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Association Between Genetic Traits for Immune-Mediated Diseases and Alzheimer Disease

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Abstract

IMPORTANCE—Late-onset Alzheimer disease (AD), the most common form of dementia, places a large burden on families and society. Although epidemiological and clinical evidence suggests a relationship between inflammation and AD, their relationship is not well understood and could have implications for treatment and prevention strategies.

OBJECTIVE—To determine whether a subset of genes involved with increased risk of inflammation are also associated with increased risk for AD.

DESIGN, SETTING, AND PARTICIPANTS—In a genetic epidemiology study conducted in July 2015, we systematically investigated genetic overlap between AD (International Genomics of Alzheimer's Project stage 1) and Crohn disease, ulcerative colitis, rheumatoid arthritis, type 1 diabetes, celiac disease, and psoriasis using summary data from genome-wide association studies at multiple academic clinical research centers. *P* values and odds ratios from genome-wide association studies of more than 100 000 individuals were from previous comparisons of patients vs respective control cohorts. Diagnosis for each disorder was previously established for the parent study using consensus criteria.

MAIN OUTCOMES AND MEASURES—The primary outcome was the pleiotropic (conjunction) false discovery rate *P* value. Follow-up for candidate variants included neuritic plaque and neurofibrillary tangle pathology; longitudinal Alzheimer's Disease Assessment Scale cognitive subscale scores as a measure of cognitive dysfunction (Alzheimer's Disease Neuroimaging Initiative); and gene expression in AD vs control brains (Gene Expression Omnibus data).

RESULTS—Eight single-nucleotide polymorphisms (false discovery rate $P < .05$) were associated with both AD and immune-mediated diseases. Of these, rs2516049 (closest gene *HLA-DRB5*; conjunction false discovery rate $P = .04$ for AD and psoriasis, 5.37×10^{-5} for AD, and 6.03×10^{-15} for psoriasis) and rs12570088 (closest gene *IPMK*; conjunction false discovery rate $P = .009$ for AD and Crohn disease, $P = 5.73 \times 10^{-6}$ for AD, and 6.57×10^{-5} for Crohn disease) demonstrated the same direction of allelic effect between AD and the immune-mediated diseases. Both rs2516049 and rs12570088 were significantly associated with neurofibrillary tangle pathology ($P = .01352$ and .03151, respectively); rs2516049 additionally correlated with longitudinal decline on Alzheimer's Disease Assessment Scale cognitive subscale scores (β [SE],

0.405 [0.190]; $P = .03$). Regarding gene expression, *HLA-DRA* and *IPMK* transcript expression was significantly altered in AD brains compared with control brains (*HLA-DRA*: β [SE], 0.155 [0.024]; $P = 1.97 \times 10^{-10}$; *IPMK*: β [SE], −0.096 [0.013]; $P = 7.57 \times 10^{-13}$).

CONCLUSIONS AND RELEVANCE—Our findings demonstrate genetic overlap between AD and immune-mediated diseases and suggest that immune system processes influence AD pathogenesis and progression.

Alzheimer disease (AD) is the most common neurodegenerative disease, with an estimated prevalence of 30 million people worldwide, a number that is expected to quadruple in the next 40 years.[1] Currently, there is no effective treatment that delays onset or slows progression of AD. With the aging of the US population and high costs associated with caring for cognitively impaired elderly individuals, identifying strategies that prevent AD is of utmost importance.

Inflammation, a core feature of many immune-mediated diseases, is being increasingly recognized as an important etiologic characteristic of AD. Complement factors and activated microglia are established histopathologic features in brains of patients with AD,[2] and observational studies and meta-analyses suggest that elevated C-reactive protein levels are associated with increased risk for developing AD.[3,4] Importantly, recent associations between AD and genetic variants encoding triggering receptor expressed on myeloid cells 2 (*TREM2*)[5,6] and myeloid cell surface antigen *CD33*[7] suggest that immune system–associated mechanisms may contribute to and drive AD pathogenesis.

Recent work[8,9] indicates that common genetic variants associated with inflammation may also increase the risk for developing AD. Herein, building on our prior work and applying a recently validated approach for investigating polygenic pleiotropy,[10,11] we systematically investigated genetic overlap between AD and immune-mediated diseases. Taking advantage of several large genome-wide association studies (GWASs),[12-17] we sought to identify single-nucleotide polymorphisms (SNPs) jointly associated with AD and 1 or more of the immune-mediated traits including Crohn disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), type 1 diabetes (T1D), celiac disease (CeD), and psoriasis (PSOR).

Methods

Participant Samples

We evaluated complete GWAS results in the form of summary statistics (*P* values and odds ratios) for clinically diagnosed AD[12] and immune-mediated diseases including CD,[13] UC,[18] RA,[14] T1D,[15] CeD,[16] and PSOR[17] (Table 1). We obtained publicly available AD GWAS summary statistics data from the International Genomics of Alzheimer's Disease Project (IGAP stages 1 and 2; for additional details, see eAppendix 2 in the Supplement and the article by Lambert et al[12]). In this study, we used the IGAP stage 1 cohort, which consisted of 17 008 patients with AD (mean [SD] age, 74.7 [7.7 years; 59.4% female) and 37 154 controls (mean [SD] age, 76.3 [8.1] years; 58.6% female) drawn from 4 different consortia across North America and Europe with genotyped or imputed data at 7 055 881 SNPs (for a description of the AD cases and controls within the IGAP stage 1 sub-studies, see the article by Lambert et al[12]). The relevant institutional review boards or ethics committees approved

the research protocol of the individual GWASs used in the current analysis, and all participants gave written informed consent. The current analysis was finalized on July 21, 2015.

For gene expression analyses, we used publicly available total RNA expression data from 1647 autopsied brain tissues (from dorsolateral prefrontal cortex, visual cortex, and cerebellum) in a total of 549 brains of 376 patients with AD and 173 nondemented healthy controls from the Gene Expression Omnibus data set GSE44772.[19] As previously described,[19] all participants were diagnosed at intake and each brain underwent extensive neuropathology examination. Tissues were profiled on a custom-made Agilent 44K array of 40 638 DNA probes.

For neuropathology analyses, we used publicly available summary statistics genetic data (major allele, *P* values, and directionality of effect) of neuropathological measures from 4914 brain autopsies.[20] This data set consists of meta-analysis results from a GWAS performed to identify genetic loci correlating with established AD neuropathologic phenotypes. We focused on neurofibrillary tangles (NFTs) and neuritic plaques (NPs). The NFTs were classified as 4 Braak groups (none, transentorhinal, limbic, isocortical) and the NPs were classified as present or absent (any NPs vs no NPs).[20]

Longitudinal cognitive decline data were obtained from 723 individuals (196 older controls, 355 individuals with mild cognitive impairment, and 172 patients with clinical AD) from the initial cohort of the Alzheimer's Disease Neuroimaging Initiative (see eAppendix 2 in the Supplement for additional description). We restricted our analyses to participants with available genotype and baseline and follow-up neuropsychological assessments with the Alzheimer's Disease Assessment Scale cognitive subscale (range, 6 months to 3.5 years; mean [SD], 1.56 [0.75] years; total of 3399 assessments).

Statistical Analysis

Conditional Quantile-Quantile plots—Using recently developed statistical methods to evaluate pleiotropic effects,[8,11,21-23] we evaluated SNPs associating with AD (IGAP stage 1) and the 6 immune-mediated diseases. For given associated phenotypes A and B, pleiotropic enrichment of phenotype A with phenotype B exists if the proportion of SNPs or genes associated with phenotype A increases as a function of increased association with phenotype B. To assess for enrichment, we constructed conditional quantile-quantile (Q-Q) plots of nominal $-\log_{10}(P)$ values for all AD SNPs and for subsets of SNPs determined by the significance of their association with the 6 immune-mediated diseases. In conditional Q-Q plots, the presence of enrichment is reflected as successive leftward deflections of the curve for phenotype A if the degree of deflection from the expected null line is dependent on the degree of association with phenotype B. To assess for polygenic effects below the standard GWAS significance threshold, we focused the Q-Q plots on SNPs with nominal $-\log_{10}(P) < 7.3$ (corresponding to $P > 5 \times 10^{-8}$). The enrichment seen can be directly interpreted in terms of true discovery rate (true discovery rate = 1 – false discovery rate [FDR]) (eAppendix 2 in the Supplement).

Conjunction FDRs—To identify specific loci involved with *both* AD and the 6 immune-mediated diseases, we computed conjunction FDRs.[10,11] *Conjunction FDR* is defined as the posterior probability that an SNP is null for either phenotype or both simultaneously, given that the *P* values for both traits are as small as or smaller than the observed *P* values. A conservative estimate of the conjunction FDR is given by the maximum statistic[24] in taking the maximum of $FDR_{trait1|trait2}$ and $FDR_{trait2|trait1}$. Unlike the conditional FDR, which ranks disease- or primary phenotype–associated SNPs based on genetic "relatedness" with secondary phenotypes,[8,11] the conjunction FDR minimizes the effect of a single phenotype driving the common association signal and pinpoints pleiotropic loci between the traits of interest (eAppendix 2 in the Supplement). We used an overall FDR threshold of less than 0.05, which means 5 expected false discoveries per 100 reported. Additionally, we constructed Manhattan plots based on the ranking of conjunction FDR to illustrate the genomic location of the pleiotropic loci.[10,11] In all analyses, we controlled for the effects of genomic inflation by using intergenic SNPs (eAppendix 2 in the Supplement). Detailed information on conjunction Q-Q plots, Manhattan plots, and conjunction FDR can be found in eAppendix 2 in the Supplement and prior reports.[10,11,21-23]

Results

Conditional Q-Q plots

We observed SNP enrichment for AD across different levels of significance with CD, UC, T1D, RA, CeD, and PSOR (Figure 1). For progressively stringent *P* value thresholds for AD SNPs, ie, increasing values of nominal $-\log_{10}(P)$, we found moderate en richment, ie, leftward shift or decreasing values of empirical $-\log_{10}(q)$, using CD, UC, T1D, and RA and minimal enrichment using CeD and PSOR (Figure 1). Removing the major histocompatibility complex (MHC)–associated SNPs did not result in attenuation of genetic enrichment (eFigure 1 in the Supplement), indicating that the observed pleiotropy between AD and the immune-mediated diseases was not confined to the MHC region. We observed a similar pattern of enrichment for CD, UC, T1D, RA, CeD, and PSOR SNPs conditional on AD SNPs, suggesting symmetric genetic enrichment between AD and the immune-mediated diseases (eFigure 2 in the Supplement).

Conjunction FDRs

At a conjunction FDR $P < .05$, we identified 8 SNPs that were associated with both AD and the immune-mediated diseases: (1) rs2516049 with PSOR; (2) rs12679874 with CD; (3) rs12570088 with CD; (4) rs2280231 with T1D; (5) rs8055533 with T1D; (6) rs7258465 with T1D; (7) rs16980051 with CD; and (8) rs2298428 with CD (Figure 2 and Table 2). Of these, rs2516049 (chromosome 6; closest gene *HLA-DRB5*; reference allele T; conjunction trait PSOR; conjunction FDR $P = .04$ for AD and PSOR, 5.37×10^{-5} for AD, and $P = 6.03 \times 10^{-15}$ for PSOR) and rs12570088 (chromosome 10; closest gene *IPMK*; reference allele A; conjunction trait CD; conjunction FDR $P = .009$ for AD and CD, 5.73×10^{-6} for AD, and 6.57×10^{-5} for CD) demonstrated the same direction of allelic effect between AD and the immune-mediated diseases (Table 2).

Gene Expression Analyses

First, we investigated whether *HLA-DRB5* and *IPMK* RNA levels are altered in AD brains vs control brains (Gene Expression Omnibus data set GSE44772).[19] Using logistic regression, we found significantly decreased *IPMK* transcript expression in AD brains compared with control brains (β [SE], −0.096 [0.013]; $P = 7.57 \times 10^{-13}$). Although we did not observe a significant effect for *HLA-DRB5* in AD brains, we found significantly increased transcript expression for *HLA-DRA* (β [SE], 0.155 [0.024]; $P = 1.97 \times 10^{-10}$).

Association With Neuropathology and Cognitive Decline

Using publicly available data,[20] we next evaluated the relationship between rs2516049 and rs12570088 and neuropatho-logical measures from 4914 brain autopsies. We found that both rs2516049 (reference allele T; $P = .01352$; direction of effect of the reference allele of this SNP is the same in the GWAS pleiotropy analysis and the analysis of NFT pathology [++]) and rs12570088 (reference allele A; $P = .03151$; direction of effect of the reference allele of this SNP is the same in the GWAS pleiotropy analysis and the analysis of NFT pathology [++]) were significantly associated with worse NFT pathology. We did not find a significant effect between rs2516049 (reference allele T; $P = .07144$; direction of effect of the reference allele of this SNP is in the opposite direction in the GWAS pleiotropy analysis vs the analysis of NP pathology [+−]) and rs12570088 (reference allele A; $P = .2168$; direction of effect of the reference allele of this SNP is the same in the GWAS pleiotropy analysis and the analysis of NP pathology [++]) and NP pathology.

Finally, we assessed the relationship between rs2516049 and rs12570088 and longitudinal cognitive decline in 723 individuals (196 older controls, 355 individuals with mild cognitive impairment, and 172 patients with clinical AD). Using linear mixed-effects models, covarying for age, sex, baseline Clinical Dementia Rating sum of box score, and *APOE* ε4 carrier status (carrier vs noncarrier), we found a significant relationship between rs2516049 and longitudinal Alzheimer's Disease Assessment Scale cognitive subscale scores (β [SE], 0.405 [0.190]; $P = .03$); we found no relationship between rs12570088 and longitudinal Alzheimer's Disease Assessment Scale cognitive subscale scores (β [SE], 0.114 [0.450]; $P = .75$).

Discussion

In this study, we found that a subset of genetic variants that were associated with increased risk for immune-mediated diseases also conferred increased risk for AD (genetic pleiotropy). Two polymorphisms, namely rs2516049 (chromosome 6; closest gene *HLA-DRB5*) and rs12570088 (chromosome 10; closest gene *IPMK*), demonstrated the same direction of allelic effect between AD and immune-mediated diseases and were associated with greater intracranial burden of NFTs. We additionally observed that *HLA-DRA* (a paralog for *HLA-DRB5*) and *IPMK* transcript expression was different in AD brains compared with control brains. Considered together, these findings suggest that immune- and inflammation-associated genes, particularly the *HLA* locus and *IPMK*, likely influence AD pathogenesis and progression.

Our results illustrate that combining GWASs from multiple diseases and phenotypes provides important insights into shared genetic risk. By leveraging genetic signal in one phenotype, we were able to identify variants in a second phenotype that would otherwise not be detected using a single-phenotype approach. Whereas the conditional FDR improves statistical power for gene discovery by conditioning on the association with secondary phenotypes, the conjunction FDR identifies loci jointly associated with 2 traits. Using this pleiotropic approach, we found 8 polymorphisms that were associated with both AD and the 6 immune-mediated diseases. We found 2 directionally consistent pleiotropic loci (closest genes *HLA-DRB5* and *IPMK*) between the 6 immune-mediated diseases and AD.

The human leukocyte antigen (HLA) region encodes proteins that are responsible for immune system regulation in humans; HLA-DR is an MHC class II cell surface receptor encoded by the HLA complex. Association with the SNP near *HLA-DRB5* builds on previous work by identifying this locus as a risk factor for AD.[12] We found evidence supporting an association between rs2516049 and greater NFT burden. We also found that *HLA-DRA* had greater expression in AD pathological brain samples, which suggests potential for increased intracranial inflammation in AD. It is important to note that we were unable to define the causal gene(s) on chromosome 6 responsible for our pleiotropic signal given the complexity of the MHC region. However, our findings suggest the need for finer mapping of the *HLA* region in AD.

Inositol polyphosphate multikinase (IPMK) catalyzes inositol polyphosphate and phosphoinositide turnover. It has also been implicated in many noncatalytic activities, including regulation of amino acid signaling to mTOR complex 1,[25] as a transcriptional activator for immediate early genes[26] and p53-mediated transcription, which facilitates cell death[27] and nuclear messenger RNA export.[28] In our study, the *IPMK* locus was associated with NFT pathology, and *IPMK* expression was lower in postmortem AD samples. Expression of *IPMK* has been shown to be lower in pathological samples from patients with Huntington disease as well as in cellular and animal models of Huntington disease.[29] Phosphatidylinositol kinase activity (one of the enzymatic functions of IPMK) has also been shown to be lower in postmortem tissue from patients with AD.[30] Considered together with our results, these studies suggest an important role for *IPMK* in neurodegeneration.

Although the primary focus of this work was on pleiotropic loci demonstrating the same direction of allelic effect, we also found 6 loci that showed an opposite direction of allelic effect between AD and the immune-mediated diseases. One hypothesis for these findings is that the observed pleiotropy between AD and these 6 loci could be due to different haplotypes or gene alleles involving the same SNPs. Another equally plausible hypothesis is that the same haplotypes or gene alleles are involved in both AD and these autoimmune diseases but the underlying biological mechanisms are distinct. Taken collectively, these findings illustrate that the genetic relationship between the immune system and AD may not be straightforward; considerable work will be required to carefully characterize the biological mechanisms underlying how each inflammation-associated genetic variant influences AD pathobiology.

We note that in this study the diagnosis of AD was established clinically. It is feasible that the individuals from the IGAP cohort who were clinically diagnosed as having AD may have had concomitant vascular brain disease with underlying inflammation, which may further contribute to their cognitive decline and dementia. As such, an alternative interpretation of our findings is that the susceptibility loci identified in this study may increase brain vulnerability to vascular and/or inflammatory insults, which in turn may exacerbate the clinical consequences of AD pathological changes.

Conclusions

We have identified genetic overlap between AD and immune-mediated diseases, implicating the *HLA* locus and *IPMK* in the pathobiology of AD. These findings provide novel insights into the relationship between inflammation and AD. Building on prior genetic and molecular evidence,[31] our results are consistent with the hypothesis that rather than representing a downstream effect of neurodegeneration, inflammation influences AD pathogenesis and progression, which may have implications for treatment and prevention strategies in AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question Is there genetic overlap between Alzheimer disease and immune-mediated diseases that promote inflammation?

Findings In a genetic epidemiology study using summary data from multiple genome-wide association studies of more than 100 000 people and validated methods to assess genetic pleiotropy, we identified 8 variants that were statistically significantly associated with both AD and immune-mediated disease. Two of these, representing the *HLA* locus and *IPMK*, demonstrated the same direction of allelic effect.

Meaning The findings demonstrate genetic overlap between Alzheimer disease and immune-mediated diseases and suggest that immune system processes influence Alzheimer disease pathogenesis and progression.

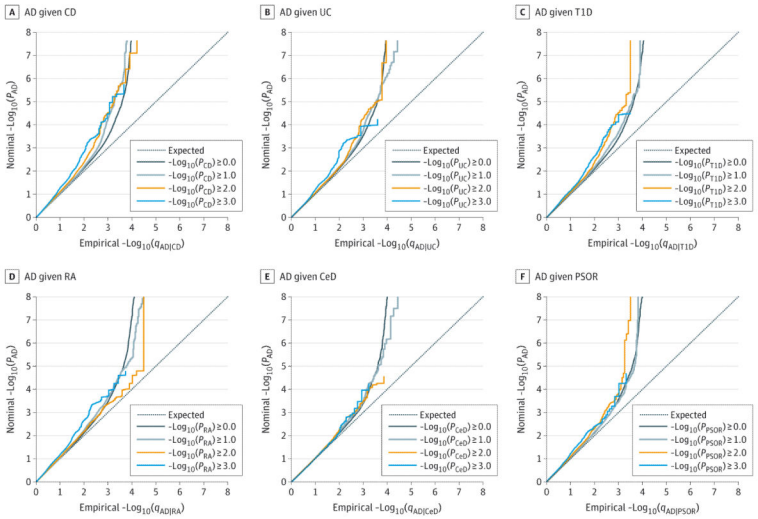

Figure 1. Single-Nucleotide Polymorphism Enrichment for Alzheimer Disease (AD) Across Different Levels of Significance

Conditional quantile-quantile (Q-Q) plots of nominal $-\log_{10}(P)$ vs empirical $-\log_{10}(q)$ (corrected for inflation) in AD below the standard genome-wide association study threshold of $P < 5 \times 10^{-8}$ as a function of significance of association with Crohn disease (CD) (A), ulcerative colitis (UC) (B), type 1 diabetes (T1D) (C), rheumatoid arthritis (RA) (D), celiac disease (CeD) (E), and psoriasis (PSOR) (F) at the level of $-\log_{10}(P) \geq 0.0$, $-\log_{10}(P) \geq 1.0$, $-\log_{10}(P) \geq 2.0$, and $-\log_{10}(P) \geq 3.0$ corresponding to $P \leq 1$, $P \leq .1$, $P \leq .01$, and $P \leq .001$, respectively. Dashed line indicates all single-nucleotide polymorphisms.

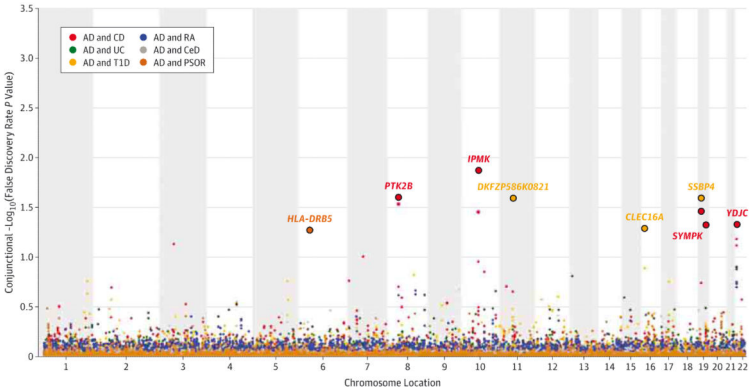

Figure 2. Shared Genetic Risk Between Alzheimer Disease (AD) and Immune-Mediated Diseases

Conjunction Manhattan plot of conjunctional $-\log_{10}$(false discovery rate P value) for AD given Crohn disease (CD), ulcerative colitis (UC), type 1 diabetes (T1D), rheumatoid arthritis (RA), celiac disease (CeD), and psoriasis (PSOR). Single-nucleotide polymorphisms with conjunctional $-\log_{10}$(false discovery rate P value) > 1.3 (ie, false discovery rate $P < .05$) are shown with large points. A black line around the large points indicates the most significant single-nucleotide polymorphism in each linkage disequilibrium block; these single-nucleotide polymorphisms were each annotated with the closest gene, which is listed with the symbol in each locus. For additional details, see eAppendix 2 in the Supplement.

Table 1

Summary Data From All Genome-wide Association Studies Used in the Current Study

Disease/Trait	Participants, No.	Single-Nucleotide Polymorphisms, No.	Source
Alzheimer disease	54 162	7 055 881	Lambert et al,[12] 2013
Crohn disease	51 109	942 858	Franke et al,[13] 2010
Ulcerative colitis	26 405	1 273 589	Anderson et al,[18] 2011
Rheumatoid arthritis	25 708	2 554 714	Stahl et al,[14] 2010
Type 1 diabetes	16 559	841 622	Barrett et al,[15] 2009
Celiac disease	15 283	528 969	Dubois et al,[16] 2010
Psoriasis	7484	1 121 166	Ellinghaus et al,[17] 2012

Table 2

Top SNPs Associated With AD and Immune-Mediated Diseases

SNP	Position	Chromosome	Nearest Gene	Reference Allele	Associated Phenotype	Min Conj FDR *P* Value	*P* Value		Direction of Allelic Effect
							AD	Associated Phenotype	
rs2516049	32570400	6	*HLA-DRB5*	T	PSOR	4.08×10^{-2}	5.37×10^{-5}	6.03×10^{-15}	++
rs12679874	27230819	8	*PTK2B*	A	CD	2.40×10^{-2}	1.64×10^{-6}	4.38×10^{-4}	−−
rs12570088	59938336	10	*IPMK*	A	CD	9.83×10^{-3}	5.73×10^{-6}	6.57×10^{-5}	++
rs2280231	47600438	11	*DKFZp586K0821/ NDUFS3*	C	T1D	2.17×10^{-2}	2.82×10^{-5}	5.50×10^{-5}	−−
rs8055533	11042239	16	*CLEC16A*	G	T1D	4.40×10^{-2}	9.85×10^{-5}	3.60×10^{-4}	−−
rs7258465	18533642	19	*SSBP4*	T	T1D	2.45×10^{-2}	3.26×10^{-5}	1.26×10^{-4}	−−
rs16980051	46345886	19	*SYMPK*	T	CD	4.59×10^{-2}	6.61×10^{-6}	9.33×10^{-4}	−−
rs2298428	21982892	22	*YDJC*	C	CD	4.11×10^{-2}	1.05×10^{-4}	3.38×10^{-10}	−−

Abbreviations: AD, Alzheimer disease; CD, Crohn disease; Min Conj FDR, minimum conjunction false discovery rate; PSOR, psoriasis; SNPs, single-nucleotide polymorphisms; T1D, type 1 diabetes; −−, negative effect estimates; ++, positive effect estimates.