Shared Genetic Risk Factors for Multiple Sclerosis/Psoriasis Suggest Involvement of Interleukin-17 and Janus Kinase–Signal Transducers and Activators of Transcription Signaling

Matthew T. Patrick, PhD,[1] Rajan P. Nair, PhD,[1] Kevin He, PhD,[2] Philip E. Stuart, MS,[1] Allison C. Billi, MD, PhD,[1] Xiang Zhou, PhD,[2] Johann E. Gudjonsson, MD, PhD,[1] Jorge R. Oksenberg, PhD,[3] James T. Elder, MD, PhD,[1] and Lam C. Tsoi, PhD[1,2,4]

Objective: Psoriasis and multiple sclerosis (MS) are complex immune diseases that are mediated by T cells and share multiple comorbidities. Previous studies have suggested psoriatic patients are at higher risk of MS; however, causal relationships between the two conditions remain unclear. Through epidemiology and genetics, we provide a comprehensive understanding of the relationship, and share molecular factors between psoriasis and MS.

Methods: We used logistic regression, trans-disease meta-analysis and Mendelian randomization. Medical claims data were included from 30 million patients, including 141,544 with MS and 742,919 with psoriasis. We used genome-wide association study summary statistics from 11,024 psoriatic, 14,802 MS cases, and 43,039 controls for trans-disease meta-analysis, with additional summary statistics from 5 million individuals for Mendelian randomization.

Results: Psoriatic patients have a significantly higher risk of MS (4,637 patients with both diseases; odds ratio [OR] 1.07, $p = 1.2 \times 10^{-5}$) after controlling for potential confounders. Using inverse variance and equally weighted trans-disease meta-analysis, we revealed >20 shared and opposing (direction of effect) genetic loci outside the major histocompatibility complex that showed significant genetic colocalization (in COLOC and COLOC-SuSiE v5.1.0). Co-expression analysis of genes from these loci further identified distinct clusters that were enriched among pathways for interleukin-17/tumor necrosis factor-α (OR >39, $p < 1.6 \times 10^{-3}$) and Janus kinase–signal transducers and activators of transcription (OR 35, $p = 1.1 \times 10^{-5}$), including genes, such as *TNFAIP3*, *TYK2*, and *TNFRSF1A*. Mendelian randomization found psoriasis as an exposure has a significant causal effect on MS (OR 1.04, $p = 5.8 \times 10^{-3}$), independent of type 1 diabetes (OR 1.05, $p = 4.3 \times 10^{-7}$), type 2 diabetes (OR 1.08, $p = 2.3 \times 10^{-3}$), inflammatory bowel disease (OR 1.11, $p = 1.6 \times 10^{-11}$), and vitamin D level (OR 0.75, $p = 9.4 \times 10^{-3}$).

Interpretation: By investigating the shared genetics of psoriasis and MS, along with their modifiable risk factors, our findings will advance innovations in treatment for patients suffering from comorbidities.

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Address correspondence to Lam C. Tsoi, PhD, Department of Dermatology, University of Michigan Medical School, Ann Arbor, MI, USA. E-mail: alextsoi@med.umich.edu

From the [1]Department of Dermatology, University of Michigan Medical School, Ann Arbor, MI, USA; [2]Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA; [3]Department of Neurology, University of California, San Francisco, San Francisco, CA, USA; and [4]Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI, USA

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Multiple sclerosis (MS), a chronic central nervous system disease that damages central nervous system myelin or white matter through immune dysregulation,[1] is associated with multiple comorbidities and risk factors that can increase susceptibility and/or accelerate neurodegeneration,[2,3] such as smoking, cardiovascular disease, and low vitamin D. Although receiving less attention, psoriasis, a complex chronic skin disease[4] associated with systemic inflammation,[5] has been found to impose a higher (odds ratio [OR] 1.29[6]) risk of MS. Notably, the risk of MS increases with psoriasis severity.[7] Certain cytokines have been implicated in the pathogenesis of both psoriasis and MS, including interleukin (IL)-17,[8,9] interferon (IFN)γ,[10,11] and tumor necrosis factor (TNF).[12,13] Clinical responses were observed in both diseases for IL-17-regulating drugs, dimethyl fumarate[14,15] and secukinumab,[16,17] as well as α4-integrin antagonist, natalizumab[18]; however, even though TNF inhibitors work well for psoriasis, they have been found to exacerbate MS.[12] Similarly, IFNβ is a common treatment for MS, but can trigger psoriasis.[19] Until now, there has been limited study to discern the effects of shared genetic and modifiable risk factors on the psoriasis/MS comorbidity, and how they are associated with the aforementioned cytokine signaling pathways. However, this is essential for understanding the mechanisms and identifying effective treatments for many patients suffering from both conditions.

Psoriasis and MS each have a substantial genetic component (~70% heritability for psoriasis[20] and 50–64% for MS[21,22]), with genetic signals from both diseases enriched among regulatory regions for $CD4^+$ and $CD8^+$ T cells.[1,4] Infiltration of activated $CD4^+$/$CD8^+$ T cells in the skin increases proliferation of keratinocytes to produce psoriatic plaques;[23] whereas in MS, T cells are involved in an inflammatory process that damages myelin nerve insulation.[24] Myelin-specific $CD4^+$ T cells are over four-fold more abundant in MS patients than controls,[25] and there is a 10-fold increase of dermal T cells in psoriasis lesions compared with healthy skin.[26] Psoriasis and MS are both characterized by T helper (Th)1 and Th17 cells,[23,27] with Th17 demonstrating greater ability to cross the choroid plexus (in MS) than other $CD4^+$ subsets;[28] whereas in psoriasis, neutrophil extracellular traps help enhance Th17 induction.[29] Both diseases are associated with class I human leukocyte antigen alleles (eg, *B**44 is protective for MS[30-32] and *C**06:02 increases the risk for psoriasis[33]), although the primary association for MS in the major histocompatibility complex (MHC) is with class II human leukocyte antigen alleles (including DRB1*15:01).[34] However, outside the MHC, little is known about the genetic components they share.

Psoriasis and MS have also been associated with overlapping modifiable risk factors. For instance, both are more prevalent in northern latitudes[35,36] and are connected with vitamin D deficiency.[37,38] There is evidence that vitamin D may be involved in modulating immune responses, including the activation of $CD4^+$/$CD8^+$ T cells,[39,40] and it has also been found to suppress IL-17 induction.[41] However, much remains to be known regarding its precise role in inflammatory diseases, such as psoriasis and MS.[42] In psoriasis, vitamin D analogs are regularly used as topical treatments,[38] whereas there have been multiple inconclusive trials for its use as an oral supplement in MS.[43,44] Ultraviolet radiation is an effective treatment for psoriasis,[45] and early trials suggest it may be beneficial for MS.[46] Obesity is another key risk factor for immune-mediated diseases in general,[47] and previous Mendelian randomization (MR) studies have suggested it can causally affect both psoriasis[48] and MS.[49] Metabolic dysfunction resulting from obesity impacts the immune system;[50] for example, through the effect of adipokines on TNF.[51] Further modifiable risk factors reported by the literature include smoking,[52,53] triggering events,[54,55] infections,[56,57] and the microbiome.[58,59] These risk factors should be taken into consideration when assessing the causal relationship between psoriasis and MS.

Understanding the pathophysiology of comorbidities is essential for precision medicine and optimal disease management, as it can provide clues to their underlying molecular mechanisms and common etiology. In the present study, we conduct epidemiological analysis on a large medical claims dataset to reveal risk factors common to both diseases, and then we apply a trans-disease meta-analysis (TDMA) to identify >20 shared genetic loci. Finally, we apply MR using genetic variants as instruments to establish a causal relationship between psoriasis and MS independent of their comorbidities and modifiable risk factors.

Methods

The genetic cohorts involved in both the psoriasis and MS genome-wide association study (GWAS) were institutional review board approved (details in previous publications). The Optum Clinformatics® data was exempt from institutional review board approval.

Epidemiology

We investigated the association between psoriasis and MS, in the context of potential confounders, through an epidemiological analysis of 30,445,892 patients from Optum's deidentified Clinformatics® Data Mart.[60] All included individuals had a recorded year of birth, self-reported sex

and race; the majority (75%) were white and just over half (55%) were female, with a mean age of 45 years (at the most recent encounter), and mean enrollment (follow-up) of 5 years. The status of the following traits among the patients was evaluated by the presence/absence of ICD-9/10 codes, as shown in Table S1 in Data S1: type 1 diabetes (T1D), type 2 diabetes (T2D), coronary artery disease (CAD), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, vitamin D deficiency, obesity/morbid obesity, smoking, and alcohol use disorder (AUD). In total, our analysis included 141,544 patients with MS, 742,919 patients with psoriasis, and 4,637 patients with both diseases.

Logistic regression was applied to medical claims data extracted for the years 2001 to 2018 from 30,445,892 patients in Optum's deidentified Clinformatics® Data Mart[60] (version 7.2; OPTUM, Eden Prairie, MN, USA). Patients were included that had a recorded year of birth (from which we calculated the age at most recent encounter), sex, and race, then we added up the total enrollment periods, to give the total enrollment for each patient. Traits were ascertained by ICD-9/10 codes, as shown in Table S1 in Data S1, including obesity, smoking, and AUD, as no quantitative data on body mass index (BMI), smoking, or alcohol consumption was readily available.

Trans-Disease Meta-Analysis

To compare genetic signals between psoriasis and MS, we performed TDMA on GWAS summary statistics from psoriasis (11,024 cases, 16,336 controls)[61] and MS (14,802 cases, 26,703 controls)[1] cohorts. Meta-analyses were prepared as per the data collection and processing steps described in their respective GWAS.[1,61] We applied the standard fixed effects inverse variance weighted (IVW) approach[62] to meta-analysis summary statistics, and also implemented TDMA using an equally weighted combination[63,64] of effect sizes ($\beta_{\mathrm{Psor,CAD}} = (\beta_{\mathrm{Psor}} + \beta_{\mathrm{CAD}})/2$) and variances ($V_{\mathrm{Psor,CAD}} = (V_{\mathrm{Psor}} + V_{\mathrm{CAD}})/4$). Loci were considered independent if they are separated by >500 kb or revealed through approximate conditional analysis (GCTA-COJO[65]), with the largest psoriasis cohort (11,675 cases and controls) being used as the reference dataset for linkage disequilibrium (LD) computation. We also applied Heritability Estimation from Summary Statistics[66] to identify locally correlated regions, using the European 1,000 Genomes data provided with the software as reference, and the recommended partitions.[67] Colocalization analysis was performed using COLOC[68] and its Sum of Single Effects (SuSiE) extension[69] on markers within ±100 kb of each lead TDMA marker, with the same reference cohort as COJO.

Mendelian Randomization

We applied MR to investigate potential causal relationships between psoriasis, MS, and their comorbidities. We used six different MR techniques (MR-PRESSO,[70] MR-Egger,[71] MR-Robust,[72] MR-RAPS,[73] MR-Median,[74] and MR-Mode[75]) to provide confidence in the results, by minimizing the risk of spurious findings due to the weaknesses of any one approach. First, MR-PRESSO[70] was used to correct for horizontal pleiotropy by removing outliers, which addressed distortion for asthma ($p = 0.012$), T1D ($p = 0.002$), and RA ($p < 3.3 \times 10^{-5}$) on MS. Then, the other techniques were used to test assumptions in different ways: MR-Egger[71] includes the intercept in its model; MR-Robust[72] uses Tukey's loss function for robust regression; MR-RAPS[73] accounts for variance in effect sizes and uses a random effects model; and MR-Median[74] and MR-Mode[75] control for heterogeneity by calculating weighted median- or mode-based estimates, respectively. We extracted genetic data from full GWAS summary statistics for 10 traits, in addition to psoriasis and MS. Genetic instruments were selected from the intersection of markers across traits, through LD clumping ($p \le 1 \times 10^{-4}$, LD ≥ 0.001, window size = 10 Mbp), using the European 1,000 Genomes data as reference. The six different MR techniques were applied in univariable analysis, to estimate the causal effect of each trait on psoriasis and MS; and then we conducted multivariable analysis using GRAPPLE,[76] by pooling the genetic markers from each trait.

Results

Epidemiology

Unlike psoriasis, MS was more strongly associated with female sex (Table 1; OR 2.36, $p = 1.2 \times 10^{-4,323}$), and both MS and psoriasis had reduced prevalence in Asian (OR 0.36, $p = 2.7 \times 10^{-513}$) and Hispanic (OR 0.62, $p = 1.7 \times 10^{-488}$) patients, while psoriasis also had lower prevalence among black patients (OR 0.67, $p = 7.2 \times 10^{-1,693}$). Vitamin D deficiency (OR 3.02, $p = 1.9 \times 10^{-368}$) had the strongest association for MS, and was also associated with psoriasis (OR 1.77, $p = 9.2 \times 10^{-8,302}$). The strongest association for psoriasis was RA (OR 3.82, $p = 1.2 \times 10^{-21,815}$), which was also associated with MS (OR 2.64, $p = 9.1 \times 10^{-1,792}$). Both MS and psoriasis were associated with AUD, smoking, asthma, T1D, T2D, CAD, IBD, and morbid obesity. When including all covariates in a conditional model, the effect of psoriasis on MS was OR 1.07 ($p = 1.2 \times 10^{-5}$), while the effect of MS on psoriasis was OR 1.10 ($p = 9.4 \times 10^{-10}$).

Shared and Opposing Genetic Loci

Table 2 shows the results of TDMA using fixed effects IVW meta-analysis, while Tables S2 and S3 in Data S1

TABLE 1. Epidemiological Analysis

	Demographics				Effect on MS		Effect on Psoriasis	
Covariate	**All**	**MS**	**Psor**	**Both**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Age in years Mean (SD)	45 (23)	54 (15)	53 (18)	56 (14)	1.47 (1.46–1.48)	$1.2 \times 10^{-4,442}$	1.49 (1.48–1.49)	$1.2 \times 10^{-24,027}$
Sex								
M Sample size (%)	13,645,873 (44.82)	36,302 (0.27)	355,342 (2.60)	1,294 (0.01)	Reference group			
F Sample size (%)	16,800,019 (55.18)	105,242 (0.63)	387,577 (2.31)	3,343 (0.02)	2.36 (2.34–2.39)	$1.2 \times 10^{-4,323}$	0.88 (0.88–0.89)	8.8×10^{-608}
Race								
White Sample size (%)	22,779,120 (74.82)	113,748 (0.50)	591,317 (2.60)	3,886 (0.02)	Reference group			
Asian Sample size (%)	1,259,402 (4.14)	2,245 (0.18)	28,175 (2.24)	68 (0.01)	0.36 (0.34–0.37)	2.7×10^{-513}	0.86 (0.85–0.87)	8.9×10^{-135}
Black Sample size (%)	3,015,614 (9.90)	15,050 (0.50)	52,679 (1.75)	366 (0.01)	1.00 (0.98–1.02)	0.92	0.67 (0.66–0.67)	$7.2 \times 10^{-1,693}$
Hispanic Sample size (%)	3,391,756 (11.14)	10,461 (0.31)	70,748 (2.09)	317 (0.01)	0.62 (0.60–0.63)	1.7×10^{-488}	0.80 (0.79–0.81)	4.5×10^{-676}

	Sample Size (%)				Effect on MS		Effect on Psoriasis	
Trait	**All**	**MS**	**Psor**	**Both**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Psoriasis	742,919 (2.44)	-	-	4,637 (0.02)	1.22 (1.20–1.24)	5.3×10^{-41}	-	-
MS	141,544 (0.46)	-	-	4,637 (0.02)	-	-	1.24 (1.22–1.26)	8.0×10^{-47}
Type 1 diabetes	923,543 (3.03)	7,158 (0.78)	33,256 (3.60)	331 (0.04)	1.34 (1.33–1.36)	3.9×10^{-126}	1.14 (1.13–1.15)	4.7×10^{-115}
Type 2 diabetes	4,767,871 (15.66)	32,595 (0.68)	172,729 (3.62)	1,405 (0.03)	1.24 (1.23–1.25)	1.5×10^{-211}	1.19 (1.19–1.20)	4.8×10^{-747}
Coronary artery disease	3,170,317 (10.41)	21,996 (0.69)	119,635 (3.77)	991 (0.03)	1.13 (1.12–1.14)	1.1×10^{-53}	1.03 (1.02–1.03)	8.5×10^{-15}
Rheumatoid arthritis	813,738 (2.67)	9,495 (1.17)	66,613 (8.19)	813 (0.10)	1.85 (1.83–1.87)	1.0×10^{-699}	3.11 (3.09–3.12)	$6.8 \times 10^{-14,924}$
Inflammatory bowel disease	403,112 (1.32)	3,935 (0.98)	18,686 (4.64)	206 (0.05)	1.76 (1.73–1.79)	6.5×10^{-265}	1.65 (1.64–1.67)	2.8×10^{-948}
Asthma	4,026,381 (13.22)	25,643 (0.64)	116,560 (2.89)	1,128 (0.03)	1.36 (1.35–1.37)	3.9×10^{-433}	1.24 (1.24–1.24)	1.0×10^{-949}
Vitamin D deficiency	3,937,160 (12.93)	43,555 (1.11)	152,644 (3.88)	1,846 (0.05)	2.30 (2.29–2.32)	$1.5 \times 10^{-3,974}$	1.42 (1.42–1.43)	$1.1 \times 10^{-2,867}$
Obesity								
Obese	3,256,617 (10.70)	19,918 (0.61)	115,156 (3.54)	806 (0.02)	1.22 (1.21–1.23)	2.4×10^{-148}	1.43 (1.42–1.43)	$1.8 \times 10^{-2,475}$
Morbidly obese	1,686,290 (5.54)	13,077 (0.78)	67,983 (4.03)	646 (0.04)	1.47 (1.46–1.48)	1.1×10^{-370}	1.68 (1.67–1.69)	$4.5 \times 10^{-3,350}$
Smoking	4,605,396 (15.13)	38,163 (0.83)	174,563 (3.79)	1,587 (0.03)	1.78 (1.77–1.79)	$3.5 \times 10^{-1,857}$	1.38 (1.38–1.39)	$2.6 \times 10^{-2,738}$
Alcohol use disorder	836,527 (2.75)	5,491 (0.66)	31,853 (3.81)	238 (0.03)	1.53 (1.51–1.55)	1.8×10^{-204}	1.43 (1.42–1.44)	4.7×10^{-803}

Note: The top portion of the table shows the effects of different demographic variables on MS/psoriasis; the bottom portion of the table illustrates the effects of other traits/diseases on MS/psoriasis, after adjusting for the demographic variables.
Abbreviations: MS = multiple sclerosis; OR = odds ratio; Psor = psoriasis.

show the results using the equally weighted approach. TDMA signals with shared or opposing direction of effect are presented as circular Manhattan plot tracks (Fig 1A, B for IVW, Figure S1a, b in Data S1 for equally weighted). In total, 22 and 20 genetic loci were identified for IVW and equally weighted approaches, respectively (counting the MHC, as a single locus due to its complex LD), in which the TDMA lead marker was: (1) genome-wide significant ($p < 5 \times 10^{-8}$) in TDMA; (2) suggestively significant ($p < 1 \times 10^{-4}$) for each trait; and (3) more significant in TDMA than in both traits. IVW and equally weighted approaches were highly concordant, with only

TABLE 2. Loci Identified by Trans-Disease Meta-Analysis

Cyt. Band	rsID	Position (hg19)	RA/NR	MS OR	MS *p*	Psoriasis OR	Psoriasis *p*	TDMA OR	TDMA *p*	Heterogeneity Q	Heterogeneity *p*	Colocalization COLOC PP	Colocalization SuSiE[a]	Nearby Genes
Shared (same direction of effect) loci														
5q33.3	rs2546890	158,759,900	A/G	1.12	1.0×10^{-12}	1.33	6.4×10^{-51}	1.21	7.1×10^{-58}	1.4×10^{-2}	0.91	4.4×10^{-7}	0	*IL12B*
6p21.1	rs59024520	42,238,973	C/T	1.16	6.3×10^{-5}	1.19	8.2×10^{-5}	1.17	2.3×10^{-8}	4.4×10^{-4}	0.98	0.83	0	*USP49*
6q23.3	rs9321623	137,958,265	C/T	1.08	4.5×10^{-6}	1.10	4.5×10^{-7}	1.09	9.5×10^{-12}	1.7×10^{-4}	0.99	1.5×10^{-3}	1	*TNFAIP3*
7p14.1	rs11767350	37,385,365	A/G	1.07	6.5×10^{-6}	1.09	7.4×10^{-6}	1.08	2.2×10^{-10}	6.4×10^{-5}	0.99	0.80	3	*ELMO1*[b]
10q22.2	rs2459446	75,601,596	C/T	1.07	7.9×10^{-5}	1.13	1.5×10^{-10}	1.09	8.9×10^{-14}	1.8×10^{-3}	0.97	0.87	3	*CAMK2G*[b]
11q13.1	rs479777	64,107,477	T/C	1.08	3.5×10^{-5}	1.13	2.1×10^{-9}	1.10	6.0×10^{-13}	9.1×10^{-4}	0.98	0.87	0	*PRDX5*[b], *RPS6KA4*[b]
12p13.31	rs4149576	6,449,115	T/C	1.11	3.5×10^{-9}	0.07	8.8×10^{-5}	1.09	6.8×10^{-12}	3.4×10^{-4}	0.99	0.07	6	*CD27*, *TNFRSF1A*[b]
13q14.2	rs9591325	50,811,220	T/C	1.24	4.2×10^{-10}	1.24	6.6×10^{-9}	1.24	2.0×10^{-17}	1.7×10^{-5}	1.00	0.99	2	*DLEU1*[b]
16p13.13	rs243324	11,354,970	A/G	1.12	5.9×10^{-12}	1.08	6.6×10^{-5}	1.10	5.5×10^{-15}	6.6×10^{-4}	0.98	3.1×10^{-4}	0	*SOCS1*, *RMI2*[b]
17q21.2	rs957970	40,519,890	A/G	1.14	1.1×10^{-13}	1.11	7.3×10^{-8}	1.13	6.4×10^{-20}	2.2×10^{-4}	0.99	0.97	7	*STAT3*[b], *STAT5A*[b]/*B*
19p13.2	rs55677033	11,166,293	T/C	1.09	2.6×10^{-6}	1.08	9.0×10^{-5}	1.09	9.5×10^{-10}	1.0×10^{-5}	1.00	0.17	2	*ILF3*, *CARM1*
Opposing (opposite direction of effect) loci														
1p36.11	rs6672420	25,291,010	A/T	1.07	2.2×10^{-5}	0.86	8.8×10^{-15}	1.11	6.3×10^{-18}	2.9×10^{-3}	0.96	0.93	3	*RUNX3*
2p16.1	rs1177213	61,079,090	A/G	0.93	4.6×10^{-6}	1.16	2.1×10^{-15}	1.11	5.2×10^{-18}	3.0×10^{-3}	0.96	0.73	6	*REL*[b], *PUS10*[b]
5q31.1	rs3843503	131,466,629	T/A	1.08	1.9×10^{-5}	0.92	2.1×10^{-5}	1.08	1.6×10^{-9}	1.5×10^{-6}	1.00	0.68	3	*CSF2*, *P4HA2*[b]
6p22.1	rs1611653	29,841,702	G/C	1.31	3.9×10^{-50}	0.73	1.5×10^{-61}	1.34	6.4×10^{-109}	1.5×10^{-3}	0.97	-	-	*HLA-B*[b]/*C*, *TNF*
6q23.3	rs7746779	138,154,501	A/G	0.90	8.8×10^{-7}	1.15	1.1×10^{-9}	1.13	1.1×10^{-14}	7.8×10^{-4}	0.98	3.2×10^{-3}	0	*TNFAIP3*, *WAKMAR2*
6q25.3	rs2451279	159,515,077	G/A	1.10	6.4×10^{-8}	0.91	3.6×10^{-6}	1.10	1.8×10^{-12}	4.3×10^{-6}	1.00	2.6×10^{-3}	2	*TAGAP*[b]
7q36.1	rs10243355	150,356,318	G/A	1.09	3.4×10^{-5}	0.89	1.8×10^{-5}	1.10	3.4×10^{-9}	6.2×10^{-4}	0.98	0.81	1	*GIMAP2*[b]/*6*[b]
10q22.3	rs1250565	81,047,015	A/G	1.12	1.0×10^{-10}	0.89	3.3×10^{-9}	1.12	2.1×10^{-18}	2.4×10^{-5}	1.00	0.83	2	*ZMIZ1*[b]
11p11.2	rs12574410	47,169,228	C/G	1.11	3.9×10^{-6}	0.90	9.3×10^{-5}	1.11	1.5×10^{-9}	1.3×10^{-5}	1.00	0.88	0	*MYBPC3*[b], *AGBL2*[b]
16p13.13	rs3862471	11,113,463	G/T	1.17	3.2×10^{-23}	0.92	6.4×10^{-6}	1.14	1.3×10^{-25}	3.0×10^{-3}	0.96	0.85	0	*CLEC16A*[b]
22q12.3	rs5756405	37,310,954	A/G	1.07	2.4×10^{-5}	0.93	4.3×10^{-5}	1.07	4.3×10^{-9}	4.7×10^{-5}	0.99	0.76	3	*CSF2RB*[b], *NCF4*

[a]Indicates the number of pairs of fine-mapped signals with evidence of colocalization (PP >0.7).
[b]eQTL evidence in eQTLGen or GTEx v8.
MS = multiple sclerosis; OR = odds ratio; SuSiE = Sum of Single Effects; TDMA = Trans-Disease Meta-Analysis.

two loci identified by each approach not by the other (two loci appear both shared and opposing in IVW). Shown in red on Figure 1A, B are 11 shared and 11 opposing loci, revealed using IVW TDMA, of which Figure 2 illustrates two shared and two opposing loci using regional association plots. We then performed conditional analysis separately on psoriasis and MS outside the MHC using conditional and joint analysis (GCTA-COJO[65]), and applied the TDMA criteria to each independent signal identified, discovering an additional two shared and one opposing IVW TDMA locus (shown in blue in Fig 1), of which one of the shared loci was identified by the equally weighted approach, leading to 27 independent TDMA signals across the three approaches (Figures S2–S24 in Data S1); we also confirmed seven shared and six opposing loci. Table 2 and Tables S4 to S5 in Data S1 present the loci identified by TDMA and COJO, respectively.

We additionally evaluated broader genetic correlations between psoriasis and MS using Heritability Estimation from Summary Statistics.[66] Three LD-independent regions[67] had significant correlation between psoriasis and MS (false discovery rate ≤5%): a chromosome 5 (157–159 Mbp; $p = 4.3 \times 10^{-17}$) and chromosome 10 (81–82 Mbp; $p = 8.6 \times 10^{-5}$) region, which encompass loci identified by our previous two approaches, and the adjacent chromosome 5 region (159–160Mbp; $p = 1.3 \times 10^{-6}$), which does not. Marker rs72804018 from this region (Table 2) is in low LD ($r^2 = 0.03$, $D' = 0.32$) with the

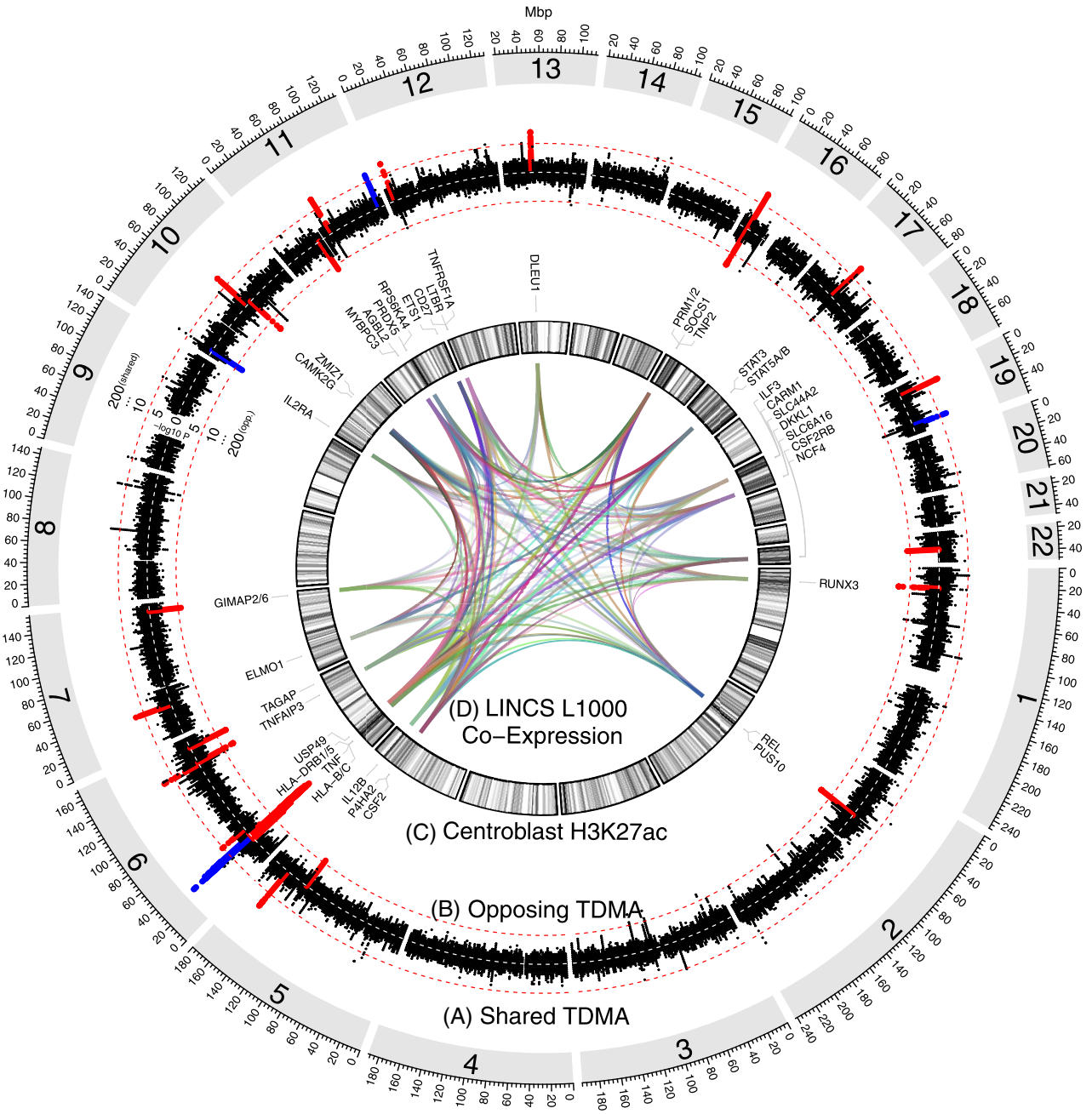

FIGURE 1: Inverse weighted trans-disease meta-analysis (TDMA). Circular diagram including the following: (A) Manhattan plot of shared (same direction of effect) psoriasis/multiple sclerosis (MS) TDMA signals, showing markers more significant in TDMA than for either trait. (B) Manhattan plot of opposing (opposite direction of effect) psoriasis/MS TDMA signals, showing markers more significant in TDMA than for either trait. Red dashed lines show the genome-wide significance ($p < 5 \times 10^{-8}$) threshold for shared and opposing signals, respectively. Loci that meet this threshold and are suggestively significant ($p < 1 \times 10^{-4}$) for both traits are highlighted in red (if identified through our original TDMA approach) or blue (for additional loci identified using GCTA-COJO). (C) Density of H3K27ac active enhancer marks for B-cell centroblasts (the most enriched cell type among the TDMA loci, compared with other established loci for psoriasis and MS). The darker the color, the higher the proportion of regulatory marks overlapping each 2-Mbp region. Genes reported by previous psoriasis and MS GWAS[1,4,96–99] are labeled for each locus. (D) Links between genes, according to co-expression in L1000 assay perturbation experiments from NIH's Library of Integrated Network-Based Cellular Signatures (LINCS). Each link has a random color, with transparency (alpha) values set proportional to the log-scaled number of experiments in which at least one gene from a locus is co-expressed with at least one gene from another locus, such that more opaque links represent pairs of loci with genes co-expressed in more experiments. IVW = inverse variance weighted; MS = multiple sclerosis. [Color figure can be viewed at www.annalsofneurology.org]

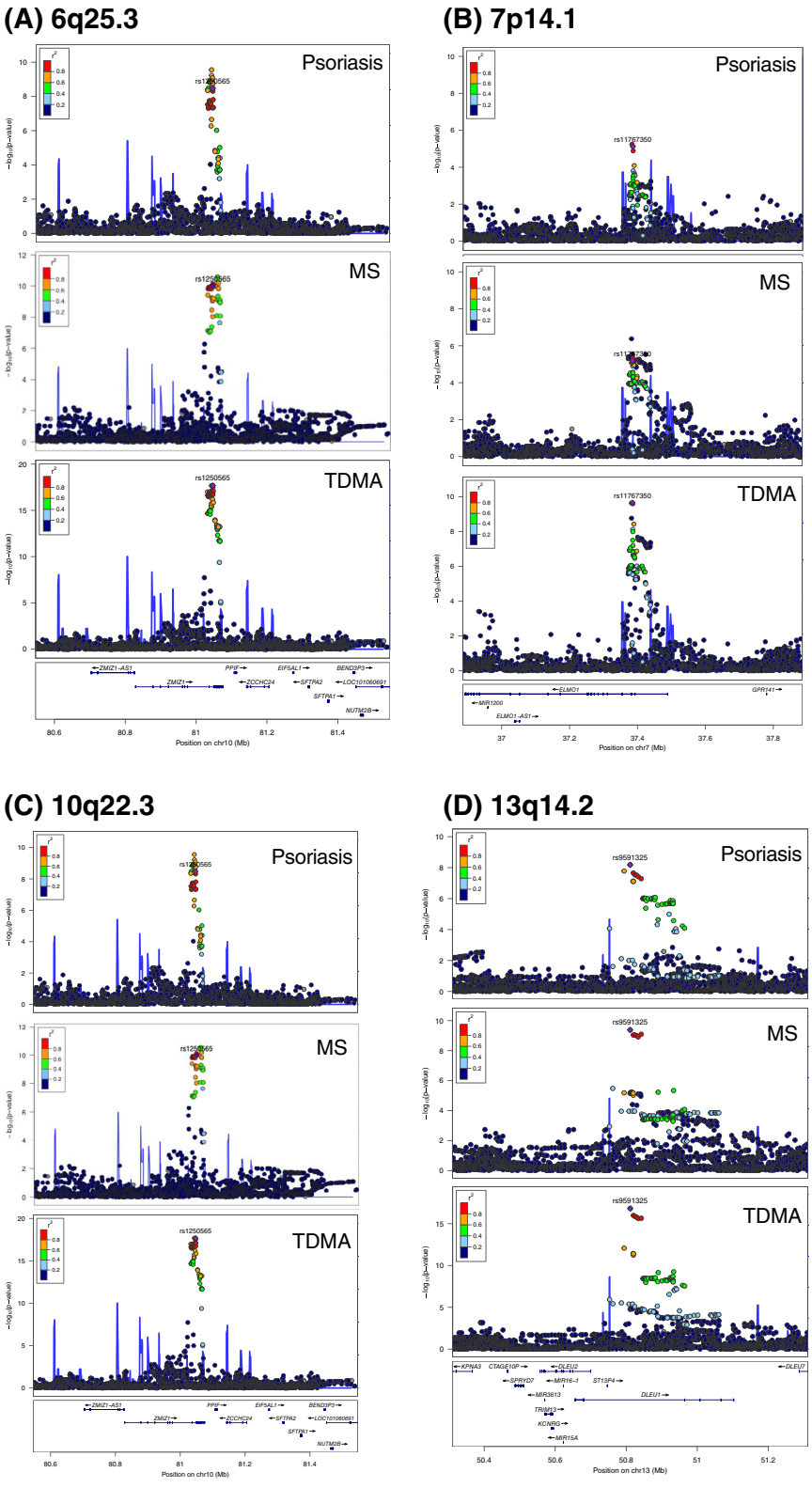

FIGURE 2: Regional association plots for four loci identified by inverse variance weighted (IVW) disease meta-analysis (TDMA). For each of the following loci, the lead TDMA marker is shown in purple, and the other markers are colored according to their linkage disequilibrium (LD) with the lead marker: (A) 6q25.3 opposing locus, with rs2451279 lead marker; (B) 7p14.1 shared locus, with rs17259252 lead marker; (C) 10q22.3 opposing locus, with rs1108618 lead marker; (D) 13q14.2 shared locus, with rs9591325 lead marker. [Color figure can be viewed at www.annalsofneurology.org]

shared locus 154 kb upstream and meets our three criteria (MS $p = 4.6 \times 10^{-7}$; psoriasis $p = 1.8 \times 10^{-7}$; IVW TDMA $p = 5.2 \times 10^{-13}$; equally weighted TDMA $p = 4.6 \times 10^{-13}$), suggesting it may be a secondary signal.

Colocalization Analysis

We investigated whether the shared and opposing loci colocalize to the same causal signals in psoriasis and MS, using COLOC[68] (Table S6 in Data S1). Of the 25 non-MHC loci (identified by the three approaches) 16 showed strong evidence of colocalization, with posterior probabilities ranging from 0.68 (for the opposing locus, centered on rs3843503 in chromosome 5) to 0.99 (for the rs9591325 shared locus in chromosome 13). For the remaining loci, we used the SuSiE COLOC extension,[69] which applies fine-mapping to provide more accurate inference by assuming the potential presence of multiple causal variants per locus. Significantly, all of the loci identified by the equally weighted TDMA approach had evidence (PP = 1.0) of colocalization with SuSiE (Table S7 in Data S1), and interestingly, it was the secondary signal (ie, rs72804018) identified by Heritability Estimation from Summary Statistics that colocalized for the chromosome 5 locus. However, none of the additional loci from the GCTA-COJO analysis had evidence of colocalization, suggesting there may be different causal variants in psoriasis and MS.

To evaluate which TDMA loci might be explained by comorbidities, we retrieved full summary statistics from the largest available GWAS of individuals of European ancestry for each comorbidity. Table S8 in Data S1 presents the shared and opposing TDMA loci that had at least suggestively significant association with each trait. Traits with the most associated loci (eg, RA, with seven loci, and IBD, with five loci) are primarily mediated by immunology rather than modifiable risk factors. T1D (an autoimmune disorder) has seven associated loci, whereas T2D (a metabolic condition) has none. The risk allele locus associated with the most traits, rs413024, is positively associated with IBD, T1D, and RA. All but one of the risk alleles for the shared loci show increased risk of the comorbidities, whereas for the opposing loci, psoriasis and MS impart increasing/decreasing risk on the same traits. These results suggest no one comorbidity dominates the genetic relationship between psoriasis and MS, with the loci instead pertaining to complex imbalances in systemic inflammation.

Functional Analysis

Using H3K27ac marks for active enhancers in 33 different cell types,[77] we conducted binomial enrichment tests to identify how the genetic signals can play regulatory roles in the specific cells involved in psoriasis/MS. Table S9 in Data S1 compares enriched cell types for the 23 equally weighted TDMA plus GCTA-COJO loci outside the MHC, against the 62 MS and 20 psoriasis genome-wide significant loci, identified from their respective GWAS outside these regions. Immune cells were the highest enriched among TDMA, psoriasis, and MS loci, with stimulated Th17 cells ranking among the most enriched in each (TDMA $p = 2.1 \times 10^{-8}$, MS $p = 2.0 \times 10^{-12}$, psoriasis $p = 0.011$). Other $CD4^+/CD8^+$ T-cell subsets were highly enriched in TDMA, including Th0 ($p = 1.5 \times 10^{-8}$), Th1 ($p = 1.4 \times 10^{-7}$) and $CD8^+$ memory T cells ($p = 6.3 \times 10^{-5}$). However, centroblasts were the most enriched cell type for TDMA ($p = 7.7 \times 10^{-12}$), whereas they were less enriched in MS ($p = 4.6 \times 10^{-7}$) and psoriasis ($p = 0.038$), respectively. Figure 1C presents the H3K27ac active enhancer marks for B-cell centroblasts as a density plot, showing that regions of higher density (darker color on the plot) often co-occur with TDMA loci. We compared enrichments in TDMA against the other psoriasis and MS loci using binomial tests, and found centroblasts to be the most significant cell type compared with psoriasis ($p = 3.4 \times 10^{-5}$) and MS ($p = 9.4 \times 10^{-4}$). As a sensitivity check, we repeated the enrichment analysis excluding the four TDMA loci identified using the conditional analysis approach (that did not colocalize), and found once again that centroblasts were more enriched in TDMA than the other psoriasis ($p = 1.4 \times 10^{-4}$) and MS ($p = 2.3 \times 10^{-3}$) loci. Interestingly, brain cell types were only significantly enriched (adjusting for false discovery rate) among the TDMA loci, and not the MS- or psoriasis-only loci. Of these, mid-frontal lobe ($p = 1.9 \times 10^{-4}$), hippocampus middle ($p = 1.0 \times 10^{-3}$) and inferior temporal lobe ($p = 1.1 \times 10^{-3}$) had the strongest enrichment.

Gene Co-Expression

Previous studies highlight the value of integrating gene co-expression networks with GWAS results to infer biological functions. Therefore, we utilized the L1000 assay perturbation experiment from NIH's Library of Integrated Network-Based Cellular Signatures (LINCS)[78] to understand the molecular network regulated by the TDMA loci. Links between these loci shown in Figure 1D indicate at least one gene from the first locus is co-expressed with a gene from the other. The opacity of each link is proportional to the log-scaled number of experiments in which the genes are co-expressed, such that pairs of loci with stronger evidence of connection are more clearly visible. As might be expected, links between the MHC and other loci are among the strongest; however, there are also connections between many of the non-MHC loci. For

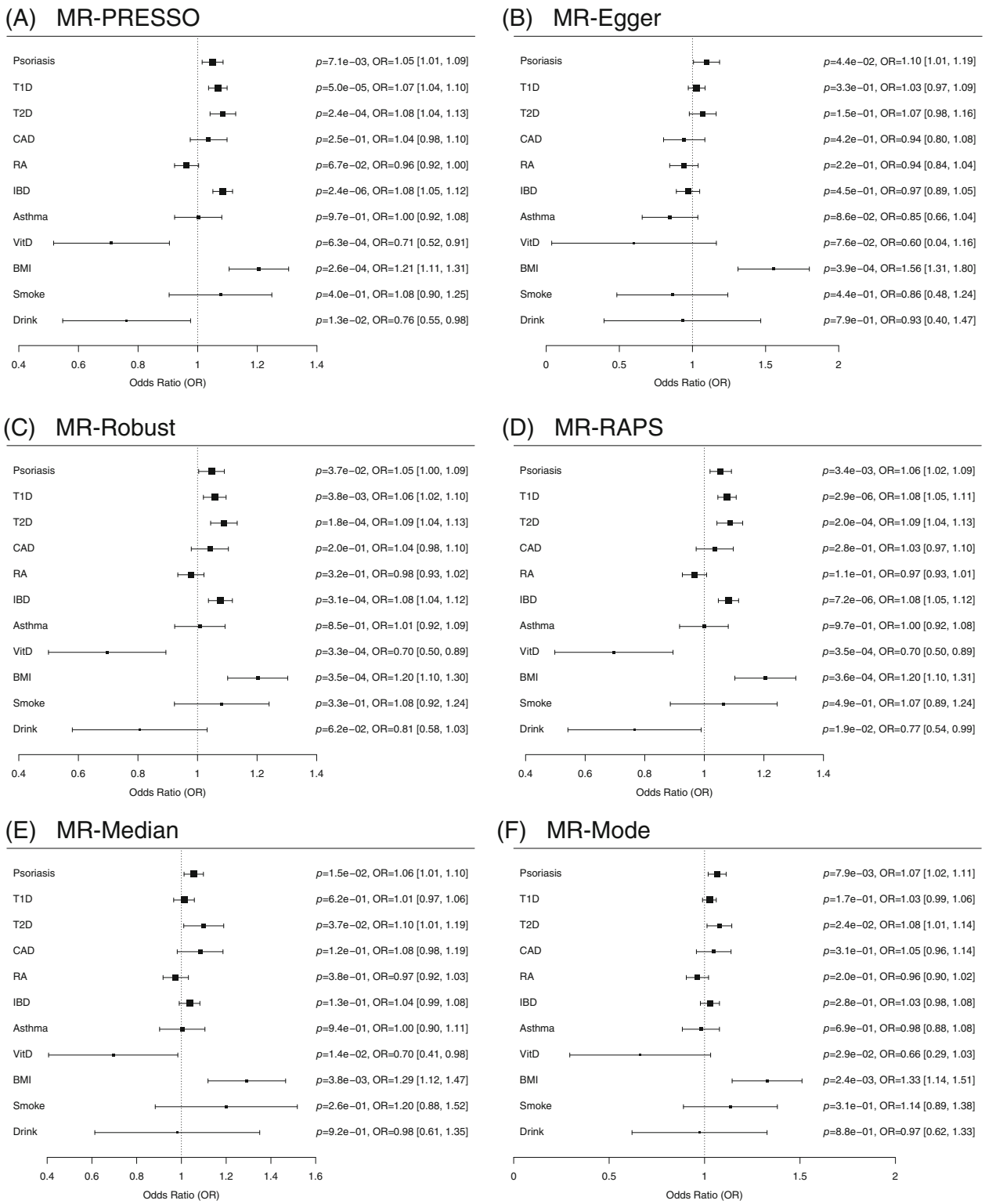

FIGURE 3: Mendelian randomization (MR) results for the effects of psoriasis and other comorbidities on multiple sclerosis. Forest plots generated from the results of six MR techniques (A–F). BMI = body mass index; CAD = coronary artery disease; Drink = drinks per week; IBD = inflammatory bowel disease; OR = odds ratio; *p* = *p* value; RA = rheumatoid arthritis; Smoke = cigarettes per day; T1D = type 1 diabetes; T2D = type 2 diabetes; VitD = vitamin D (25OHD).

example, the 17q21.2 (*STAT3*, *STAT5A/B*) shared locus is highly connected with the 7p14.1 (*ELMO1*) shared locus (co-expressing in 642 experiments), whereas the 5q31.1 (*CSF2*, *P4HA2*) opposing locus is highly connected with the 2p16.1 (*REL*, *PUS10*) opposing locus (in 505 experiments).

We inferred distinct groups of loci/genes from the log-weighted LINCS data by applying four different community detection algorithms (leading eigenvector, Louvain, optimal integer programming, and spin-glass) in the iGraph software package.[79] Three co-expressing clusters (Table S10 in Data S1) were consistently identified by all four algorithms and were unaffected by including or excluding the MHC. We applied pathway enrichment analysis (excluding the MHC) using Enrichr,[80] which aggregates annotations from multiple sources. In the Kyoto Encyclopedia of Genes and Genomes, the most significant pathway for cluster 1 (including *CSF2* and *TNFAIP3*) was IL-17 signaling (OR 39.32, $p = 1.6 \times 10^{-3}$), for cluster 2 (including *IL12B* and *TYK2*) it was Janus kinase–signal transducers and activators of transcription (JAK–STAT) signaling (OR 35.85, $p = 1.1 \times 10^{-5}$), and for cluster 3 (including *CAMK2G* and *TNFRSF1A*) it was necroptosis (OR 161.01, $p = 3.7 \times 10^{-9}$).

Cluster 1 was also significantly enriched for TNFα signaling pathways in the National Center for Advancing Translational Sciences BioPlanet (OR 67.37, $p = 1.4 \times 10^{-6}$) and the Molecular Signatures Database (OR 30.14, $p = 2.7 \times 10^{-4}$), whereas cluster 2 and 3 were both significant for IL-6–JAK–STAT3 signaling in the Molecular Signatures Database (OR 47.38, $p = 6.2 \times 10^{-5}$ and OR 118.49, $p = 6.6 \times 10^{-6}$, respectively). Cluster 2 was also significantly enriched for IL-12 signaling in BioPlanet (OR 93.31, $p = 3.0 \times 10^{-7}$). Overall, there appear to be two main mechanisms in which the TDMA loci are involved: IL-17–TNFα signaling (cluster 1) and JAK–STAT signaling (clusters 2 and 3). We annotated Table S10 in Data S1 to show which loci have genes involved in each pathway.

Mendelian Randomization

Figure 3 provides estimates of causal effects on MS for each MR technique we applied, whereas Figure S25 in Data S1 presents the same for psoriasis. Psoriasis was estimated to have a significant (false discovery rate <0.05) effect on MS by four of the six techniques, whereas it was nominally significant for the remaining two (MR-Egger and MR-Robust). By contrast, none of the techniques indicated a significant effect for MS on psoriasis, and only one (MR-RAPS) was nominally significant. Consistent with the (covariate adjusted) epidemiological analysis, estimates of the effect of psoriasis on MS ranged from $p = 7.1 \times 10^{-3}$, OR 1.05 for MR-PRESSO to $p = 7.9 \times 10^{-3}$, OR 1.07 for MR-Mode. We confirmed the causal effect of psoriasis on MS with a significant Steiger test result ($p = 6.6 \times 10^{-298}$), indicating higher correlation between the genetic instruments with psoriasis ($r^2 = 0.144$) than MS ($r^2 = 0.011$).

Selecting the six comorbidities/traits (T1D, T2D, IBD, vitamin D, BMI, and drinks/week) estimated to have a significant causal effect by at least one technique, we conducted a multivariable analysis using MR-GRAPPLE.[76] The causal effect of psoriasis on MS remained significant (OR = 1.04, $p = 5.8 \times 10^{-3}$), after conditioning on effects of T1D (OR 1.05, $p = 4.3 \times 10^{-7}$), T2D (OR 1.08, $p = 2.3 \times 10^{-3}$), IBD (OR 1.11, $p = 1.6 \times 10^{-11}$), and vitamin D levels (OR 0.75, $p = 9.4 \times 10^{-3}$); however, BMI and drinks/per week were no longer even nominally significant. Whereas by univariable analysis BMI was the only trait (apart from psoriasis) estimated to have at least a nominally significant effect on MS by all six techniques, it is known to have a causal effect on other traits, so it is possible that it affects MS indirectly.

Discussion

By combining large-scale epidemiological analysis with genetics, we confirmed a significant and causal association between psoriasis and MS that is independent of different confounding factors. A fully adjusted OR of 1.07 ($p = 1.2 \times 10^{-5}$) was estimated using medical claims data from ∼900,000 patients with psoriasis and/or MS and ∼30 million controls. MR techniques gave comparable effect sizes (OR 1.05–1.07), with OR 1.04 ($p = 5.8 \times 10^{-3}$) when conditioning on T1D, T2D, IBD, vitamin D, BMI, and drinks/per week (traits significant in univariable analysis), whereas no significant causal effect was observed for MS on psoriasis. In total, >20 non-MHC genome-wide significant shared or opposing genetic loci were identified between psoriasis and MS that were at least suggestively significant ($p < 1 \times 10^{-4}$) for each trait and more significant in TDMA than both traits. In an independent replication study for MS, two of the suggestively significant loci (rs6672420 and rs5756405) were genotyped, and both were confirmed to be genome-wide significant (OR 1.06, $p = 1.5 \times 10^{-9}$; OR 1.07, $p = 5.4 \times 10^{-11}$).[1] No significant heterogeneity was identified for these markers between the main MS and replication cohorts, nor between the individual psoriasis cohorts. When combining the MS and psoriasis cohorts together (rather than applying TDMA), rs6672420 has nominally significant ($p = 0.01$) heterogeneity, whereas for rs5756405 it is not significant ($p = 0.98$). The mixture of shared and opposing loci is interesting, as it suggests a complex genetic relationship between psoriasis and MS. This could help explain why certain treatments (eg, TNFα inhibitors and IFNβ) are beneficial in only one of the two diseases. Our analysis of the co-expression of genes at these loci suggests IL-17/TNFα and JAK–STAT signaling to be particularly important mechanisms for the psoriasis/MS comorbidity.

We evaluated multiple different approaches for TDMA: inverse weighted meta-analysis,[62] typically used for single-trait GWAS, can favor loci that are dominated by one or the other trait, whereas equally weighted TDMA avoids this bias; however, it does not fully take advantage of the greater accuracy provided by larger studies; we also applied approximate conditional analysis (GCTA-COJO). It is reassuring that most of the loci were found by all three approaches; however, the loci from our equally weighted TDMA all had evidence of colocalization (through COLOC and SuSiE), whereas not all of the additional loci from the other approaches did. This does not rule out these loci from affecting the same genes and pathways in psoriasis and MS, but it suggests they may have different causal variants that could affect these pathways in different ways (ie, pleiotropy). We addressed potential pleiotropy in MR by removing any outliers detected by MR-PRESSO and using five other techniques that test the assumptions of MR. Furthermore, by applying multivariable analysis in addition to the traditional univariable approach, we controlled for the effect of confounding factors.

The TDMA loci we identified are enriched in H3K27ac active enhancer marks for B-cell centroblasts, both compared with the rest of the genome and with the psoriasis/MS-specific loci. Although the role of B cells has been elucidated in MS,[1] they have been less well studied in psoriasis, potentially because they are detected in smaller numbers than T cells in lesional skin.[81] Nevertheless, regulatory B-cell involvement in responses to the phosphodiesterase 4 inhibitor, apremilast, has recently been reported,[82] and they are able to suppress IL-23-mediated inflammation.[83] Previous research showed tonsils from psoriasis patients had a lower germinal center to marginal zone area ratio,[84] and germinal center affinity maturation plays an important role in MS.[85] B-cell activation is believed to be enhanced by neutrophil extracellular traps in MS,[86] as well as in lupus.[87] Although neutrophil extracellular traps have been found to promote psoriatic inflammation, particularly through Th17,[29,88] it has yet to be investigated whether they assist B-cell maturation in a similar way to other diseases. Biological effects of genetic signals are challenging to identify, and require mechanistic study; for example, through multiomic analysis. In Table 2, we show which genes have eQTL support in two large datasets (eQTLGen[89] and GTEx[90]), finding the lead marker of 80% of the loci to be an eQTL; however, further work is required to pinpoint and validate specific gene targets.

The use of medical claims data can have limitations, as they are primarily collected for billing purposes rather than research. We also did not have access to quantitative data on obesity, smoking, and alcohol use, and so used ICD-9/10 codes for these covariates instead. It is conceivable that this information would only be recorded if the physician considers these details to be relevant to the patient's health; for example, ICD codes reflect AUD, rather than the number of drinks consumed, and only 16% of patients were indicated as obese, whereas other studies suggest the proportion may be almost twice as high in the USA.[91] The overall consistency with genetic and MR results was reassuring. However, psoriatic arthritis occurs in up to 30% of psoriasis patients,[92] and can sometimes be misdiagnosed as RA. This could explain the strong effect sizes observed for RA in epidemiology, and lack of significance in MR, in which patients were assessed by rheumatologists. A recent survey[93] found the ICD-9/10 codes for MS have up to 92.4% sensitivity and 92.6% specificity, whereas for psoriasis, 81% of patients who have an ICD-10 code had a confirmed diagnosis,[94] with 88% sensitivity for ICD-9 codes.[95] However, ICD codes can still be inaccurate, especially for diseases such as MS that have variable symptoms, and future work will focus on developing and applying more rigorous case definitions; for example, based on prescriptions for disease-modifying therapies, or multiple visits to relevant specialists (as is recorded in Optum's deidentified Clinformatics® Data Mart[60]).

These limitations notwithstanding, the present study provides genetic and epidemiological evidence for similarity and the causal relationship between MS and psoriasis immunomes, while identifying important differences between these two complex diseases that should help guide future research.

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Author Contributions

M.T.P. and L.C.T. contributed to the conception and design of the study; M.T.P., R.P.N., J.E.G., L.T.E., and L.C.T. contributed to the acquisition and analysis of data; M.T.P. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

L.C.T. has received support from Galderma, Janssen, and Novartis. J.E.G. has served as a consultant to Almirall, BMS, Sanofi, AbbVie, Novartis, Eli Lilly, Pfizer, and Galderma; and has received research support from Almirall, Janssen, Novartis, Pfizer, BMS/Celgene, Timberpharma, and Galderma.

Data Availability Statement

The medical claims data is available by applying for access to Optum's deidentified Clinformatics® Data Mart. Access to the GWAS summary statistics is detailed in the manuscript for each study. Pathway and LINCS L1000 gene sets are available through the Enrichr website (https://maayanlab.cloud/Enrichr/).

References

1. Patsopoulos A. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. Science 2019;365: eaav7188.
2. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol 2017;13:25–36.
3. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: a review. JAMA 2021;325:765–779.
4. Tsoi LC, Stuart PE, Tian C, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun 2017;8:15382.
5. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. J Eur Acad Dermatol Vener 2012; 26:3–11.
6. Liu CY, Tung TH, Lee CY, et al. Association of multiple sclerosis with psoriasis: a systematic review and meta-analysis of observational studies. Am J Clin Dermatol 2019;20:201–208.
7. Egeberg A, Mallbris L, Gislason GH, et al. Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study. J Invest Dermatol 2016;136:93–98.
8. Luchtman DW, Ellwardt E, Larochelle C, Zipp F. IL-17 and related cytokines involved in the pathology and immunotherapy of multiple sclerosis: current and future developments. Cyt Growth Factor Rev 2014;25:403–413.
9. Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. Clin Rev Allergy Immunol 2018; 55:379–390.
10. Lees JR, Cross AH. A little stress is good: IFN-gamma, demyelination, and multiple sclerosis. J Clin Invest 2007;117:297–299.
11. Johnson-Huang LM, Suárez-Fariñas M, Pierson KC, et al. A single intradermal injection of IFN-γ induces an inflammatory state in both non-lesional psoriatic and healthy skin. J Invest Dermatol 2012;132: 1177–1187.
12. Lozeron P, Denier C, Lacroix C, Adams D. Long-term course of demyelinating neuropathies occurring during tumor necrosis factor-alpha-blocker therapy. Arch Neurol 2009;66:490–497.
13. Mylonas A, Conrad C. Psoriasis: classical vs. paradoxical. The Yin-Yang of TNF and type I interferon. Front Immunol 2018;9:2746.
14. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012; 367:1098–1107.
15. Altmeyer PJ, Mattlies U, Pawlak F, et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. J Am Acad Dermatol 1994;30:977–981.
16. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med 2014;371: 326–338.
17. Havrdova E, Belova A, Goloborodko A, et al. Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study. J Neurol 2016; 263:1287–1295.
18. Berkovich R, Yakupova A, Eskenazi J, et al. Improvement of comorbid psoriasis in patients with MS treated with natalizumab. Neurol Neuroimmunol Neuroinflamm 2021;8:e961.
19. Toussirot E, Bereau M, Bossert M, et al. Occurrence of psoriatic arthritis during interferon Beta 1a treatment for multiple sclerosis. Case Rep Rheumatol 2014;2014:949317.
20. Lonnberg AS, Skov L, Skytthe A, et al. Heritability of psoriasis in a large twin sample. Br J Dermatol 2013;169:412–416.
21. Fagnani C, Neale MC, Nisticò L, et al. Twin studies in multiple sclerosis: a meta-estimation of heritability and environmentality. Mult Scler 2015;21:1404–1413.
22. Westerlind H, Ramanujam R, Uvehag D, et al. Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. Brain 2014;137:770–778.
23. Cai Y, Fleming C, Yan J. New insights of T cells in the pathogenesis of psoriasis. Cell Mol Immunol 2012;9:302–309.
24. Steinman L. Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. Cell 1996;85:299–302.
25. Bielekova B, Sung MH, Kadom N, et al. Expansion and functional relevance of high-avidity myelin-specific $CD4^+$ T cells in multiple sclerosis. J Immunol 2004;172:3893–3904.
26. Cheuk S, Wikén M, Blomqvist L, et al. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. J Immunol 2014;192:3111–3120.
27. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. Nat Rev Immunol 2015;15:545–558.
28. Nishihara H, Soldati S, Mossu A, et al. Human $CD4^+$ T cell subsets differ in their abilities to cross endothelial and epithelial brain barriers in vitro. Fluids Barriers CNS 2020;17:3.
29. Lambert S, Hambro CA, Johnston A, et al. Neutrophil extracellular traps induce human Th17 cells: effect of psoriasis-associated TRAF3IP2 genotype. J Invest Dermatol 2019;139:1245–1253.
30. Cree BA, Rioux JD, McCauley JL, et al. A major histocompatibility class I locus contributes to multiple sclerosis susceptibility independently from HLA-DRB1*15:01. PLoS One 2010;5:e11296.
31. Mack SJ, Udell J, Cohen F, et al. Correction: high resolution HLA analysis reveals independent class I haplotypes and amino-acid motifs protective for multiple sclerosis. Genes Immun 2019;20:340.
32. Osoegawa K, Creary LE, Montero-Martín G, et al. High resolution haplotype analyses of classical HLA genes in families with multiple sclerosis highlights the role of HLA-DP alleles in disease susceptibility. Front Immunol 2021;12:644838.
33. Stuart PE, Tsoi LC, Nair RP, et al. Transethnic analysis of psoriasis susceptibility in south Asians and Europeans enhances fine mapping in the MHC and genome wide. HGG Adv 2022;3:100069.
34. Hollenbach JA, Oksenberg JR. The immunogenetics of multiple sclerosis: a comprehensive review. J Autoimmun 2015;64:13–25.
35. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133:377–385.
36. Simpson S Jr, Wang W, Otahal P, et al. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an

updated meta-analysis. J Neurol Neurosurg Psychiatry 2019;90: 1193–1200.

37. Sintzel MB, Rametta M, Reder AT. Vitamin D and multiple sclerosis: a comprehensive review. Neurol Ther 2018;7:59–85.
38. Barrea L, Savanelli MC, di Somma C, et al. Vitamin D and its role in psoriasis: an overview of the dermatologist and nutritionist. Rev Endocr Metab Disord 2017;18:195–205.
39. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab 2008;4:80–90.
40. von Essen MR, Kongsbak M, Schjerling P, et al. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nat Immunol 2010;11:344–349.
41. Tang J, Zhou R, Luger D, et al. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. J Immunol 2009;182:4624–4632.
42. Giustina A, Adler RA, Binkley N, et al. Controversies in vitamin D: summary statement from an international conference. J Clin Endocrinol Metab 2019;104:234–240.
43. Darwish H, Haddad R, Osman S, et al. Effect of vitamin D replacement on cognition in multiple sclerosis patients. Sci Rep 2017;7: 45926.
44. Burton JM, Kimball S, Vieth R, et al. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. Neurology 2010;74: 1852–1859.
45. Boswell K, Cameron H, West J, et al. Narrowband ultraviolet B treatment for psoriasis is highly economical and causes significant savings in cost for topical treatments. Br J Dermatol 2018;179:1148–1156.
46. Hart PH, Jones AP, Trend S, et al. A randomised, controlled clinical trial of narrowband UVB phototherapy for clinically isolated syndrome: the PhoCIS study. Mult Scler J Exp Transl Clin 2018;4: 2055217318773112.
47. Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev 2014;13: 981–1000.
48. Budu-Aggrey A, Brumpton B, Tyrrell J, et al. Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study. PLoS Med 2019;16:e1002739.
49. Mokry LE, Ross S, Timpson NJ, et al. Obesity and multiple sclerosis: a Mendelian randomization study. PLoS Med 2016;13:e1002053.
50. Zmora N, Bashiardes S, Levy M, Elinav E. The role of the immune system in metabolic health and disease. Cell Metab 2017;25: 506–521.
51. Zhao XY, Zhou L, Chen Z, et al. The obesity-induced adipokine sST2 exacerbates adipose T(reg) and ILC2 depletion and promotes insulin resistance. Sci Adv 2020;6:eaay6191.
52. Hedstrom AK, Olsson T, Alfredsson L. Smoking is a major preventable risk factor for multiple sclerosis. Mult Scler 2016;22:1021–1026.
53. Armstrong AW, Harskamp CT, Dhillon JS, Armstrong EJ. Psoriasis and smoking: a systematic review and meta-analysis. Br J Dermatol 2014;170:304–314.
54. Saul A, Ponsonby AL, Lucas RM, et al. Stressful life events and the risk of initial central nervous system demyelination. Mult Scler 2017; 23:1000–1007.
55. Stewart TJ, Tong W, Whitfeld MJ. The associations between psychological stress and psoriasis: a systematic review. Int J Dermatol 2018; 57:1275–1282.
56. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol 2007;61:288–299.
57. Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. Clin Dermatol 2007;25:606–615.
58. Jangi S, Gandhi R, Cox LM, et al. Alterations of the human gut microbiome in multiple sclerosis. Nat Commun 2016;7:12015.
59. Chang HW, Yan D, Singh R, et al. Alteration of the cutaneous microbiome in psoriasis and potential role in Th17 polarization. Microbiome 2018;6:154.
60. Gunaseelan V, Kenney B, Lee JS, Hu HM. Databases for surgical health services research: Clinformatics data Mart. Surgery 2019;165: 669–671.
61. Patrick MT, Stuart PE, Raja K, et al. Genetic signature to provide robust risk assessment of psoriatic arthritis development in psoriasis patients. Nat Commun 2018;9:4178.
62. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26: 2190–2191.
63. Patrick MT, Stuart PE, Zhang H, et al. Causal relationship and shared genetic loci between psoriasis and type 2 diabetes through trans-disease meta-analysis. J Invest Dermatol 2021;141:1493–1502.
64. Patrick MT, Zhang H, Wasikowski R, et al. Associations between COVID-19 and skin conditions identified through epidemiology and genomic studies. J Allergy Clin Immunol 2021;147:857–869.e7.
65. Yang J, Ferreira T, Morris AP, et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. Nat Genet 2012;44:s1–s3.
66. Shi H, Mancuso N, Spendlove S, Pasaniuc B. Local genetic correlation gives insights into the shared genetic architecture of complex traits. Am J Hum Genet 2017;101:737–751.
67. Berisa T, Pickrell JK. Approximately independent linkage disequilibrium blocks in human populations. Bioinformatics 2016;32:283–285.
68. Giambartolomei C, Vukcevic D, Schadt EE, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet 2014;10:e1004383.
69. Wallace C. A more accurate method for colocalisation analysis allowing for multiple causal variants. PLoS Genet 2021;17:e1009440.
70. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018;50:693–698.
71. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through egger regression. Int J Epidemiol 2015;44:512–525.
72. Burgess S, Bowden J, Dudbridge F, Thompson SG. Robust instrumental variable methods using multiple candidate instruments with application to Mendelian randomization. arXiv 2016.
73. Zhao Q, Wang J, Hemani G, et al. Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. arXiv 2018.
74. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40: 304–314.
75. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol 2017;46:1985–1998.
76. Wang J, Zhao Q, Bowden J, et al. Causal inference for heritable phenotypic risk factors using heterogeneous genetic instruments. PLoS Genet 2021;17:e1009575.
77. Farh KK, Marson A, Zhu J, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature 2015;518: 337–343.
78. Subramanian A, Narayan R, CORsello SM, et al. A next generation connectivity map: L1000 platform and the first 1,000,000 profiles. Cell 2017;171:1437–1452.e17.

79. Csardi G, Nepusz T. The Igraph software package for complex network research. Int J Complex Syst 2005;1695.

80. Kuleshov MV, Jones MR, Rouillard AD, et al. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. Nucleic Acids Res 2016;44:W90–W97.

81. Grän F, Kerstan A, Serfling E, et al. Current developments in the immunology of psoriasis. Yale J Biol Med 2020;93:97–110.

82. Mavropoulos A, Zafiriou E, Simopoulou T, et al. Apremilast increases IL-10-producing regulatory B cells and decreases proinflammatory T cells and innate cells in psoriatic arthritis and psoriasis. Rheumatology (Oxford) 2019;58:2240–2250.

83. Mizumaki K, Horii M, Kano M, et al. Suppression of IL-23-mediated psoriasis-like inflammation by regulatory B cells. Sci Rep 2021;11: 2106.

84. Sigurdardottir SL, Thorleifsdottir RH, Valdimarsson H, Johnston A. The association of sore throat and psoriasis might be explained by histologically distinctive tonsils and increased expression of skin-homing molecules by tonsil T cells. Clin Exp Immunol 2013;174: 139–151.

85. Corcione A, Aloisi F, Serafini B, et al. B-cell differentiation in the CNS of patients with multiple sclerosis. Autoimmun Rev 2005;4: 549–554.

86. Parker Harp CR, Archambault AS, Cheung M, et al. Neutrophils promote VLA-4-dependent B cell antigen presentation and accumulation within the meninges during neuroinflammation. Proc Natl Acad Sci U S A 2019;116:24221–24230.

87. Gestermann N, di Domizio J, Lande R, et al. Netting neutrophils activate autoreactive B cells in lupus. J Immunol 2018;200:3364–3371.

88. Herster F, Bittner Z, Archer NK, et al. Neutrophil extracellular trap-associated RNA and LL37 enable self-amplifying inflammation in psoriasis. Nat Commun 2020;11:105.

89. Võsa U, Claringbould A, Westra HJ, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet 2021;53: 1300–1310.

90. Aguet F. The GTEx consortium atlas of genetic regulatory effects across human tissues. Science 2020;369:1318–1330.

91. Inoue Y, Qin B, Poti J, et al. Epidemiology of obesity in adults: latest trends. Curr Obes Rep 2018;7:276–288.

92. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/north American dermatology clinics. J Am Acad Dermatol 2013;69:729–735.

93. St Germaine-Smith C, Metcalfe A, Pringsheim T, et al. Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. Neurology 2012;79:1049–1055.

94. Löfvendahl S, Theander E, Svensson Å, et al. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden—a population-based register study. PLoS One 2014;9:e98024.

95. Asgari MM, Wu JJ, Gelfand JM, et al. Validity of diagnostic codes and prevalence of psoriasis and psoriatic arthritis in a managed care population, 1996–2009. Pharmacoepidemiol Drug Saf 2013;22: 842–849.

96. Tsoi LC, Spain SL, Knight J, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. Nat Genet 2012;44:1341–1348.

97. Beecham AH, Patsopoulos NA, Xifara DK, et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat Genet 2013;45:1353–1360.

98. Bowes J, Budu-Aggrey A, Huffmeier U, et al. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. Nat Commun 2015;6:6046.

99. Sheng Y, Jin X, Xu J, et al. Sequencing-based approach identified three new susceptibility loci for psoriasis. Nat Commun 2014;5:4331.