networks represented by pleiotropic and PD loci (**Figure 3**). The network analyses revealed interaction between the 17 loci identified in our study with nodes defined by PD loci (eg, *GUCY1A3*, *KANSL1*, *CRHR1*, *WNT3*, and *BOLA2*). This finding

Table 1. Seventeen Independent Pleiotropic Loci in Parkinson Disease (PD) and Autoimmune Diseases With Conjunction False Discovery Rate (FDR) Less Than 0.05[a]

Locus	SNP	Gene	OMIM Accession No.	Chromosome	Human Genome Build 19 Position	PD *P* Value	PD FDR	Minimum Conjunction FDR	Phenotype	Direction	NeuroX *P* Value	PDGene Meta-analysis *P* Value
1	rs616519	*CASZ1*	609895	1	10,768,002	2.03E-04	2.03E-01	3.59E-02	Celiac disease	Same	NA	<.05
2	rs7515174	*FCGR2A*	146790	1	161,476,949	2.68E-04	2.28E-01	4.38E-02	RA	Not available	NA	<.05
3	rs1572789	*MROH3P*	NA	1	200,932,305	4.79E-04	3.24E-01	4.68E-02	CD	Same	NA	<.05
4	rs2011946	*CXCR4*	162643	2	136,817,616	2.44E-04	2.28E-01	4.64E-02	T1D	Opposite	NA	6.20E-07
5	rs2243123	*IL12A*	161560	3	159,709,651	2.98E-04	2.57E-01	3.30E-02	MS	Opposite	NA	<.05
6	rs3755963	*GAK*	602052	4	894,255	2.36E-05	5.77E-02	4.38E-02	RA	Opposite	NA	1.41E-10
7	rs2625276	*GUCY1A3*	139396	4	156,600,197	6.47E-05	1.06E-01	3.76E-02	UC	Same	NA	<.05
8	rs9261531	*TRIM10*	605701	6	30,120,268	1.11E-04	1.38E-01	1.81E-02	UC	Opposite	NA	<.05
8	rs2022065	*TRIM10*	605701	6	30,121,460	2.25E-04	2.28E-01	2.71E-02	MS	Same	NA	<.05
8	rs9261535	*TRIM10*	605701	6	30,127,323	1.36E-04	1.58E-01	1.82E-02	Celiac disease	Same	.047	<.05
9	rs9268480	*BTNL2*	606000	6	32,363,844	5.60E-06	1.66E-02	1.29E-03	UC	Same	NA	<1.00E-04
9	rs3763312	*BTNL2*	606000	6	32,376,348	1.25E-05	3.51E-02	2.00E-03	Celiac disease	Same	NA	1.20E-11
9	rs28366337	*HLA-DRB5*	604776	6	32,564,699	8.53E-05	1.21E-01	1.51E-02	UC	Same	NA	NA
9	rs17425622	*HLA-DRB5*	604776	6	32,571,961	1.43E-06	6.07E-03	4.26E-04	UC	Same	1.37E-05	8.07E-05
9	rs4642516	*HLA-DQB1*	604305	6	32,657,543	2.69E-04	2.28E-01	3.64E-02	UC	Same	NA	<.05
9	rs9275328	*HLA-DQB1*	604305	6	32,666,822	2.18E-05	4.91E-02	3.17E-03	Celiac disease	Same	NA	1.65E-07
9	rs9275356	*HLA-DQB1*	604305	6	32,667,850	1.19E-05	3.51E-02	1.59E-03	CD	Not available	NA	2.52E-12
10	rs12242110	*CCNY*	612786	10	35,535,695	8.71E-06	2.44E-02	1.01E-03	CD	Same	.339	<1.00E-04
11	rs7960662	*SLC2A13*	611036	12	40,479,067	2.33E-05	5.77E-02	1.24E-02	RA	Same	NA	<.05
12	rs17467164	*LRRK2*	609007	12	40,814,197	1.06E-04	1.38E-01	1.17E-02	CD	Same	.030	1.07E-07
13	rs4787495	*BOLA2*	613182	16	30,165,725	3.50E-06	1.12E-02	1.54E-02	RA	Opposite	NA	<.05
14	rs11640961	*SETD1A*	611052	16	30,979,818	3.99E-05	7.89E-02	2.75E-02	Psoriasis	Opposite	2.81E-06	3.07E-07
15	rs1975974	*BC070367*	601519	17	21,707,060	5.15E-05	9.16E-02	1.72E-02	Psoriasis	Same	NA	>.05
16	rs2867316	*MAP3K14*	604655	17	43,376,447	1.83E-04	2.03E-01	3.66E-02	T1D	Same	.967	8.29E-10
16	rs393152	*CRHR1*	122561	17	43,719,143	1.31E-18	6.84E-07	9.18E-03	T1D	Same	.074	<5.00E-08
16	rs1467967	*MAPT*	157140	17	43,986,179	6.07E-08	3.38E-04	3.15E-04	CD	Same	NA	<5.00E-08
16	rs17652121	*MAPT*	157140	17	44,073,973	3.41E-18	6.84E-07	3.18E-02	CD	Same	.034	<5.00E-08
16	rs17661428	*KANSL1*	612452	17	44,208,144	3.60E-15	6.84E-07	1.64E-03	T1D	Same	NA	<5.00E-08
16	rs2074404	*WNT3*	165330	17	44,865,439	5.27E-11	6.84E-07	5.22E-03	Celiac disease	Same	.599	<5.00E-08
17	rs12463359	*RSPH6A*	607548	19	46,304,585	9.31E-06	2.94E-02	3.86E-02	CD	Same	NA	<.05
17	rs10500292	*SYMPK*	602388	19	46,327,933	8.82E-06	2.44E-02	3.86E-02	CD	Same	NA	<.05

Abbreviations: CD, Crohn disease; MS, multiple sclerosis; NA, not applicable; RA, rheumatoid arthritis; SNP, single-nucleotide polymorphism; T1D, type 1 diabetes; and UC, ulcerative colitis.

[a] Listed are independent gene loci with SNPs with conjunction FDR less than 0.05 in both PD and the associated autoimmune disease represented by the SNP with the minimum conjunction FDR in each linkage disequilibrium block (r^2<0.200). For comparison, the conjunction FDR values for each identified SNP are listed for all phenotypes, as well as the minimum conjunction FDR across all phenotypes. One SNP is listed for the major histocompatibility complex region on chromosome 6. Nine of the top loci were available for association testing within the NeuroX data set. Meta-analysis association *P* values in the study by Nalls et al[3] were obtained from publicly available PDGene (pdgene.org).

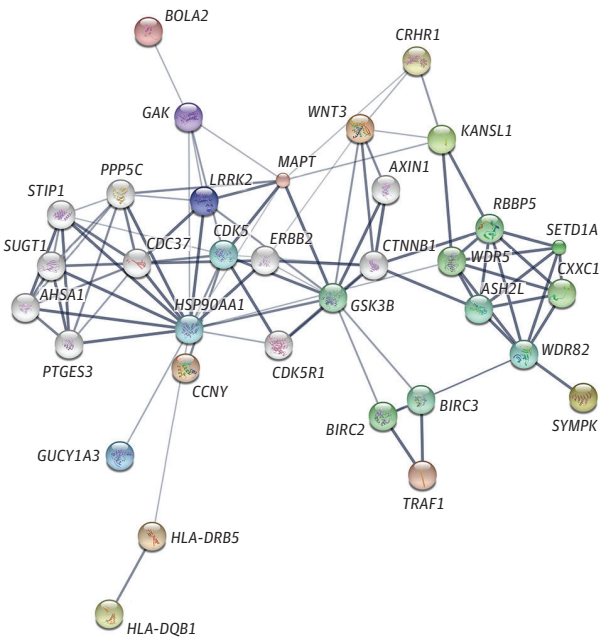
Table 2. Overview of Expression Quantitative Trait Loci (eQTL) and Methylation Effects Related to the Immune System

SNP	Chromosome	Human Genome Build 19 Position	Major Allele, Minor Allele	maf Data Set[a]	European maf 1000G	Assay	Tissue	Trait	Gene	Effect Size of Minor Allele	P Value
rs7515174	1	161,476,949	C, G	0.15	0.14	CpG	Frontal cortex	cg24422489	*FCGR2A*	−0.603	8.58×10^{-7}
rs9261531	6	30,120,268	C, T	0.23	0.25	CpG	Cerebellum	cg00679556	*TRIM31*	0.467	1.29×10^{-6}
				0.23	0.25	CpG	Frontal cortex	cg20879959	*HLA-A*	−0.458	2.08×10^{-6}
rs9261535	6	30,127,323	G, A	0.23	0.23	CpG	Cerebellum	cg00679556	*TRIM31*	0.472	1.27×10^{-6}
				0.23	0.23	CpG	Frontal cortex	cg20879959	*HLA-A*	−0.453	3.20×10^{-6}
rs9268480	6	32,363,844	C, T	0.27	0.27	eQTL C	Frontal cortex	L2 None chr6 − 32557582	*HLA-DRB1*	−0.485	1.44×10^{-5}
rs4642516	6	32,657,543	T, G	0.52	0.48	CpG	Cerebellum	cg25764570	*HLA-DRA*	−0.352	3.85×10^{-5}
rs1059504	17	43,472,321	G, A	0.43	0.49	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	−0.300	5.67×10^{-5}
rs11012	17	43,513,441	C, T	0.23	0.19	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.599	1.18×10^{-16}
rs393152	17	43,719,143	A, G	0.27	0.24	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.610	1.85×10^{-22}
rs8072451	17	43,893,716	C, T	0.26	0.24	eQTL M	Cerebellum	ILMN 1709549	*PLEKHM1*	−0.507	8.62×10^{-10}
rs2301689	17	43,935,838	C, T	0.33	0.32	CpG	Frontal cortex	cg07321605	*NSF*	−0.442	4.65×10^{-6}
rs17652121	17	44,073,973	T, C	0.25	0.24	eQTL M	Cerebellum	ILMN 1709549	*PLEKHM1*	−0.499	9.54×10^{-10}
				0.25	0.24	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.569	1.27×20^{-19}
rs4792827	17	44,131,305	C, T	0.44	0.41	CpG	Cerebellum	cg07321605	*NSF*	−0.347	8.82×10^{-5}
rs17661428	17	44,208,144	C, G	0.25	0.24	eQTL M	Cerebellum	ILMN 1709549	*PLEKHM1*	−0.759	2.50×10^{-5}
rs183211	17	44,788,310	G, A	0.27	0.26	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.566	1.32×10^{-21}
				0.27	0.26	eQTL C	Frontal cortex	L2 None chr17 + 43861684	*CRHR1*	0.169	6.21×10^{-5}
rs169201	17	44,790,203	A, G	0.24	0.22	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.615	6.57×10^{-5}
				0.24	0.22	eQTL C	Frontal cortex	L2 None chr17 + 43861684	*CRHR1*	0.192	1.11×10^{-5}
rs142167	17	44,795,234	A, G	0.27	0.26	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.566	1.32×10^{-5}
				0.27	0.26	eQTL C	Frontal cortex	L2 None chr17 + 43861684	*CRHR1*	0.169	6.21×10^{-5}
rs199533	17	44,828,931	G, A	0.24	0.22	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.603	1.95×10^{-23}
				0.24	0.22	eQTL C	Frontal cortex	L2 None chr17 + 43861684	*CRHR1*	0.197	5.61×10^{-6}
rs199515	17	44,856,641	C, G	0.23	0.22	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.616	8.35×10^{-23}
rs2074404	17	44,865,439	T, G	0.26	0.27	eQTL C	Frontal cortex	L2 None chr17 + 44270964	*CRHR1*	0.562	3.08×10^{-20}

Abbreviations: CAGE, cap analysis gene expression; CpG, methylation assay; eQTL C, eQTL assay based on CAGE expression data; eQTL M, eQTL assay based on microarray expression data; maf, minor allele frequency; SNP, single-nucleotide polymorphism; Trait, probe name of methylation or expression assay.

[a] In North American Brain Expression Consortium (NABEC), United Kingdom Brain Expression Consortium (UKBEC), or CAGE data set.

Figure 3. Functional Gene Network for Novel Pleiotropic Loci From the Present Analysis and Previously Confirmed Parkinson Disease



The protein-coding genes closest to the most associated single-nucleotide polymorphism in the pleiotropic loci and the previously confirmed Parkinson disease loci were used to construct a functional similarity network of genes (see the Methods section). Nodes are colored to show association. The thickness of lines connecting nodes indicates the strength of the association between nodes.

demonstrates biological relatedness between the pleiotropic loci from the present analysis and PD loci from previous reports.[47]

Discussion

Genetic comorbidities between PD and immune-related genes have only been explored for high-risk PD loci.[5,6,22] Our study using a genome-wide unbiased statistical approach identified 17 shared loci between PD and 7 autoimmune diseases. This finding strengthens the hypothesis that known PD risk genes might contribute to PD through immune system defects (eg, *LRRK2*, *GAK*, *HLA*, and *MAPT*),[21,48] while suggesting that additional loci with weaker associations also contribute to pleiotropy (Table 1). *TRIM10* is closely positioned to the *HLA* region, and, although not extensively described, variants in SE*TD1A* have also previously been associated with PD.[49,50] While we found an overlap between genetic risk factors for autoimmune diseases and PD, the specific loci involved for each trait differed. This result is consistent with the findings that some susceptibility loci are associated with risk in multiple immune-mediated diseases.[51]

Because our method considers joint *P* values, some SNPs with strong association with PD might not pass the significance threshold if they only had marginal association with the autoimmune disease, and vice versa. For instance, a locus in *SNCA* has one of the strongest associations in PD[4] (PD $P = 3.67 \times 10^{-26}$), but it is not associated with autoimmune diseases (RA $P = .6184$). Taking the 2 *P* values together, its conjunction false discovery rate is not significant (PD and rheumatoid arthritisconjunction false discovery rate of 0.9856). Among the 13 significant genes in our PD data set,[4] we did not find significant conjunction false discovery rate loci among *SYT11*, *ACMSD*, *STK39*, *MCCC1/LAMP3*, *BST1*, *SNCA*, and *CCDC62/HIP1R* owing to weak association with autoimmune disorders (eTable 7 in the Supplement). Likewise, some known risk loci for immune diseases were not found in our results: one locus near *CARD15/NOD2* was significant in Crohn disease ($P = 1.21 \times 10^{-58}$) but not in PD ($P = .2163$), and its conjunction false discovery rate of 0.8496 did not pass our threshold. *MC1R* has been reported to be associated with PD and immune-mediated diseases,[52,53] but it had not been reported in our data sets of PD ($P = .2936$) or Crohn disease ($P = .2936$).

Our brain-based QTL analyses suggest immune function–related genes for which the expression or methylation level is changed by of one of our identified susceptibility loci. Most of these genes are located in the *HLA* locus or *MAPT* locus, and owing to the complex underlying LD structures, it is difficult to define the true causal genes. However, our analyses implicate that, in addition to the PD-associated *HLA* genes and *MAPT* in these loci, *TRIM31*, *CRHR1*, *PLEKHM1*, and *NSF* might also be related to PD through defective components of the immune system.[54-56] For example, methylation levels of *TRIM31* seem to be affected in the cerebellum by 2 susceptibility loci (rs9261531 and rs9261535) in *TRIM10*. It is hypothesized that TRIM family proteins are active in the innate immune response to intracellular infectious agents.[57,58] In addition to known PD loci, there is one novel susceptibility locus that has an effect on methylation levels. This variant (rs7515174) is located in the third intron and affects the frontal cortex methylation state of *FCGR2A*. This gene encodes a protein belonging to the IgGFc receptor gene family in which the encoded proteins are located on the surface of many immune response cells and take part in clearing of immune complexes and phagocytosis.[59-61] Variants in *FCGR2A* have been associated with inflammatory bowel disease, Crohn disease, and ulcerative colitis,[62] and variants in other genes from the same family were associated with RA.[63] Of further interest are the 8 identified genes in which the expression is regulated by 10 pleiotropic SNPs (from 5 loci) in several specific immune cell types.[46] Five of the 8 genes are located in 3 loci previously associated with PD.[3] For example, *SNCA* expression is regulated by a pleiotropic variant (rs2736990) in intron 2 of *SNCA* in monocytes. This finding seems in line with a previous study[64] describing an increase of monocytes in peripheral blood of patients with PD, implying an immune-related manifestation of PD through monocytes. *RNPS1*, *DMPK*, and *DMWD* (with the latter 2 genes involved in myotonic dystrophy[65]) are 3 of the 8 immune-based eQTL that are newly associated with PD in the present study. The biologi-

cal functions of these genes involve messenger RNA modification and intracellular trafficking or are unknown.[66,67]

We used pathway analyses to discern the underlying relevant pathways; however, functional studies are pertinent to provide biological insight. Performing downstream pathogenetic analyses using cell-based models is beyond the scope of the present work. Nevertheless, we anticipate that the genetic loci highlighted in our study will motivate the scientific community to pursue this line of research.

The strong pleiotropic enrichment observed between PD and Crohn disease suggests a common pathogenetic link between these 2 phenotypes. Previous studies[21,48] highlighted *LRRK2* as a significant risk factor for both of these phenotypes. *LRRK2* has been identified as having 2 independent Crohn disease risk loci (rs11564258 and rs3761863)[68]: only one of them is in high LD to our shared susceptibility locus rs17467164 (r^2 = 0.992 and r^2 = 0.075, respectively). The observed association between PD and Crohn disease indicates that defects in cargo transport mechanism might underline the disease pathogenesis in both phenotypes.[69] It is known that gastrointestinal tract dysfunction is associated with PD, perhaps even preceding the onset of central motor symptoms.[70] Several of the identified overlapping genes (*CCNY*, *LRRK2*, *MAPT*, *RSPH6A*, and *SYMPK*) are involved in basic cellular functions that may be related to alterations in enteric neurotransmission or intestinal motility disturbances.[71] Furthermore, the shared gene *HLA-DQB1* has a central role in the immune system by introducing peptides derived from extracellular proteins, which implicate overlapping factors related to the immune system (CD4 T cells).

We found moderate polygenic pleiotropic enrichment between PD and ulcerative colitis or RA, whereas genetic enrichment with type 1 diabetes, celiac disease, psoriasis, and multiple sclerosis was weak. In comparison, in a population-based study,[13] the risk for PD was observed to increase in a subset of the cohort with autoimmune diseases and ulcerative colitis and to decrease in those with a previous diagnosis of RA. The epidemiological data in that investigation are in agreement with a recently published study[22] in which genetic comorbidities with PD were explored using top loci from diverse phenotypes. The authors observed a decreased risk for rheumatoid arthritisand psoriasis, but the findings were not statistically significant because of the small sample size. It is unlikely that patients with unrecognized immune-related disorders were included in the PD study[13] population in large enough numbers to affect the results; however, some participants in the autoimmune disorders population[13] could develop PD over time.

Inflammation of microglia, the major resident immune cells in the brain,[72] has been involved in degeneration of dopaminergic neurons affecting PD.[19,73] The extent of genetic pleiotropy observed between PD and autoimmune diseases will help us to understand novel pathogenetic aspects of neurodegeneration in PD, a chronic immune activation of microglia, which may cause or contribute to degeneration of neurons. For example, it has been shown that aggregated α-synuclein protein (by overexpression of *SNCA*) activates the microglia, which increases nitration of α-synuclein and maintains the proinflammatory innate immune response in PD.[74] In this context, the present findings of a polygenic link between PD and inflammatory biological function are likely to be relevant. Furthermore, recent evidence suggests that immune factors are also involved in other neurodegenerative diseases, such as AD.[23]

Limitations and Strengths

Our pleiotropy-based statistical framework was limited to GWAS with a high coverage of SNPs (>500 000); therefore, autoimmune disorders selected for this study were based on available GWAS data that fit these criteria. With more extensive GWAS data, it would be worthwhile to study a larger set of immune disorders associated with PD from epidemiological or clinical studies (eg, thyroid disease).[12] Our study is also limited in distinguishing between immune-mediated and autoimmune disease. It has been hypothesized that PD itself is an autoimmune disease.[75] Although we have shown herein using GWAS of autoimmune disorders that PD has a strong immune component, the conclusion of the hypothesis that PD is an autoimmune disease should be investigated through further cell-based functional studies.

This work has clinical implications. Our data suggest more extensive clinical studies of patients with immune-mediated disorders for PD signs to develop possible screening schemes for PD, and vice versa, for monitoring immune and inflammatory status among individuals with an increased risk for PD.[76] According to our study, apparently healthy individuals with a high load of these shared risk genotypes, predisposing them to inflammation disturbances, could be at particularly increased risk for developing PD. Further prospective studies in these individuals may clarify these issues. Our findings also suggest the need for further investigation of the role of immune-modulating agents in the treatment of PD. There is some evidence indicating that anti-immune drugs could be a viable option for therapeutic interventions in PD. A 2004 study[76] showed that candesartan cilexetil, a drug used for hypertension, reduces the α-synuclein–induced microglia phenotype. Therefore, data generated from our study may facilitate novel treatment strategies by increasing our understanding of the pathogenetic mechanisms influenced by pleiotropic disease loci.

Conclusions

In summary, our study highlights the usefulness of cross-phenotype analyses to identify genetic overlap (ie, pleiotropic loci) between PD and a selection of autoimmune disorders. Our results suggest that these PD-associated loci contribute to PD through immune defects and that immune dysfunction is not simply the end product of the neurodegeneration process. The findings strongly support the presence of interaction between the immune system and neurodegeneration in PD.

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