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Genome-wide Association Study of Dermatomyositis Reveals Genetic Overlap with other Autoimmune Disorders

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AUTHOR CONTRIBUTIONS

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Abstract

Objective—To identify new genetic associations with juvenile and adult dermatomyositis (DM).

Methods—We performed a genome-wide association study (GWAS) of adult and juvenile DM patients of European ancestry (n = 1178) and controls (n = 4724). To assess genetic overlap with other autoimmune disorders, we examined whether 141 single nucleotide polymorphisms (SNPs) outside the major histocompatibility complex (MHC) locus, and previously associated with autoimmune diseases, predispose to DM.

Results—Compared to controls, patients with DM had a strong signal in the MHC region consisting of GWAS-level significance ($P < 5x10^{-8}$) at 80 genotyped SNPs. An analysis of 141 non-MHC SNPs previously associated with autoimmune diseases showed that three SNPs linked with three genes were associated with DM, with a false discovery rate (FDR) < 0.05. These genes were phospholipase C like 1 (*PLCL1*, rs6738825, FDR=0.00089), B lymphoid tyrosine kinase (*BLK*, rs2736340, FDR=0.00031), and chemokine (C-C motif) ligand 21 (*CCL21*, rs951005, FDR=0.0076). None of these genes was previously reported to be associated with DM.

Conclusion—Our findings confirm the MHC as the major genetic region associated with DM and indicate that DM shares non-MHC genetic features with other autoimmune diseases, suggesting the presence of additional novel risk loci. This first identification of autoimmune disease genetic predispositions shared with DM may lead to enhanced understanding of pathogenesis and novel diagnostic and therapeutic approaches.

Keywords

dermatomyositis; adult; juvenile; shared autoimmunity genes

The idiopathic inflammatory myopathies, or myositis syndromes, are a heterogeneous group of systemic disorders that have been proposed to be autoimmune diseases based largely on the presence of unique autoantibodies and/or self-directed T or B lymphocyte responses in some subsets of patients [1]. Myositis patients themselves can develop additional autoimmune diseases, and there is an elevated occurrence of other autoimmune diseases in close relatives [2; 3]. Recent genome-wide association studies (GWAS) have identified many novel genes associated with several autoimmune diseases [4]. However, outside of the human leukocyte antigen region, there is limited direct evidence supporting a genetic relationship between the idiopathic inflammatory myopathies and other autoimmune disorders [5]. The idiopathic inflammatory myopathies are relatively rare, with a prevalence of 10–15 cases per 100,000, and this has hindered progress in genetic mapping studies [6].

We assembled a large international collection of samples from subjects with dermatomyositis (DM), the most frequent and readily identified phenotype of the idiopathic inflammatory myopathies, to identify new genetic associations with myositis. DM is defined by pathognomonic rashes and chronic muscle inflammation, consisting primarily of CD4+ T lymphocytes, B lymphocytes, dendritic cells, and macrophages [1; 7]. DM in adults and children has similar clinical and pathologic features [6; 8] that likely share pathogenic mechanisms, including the involvement of type I interferon pathways [7]. To define the genetic architecture of DM, we performed the first GWAS of this disease, which confirmed a strong signal in the major histocompatibility complex (MHC) region and revealed enrichment of genetic loci that have been associated with a variety of other autoimmune disorders.

PATIENTS AND METHODS

Study populations

Investigators with collections of DNA samples from myositis patients formed a collaboration called the Myositis Genetics Consortium (MYOGEN) with the goal of identifying new genetic factors associated with myositis. We focused our first study on DM because of its relatively higher frequency in children and adults and more homogeneous features compared to other myositis phenotypes [6]. The criteria for inclusion of DM cases were predetermined to be probable or definite DM as defined by proximal weakness, myopathy on electromyography, muscle biopsy consistent with idiopathic inflammatory myopathy or elevated serum muscle enzymes, and the presence of Gottron's papules/sign or heliotrope rash, with exclusion of other causes of muscle disease per Bohan and Peter criteria [9]. Age at onset of less than 18 years defined juvenile DM. After excluding 241 cases due to low call rates (n = 123), outliers (n = 55), or related individuals (n = 48), 1178 Caucasian cases with either adult DM (n = 705) or juvenile DM (n = 473) from clinical centers in the US and Europe were analyzed.

The US cases were obtained from three centers, including the National Institutes of Health (234 adult DM and 140 juvenile DM), the Mayo Clinic (53 adult DM and 36 juvenile DM), and the Children's Memorial Research Center in Chicago (107 juvenile DM). The UK cases were obtained from the UK Adult Onset Myositis Immunogenetic Collaboration (149 adult DM) and the UK Juvenile Dermatomyositis Research Group (159 cases). Other European samples came from the Czech Republic (114 adult and 11 juvenile DM), Hungary (64 adult and 12 juvenile DM), Spain (43 adult and 4 juvenile DM), Sweden (37 adult and 4 juvenile DM), and the Netherlands (11 adult DM).

In order to optimize case-control matching, we utilized separate control groups for each geographic collection of patients. For control samples, single nucleotide polymorphism (SNP) genotyping of healthy Czech and Hungarian volunteers from the Institute of Rheumatology, Prague, Czech Republic or the University of Debrecen, Debrecen, Hungary was performed on either the Illumina Human1M-Duo v3 BeadChip (n = 235: 166 Czechs and 69 Hungarians) or the Illumina Human660W-Quad v1 BeadChip (n = 21: all Hungarian). US controls were taken from previously available data from the North American Rheumatoid Arthritis Consortium [10]. UK controls were taken from the available data from The Wellcome Trust Case-Control Consortium (WTCCC 1958 birth cohort on the Illumina Human1M-Duo v3 BeadChip (n = 2415; http://www.wtccc.org.uk/ccc1). Swedish and Dutch controls (n = 642) were taken from previously published datasets [11], and Spanish controls (n = 259) were obtained from blood bank volunteers in Granada, Spain using data generated on the Illumina Human1M-Duo v3 BeadChip. All subjects consented to be enrolled in protocols approved by local ethics boards.

Genotyping and quality control

Genotyping of cases was carried out using various Illumina GWAS arrays at the Feinstein Institute for Medical Research, Manhasset, New York, US. Since the genotyping was done over several years, the specific Illumina chip used for analysis was upgraded as new platforms became available. Among the cases, 86 were genotyped using the Illumina HumanHap550 BeadChip, 221 were genotyped using the Illumina HumanCNV370-Duo v1 BeadChip, 293 were genotyped using the Illumina Human610-Quad v1 BeadChip, and 578 were genotyped using the Illumina Human660W-Quad v1 BeadChip, according to the manufacturer's protocols (Illumina Inc., San Diego, CA). Only SNPs that were present on all platforms were evaluated. SNPs that yielded $P < 0.001$ in association tests between cases

genotyped on different chips within each geographic group were dropped in the final results (n=1372).

All data underwent quality control before merging and final statistical analyses. The following data were excluded: SNPs with a call rate of <95% on any platform, individuals with >10% missing rates in genotypes, and SNPs of minor allele frequency of ≤0.01 or Hardy-Weinberg equilibrium in controls with a *P* value ≤ 10^{-5}. Merged data were separated into five groups according to geographic region. Relatedness was checked by estimating the identity-by-descent coefficient in PLINK (http://pngu.mgh.harvard.edu/purcell/plink/) [12].

A PI-HAT (representing the estimated identity-by-descent sharing among relatives, with 0 indicating unrelated and 1 indicating an identical twin) threshold > 0.15 was used, and we retained only one member of each set of duplicated or related samples (n=48). Outliers identified in the clustering in PLINK (Z > 4 or < −4) were removed (n=15). Additional outliers (n=6) that deviated by more than 4 standard errors from the centroid were identified by principal component analysis in Eigenstrat (http://genepath.med.harvard.edu/~reich/Software.htm) using 16,819 SNPs that are in the linkage disequilibrium (LD)-pruned SNP set provided by The Gene, Environment Association Studies consortium (GENEVA) coordinating center [13]. We included the principal components in which cases and controls had significantly different loadings for each site, and this analysis required that we adjust for the top five principal components for analysis of the US data, no principal components for analysis of the UK data, six principal components for analysis of the Dutch data, one principal component for analysis of Central European data, and one principal component for analysis of Spanish data.

Statistical analysis

The additive model was used in the PLINK logistic association test for each group separately, including the top principal components as covariates to remove residual population structure. Then meta-analysis using PLINK was done for all five groups. For the focused analysis of autoimmune-related SNPs, we adopted a Benjamini Hochberg false discovery rate (FDR) of <0.05.

RESULTS

GWAS identified the MHC locus as the strongest genetic risk region for DM

The GWAS of 1178 cases and 4724 control samples included in this study (Table 1) showed GWAS-level significance ($P < 5x10^{-8}$) at 80 genotyped SNPs across the MHC region (Figure 1), which is consistent with prior targeted gene studies that associated this region with myositis phenotypes [5]. No significant differences were noted between males and females or between adult and juvenile DM in these analyses.

We used quantile-quantile (Q-Q) plots, which is a method for comparing two probability distributions by plotting quantiles against each other, to evaluate the comparability of tests we conducted to their expected distributions. We included any significant principal components as covariates to remove the residual population structure in GWAS for each geographic group before the meta-analysis (Table 1); therefore, we did not adjust population structure again in the meta-analysis. For the fixed-effect *P* values of genotyped SNPs in the GWAS meta-analysis, when comparing the observed versus the expected distribution of tests, we found no overall systematic inflation of the number of positive tests (Figure 2A), as the ratio of the median chi-square test to the expected value gave a lambda ratio of 1.043, which is close to the expected value of 1.0 (Table 1). These findings were essentially unchanged after eliminating the MHC region (lambda = 1.037, Figure 2B). The random-

effect *P* values of genotyped SNPs in the GWAS meta-analysis were essentially the same as or very similar to the fixed-effect *P* values (data not shown).

GWAS of DM reveals genetic overlap with other autoimmune disorders

Given the familial aggregation of DM with several common autoimmune diseases, we tested the hypothesis that DM has a genetic architecture similar to that of other autoimmune diseases that have been found to be associated with first-degree relatives of DM patients [2; 3]. Therefore, we selected 269 SNPs that had been associated with rheumatoid arthritis (RA) [14; 15], systemic lupus erythematosus (SLE) [16; 17], type 1 diabetes [18; 19] [20], Crohn's disease [21; 22] [23], thyroid disease [24], gluten-sensitive enteropathy [25], or multiple sclerosis [26], and assessed their association with DM. Of these 269 SNPs, 141 were genotyped or were in LD (r^2 >0.9) with genotyped SNPs in DM, based on publicly accessible LD data from Hapmap 3 CEU (see data in Supplementary Table S1 for all 141 SNPs). Of these 141 SNPs, SNPs related to three genes, which had not been previously associated with DM, were found to have significant (FDR < 0.05) associations with DM (Table 2). These SNPs were related to phospholipase C like 1 (*PLCL1*: rs6738825 in LD with rs7572733, FDR=0.00089, also in LD with rs1518364, FDR=0.0037, and in LD with rs938929, FDR=0.0030); B lymphoid tyrosine kinase (*BLK*: rs2736340, FDR=0.0031); and chemokine (C-C motif) ligand 21 (*CCL21*: rs951005, FDR=0.0076, and in LD with rs2492358, FDR=0.0060) (see data in Supplementary Table S1 for all 141 SNPs). None of these SNPs was in LD with SNPs from the other genes. Minor variations were noted in the SNP associations between the adult and juvenile DM cohorts, but no significant differences were seen.

To assess the relevance of these autoimmune-related SNPs to DM, we evaluated Q-Q plots of these SNPs in DM and found a marked excess of positive associations of these SNPs with DM across the range of variants (Figure 3, lambda = 2.59). The current study had a low value of lambda in the entire population of SNPs that had been genotyped.

DISCUSSION

This work, which to our knowledge is the first GWAS of any form of myositis, is consistent with previous targeted studies suggesting that the MHC is the major genetic region associated with DM [5]. In addition, we have provided initial evidence that a number of non-MHC genes that were previously associated with other autoimmune diseases are also associated with DM. None of these new associations, which require replication for confirmation, has been previously reported for any form of myositis. Sufficient numbers of myositis samples are not yet available to allow independent consideration of other myositis phenotypes, and these should be addressed in future investigations.

Although this GWAS had a sample size comparable to similar studies of other autoimmune diseases that did identify significant non-MHC signals, no genetic signals with a genome-wide level of significance were observed outside of the MHC. This may be due to a relatively weaker genetic influence and stronger environmental influence on DM susceptibility compared to other autoimmune diseases, or it could be a reflection of disease heterogeneity [1].

By focusing our analysis on a subset of SNPs that are known to be associated with various forms of autoimmunity, we have been able to evaluate these associations in DM without the statistical implications of multiple testing that are associated with a full GWAS analysis. Thus, we have provided evidence for associations between DM and a number of genes previously identified as risk factors for other forms of autoimmunity. These data are consistent with the familial clustering of multiple autoimmune diseases [27], as well as the

higher frequencies of certain autoimmune diseases in close relatives of myositis patients [2; 3]. The direction and strength of association with these risk alleles were consistent with published findings in other autoimmune diseases [14; 16; 19; 21; 26]. Nonetheless, we do not believe that our current findings allow us to effectively compare genetic risk scores for DM and other autoimmune diseases at this time.

The strongest non-MHC association of SNPs with DM that are seen in other autoimmune diseases was a suggestive signal on chromosome 2q that was observed in a region containing *PLCL1*, which is involved in an inositol phospholipid-based intracellular signaling cascade (http://www.omim.org/entry/600597). In this case three typed SNPs (rs7572733, rs1518364, and rs938929) were in strong LD with a *PLCL1* SNP (rs6738825), which was previously associated with SLE. PLCL1 is involved not only in the inositol phospholipid-based intracellular signaling cascade, but also regulates the turnover of receptors, and thus it contributes to the maintenance of muscle tone and of gamma-aminobutyric acid–mediated synaptic inhibition [28]. Yet the exact mechanism by which PLCL1 could be associated with the pathogenesis of DM is not clear and will require additional study.

The other autoimmunity genes that are shared with DM encode proteins that current studies suggest are likely to play a role in the pathogenesis of DM. Among the genes found to be common with other autoimmune diseases, *BLK* encodes a nonreceptor tyrosine kinase of the src family of proto-oncogenes that are typically involved in cell proliferation and differentiation. The BLK protein has a role in B cell receptor signaling and B cell development, and B cells are prominent forms of mononuclear cells found in DM skin and muscle biopsies [29] as well as markers of disease activity [8]. Further evidence for the role of B cells in DM comes from the growing list of disease-specific autoantibodies and from anecdotal reports of the efficacy of anti-B cell therapies [1]. The *BLK* gene has been associated with SLE [30], systemic sclerosis [31], Sjögren's syndrome [32], and RA [10], diseases for which B cells are suspected to play important pathogenic roles and with which DM may occasionally form an overlap syndrome. The function of BLK in human B cells and other hematopoietic cells is not well studied, so little information is available regarding the regulation of *BLK* at the mRNA and protein levels in cell lines. Nonetheless, the rs922483 allele in the *BLK* gene, which is in LD with rs2736340, is reported to downregulate both *BLK* mRNA and protein expression in primary human transitional and naïve B cells from cord blood but not from adult B cell subsets, suggesting that involvement of BLK in the risk for autoimmune disease occurs during the early stages of B cell development [33].

CCL21 is one of several chemokine genes clustered on the p-arm of chromosome 9. The protein encoded by this gene inhibits hematopoiesis and stimulates chemotaxis *in vitro* for thymocytes and activated T cells [34]. The CCL21 protein may also play roles in mediating the homing of lymphocytes to secondary lymphoid organs in angiogenesis [35] and in B cell migration and proliferation [36] in RA. It is a high-affinity functional ligand for chemokine receptor 7 (CCR7) that is expressed on T and B lymphocytes. CCR7 and CCL21 are both expressed on mononuclear cells in the muscles of myositis patients, and CCL21 is also expressed on plasmacytoid dendritic cells, which are important sources for the interferon signature seen in both adult and juvenile DM [37]. CCL21 is also expressed in the extranodal lymphoid microstructures in muscle in juvenile DM [38]. SNPs of CCL21 have been associated with RA, although the functional nature of these SNPs and their possible role in pathogenesis remain to be elucidated [14].

Given the limited information available on the pathogenic mechanisms in DM, as well as the specific functions of the alleles of genes associated with autoimmunity, more investigation is needed to understand the implications of these SNP associations.

The limitations of this study include its moderate statistical power, use of multiple Illumina arrays, and possible heterogeneity from multiple autoantibody phenotypes whose genetic associations sometimes vary from the clinical phenotypes [5], which should all be addressed in future larger confirmatory studies.

Taken together, our findings suggest that DM shares genetic features with other autoimmune diseases, including major genetic contributions in the MHC region and several non-MHC genes that may interact in common functional pathways [39]. This is the first systematic identification of genetic predispositions that are common to autoimmune diseases and that promote the development of DM. An enhanced appreciation of the autoimmune pathogenesis of DM and identification and confirmation of additional genetic risk factors should ultimately lead to molecular profiles that could catalyze novel diagnostic and therapeutic advances.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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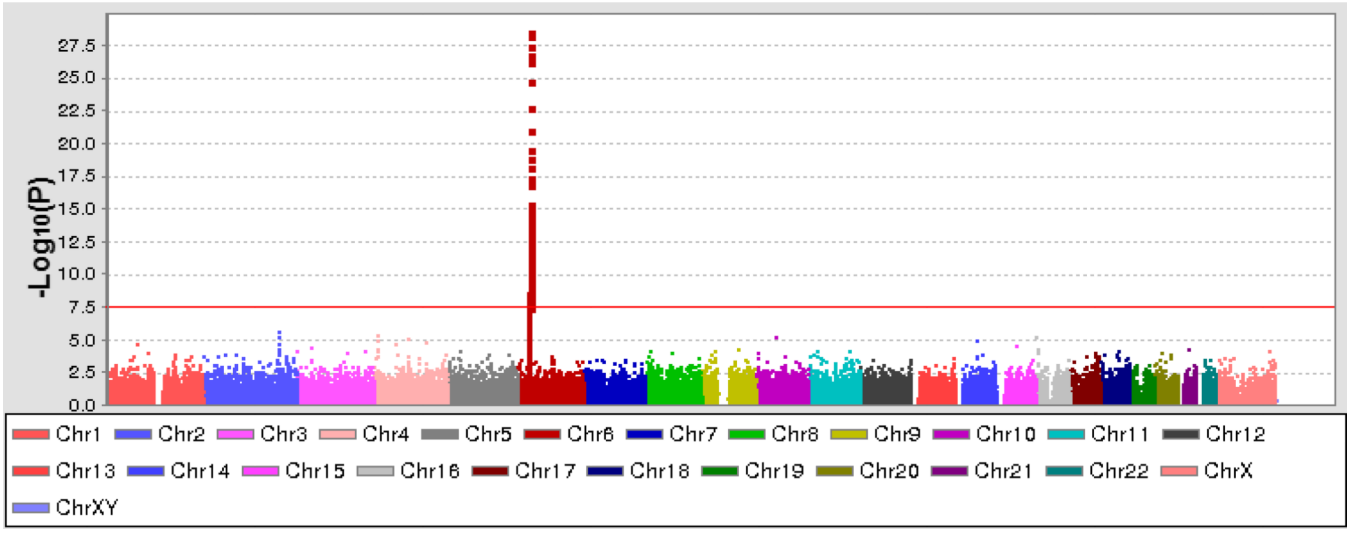

Figure 1.

Results of genome-wide association analysis of dermatomyositis plotted on a genomic scale (Manhattan plot) showing *P* values for 242,876 successfully genotyped single-nucleotide polymorphisms. The orange line represents the genome-wide level of significance ($P = 5x10^{-8}$). Chr = chromosome.

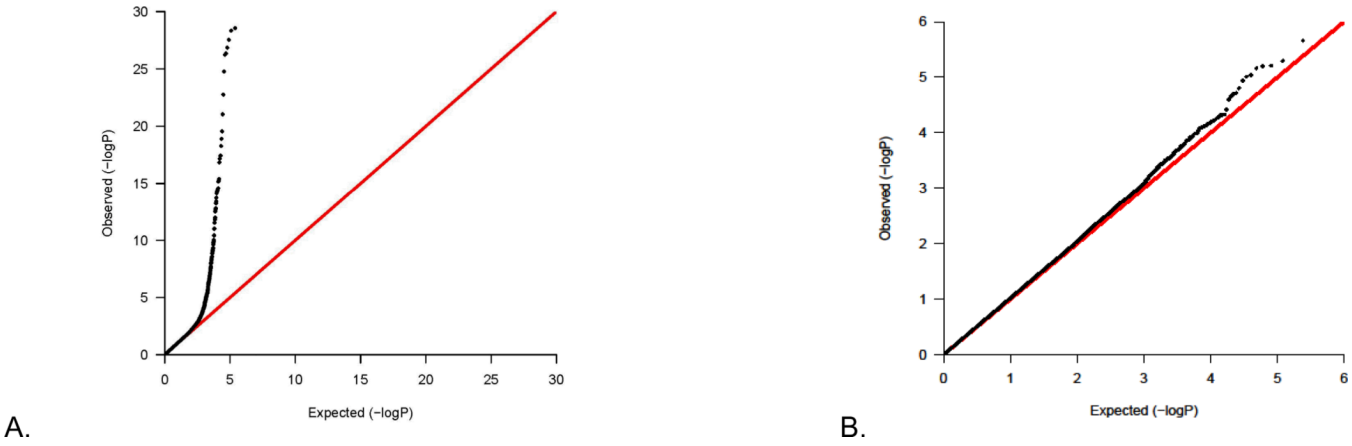

Figure 2.

(A) Quantile-quantile (Q-Q) plot of the genome-wide meta-analysis (lambda = 1.043). (B) Q-Q plot of the genome-wide meta-analysis without the major histocompatibility complex region (lambda = 1.037).

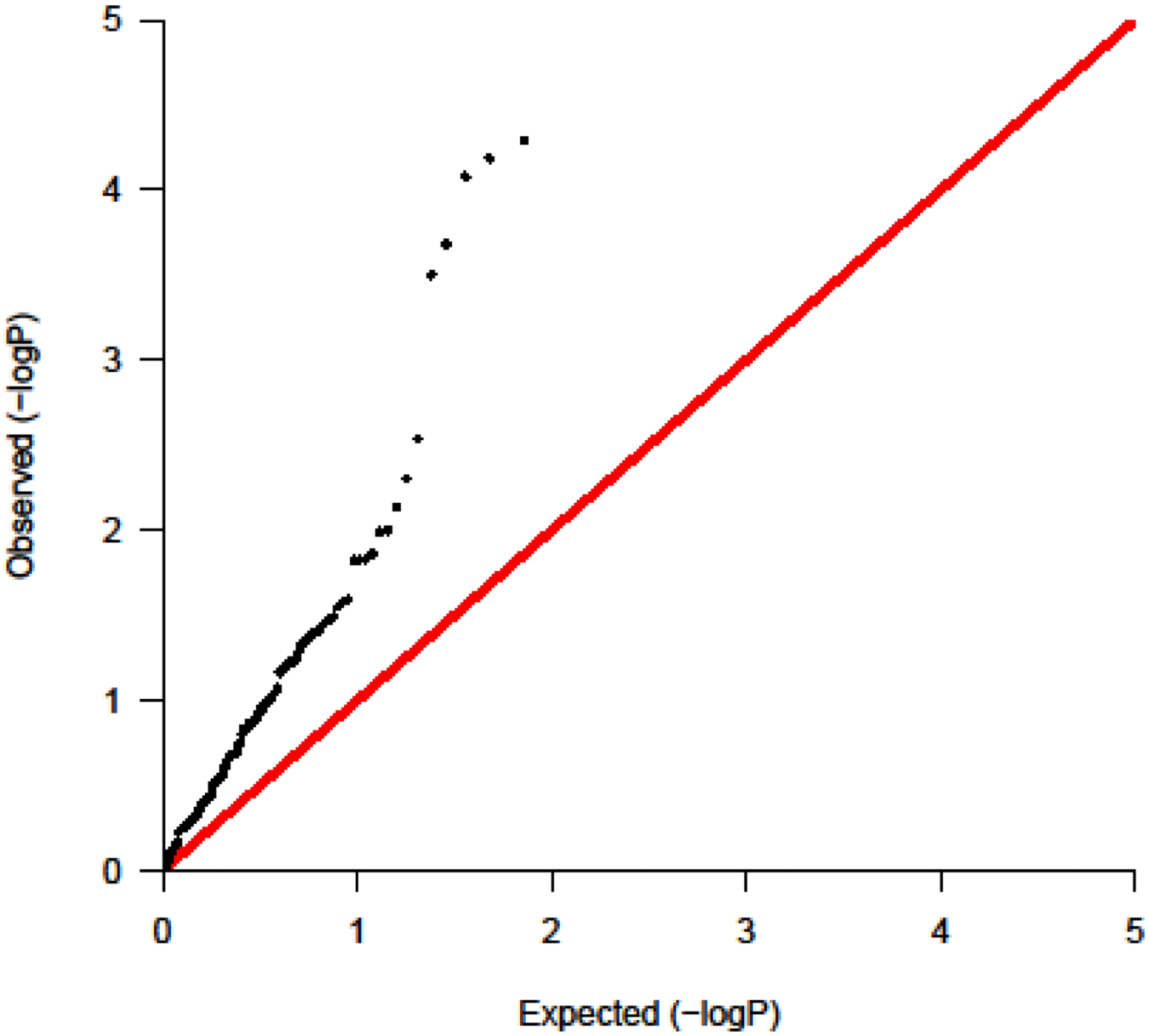

Figure 3.
Quantile-quantile (Q-Q) plot showing an excess of positive associations of published genome-wide association study non-major histocompatibility complex single-nucleotide polymorphisms for autoimmune diseases with those for dermatomyositis (lambda = 2.59).

Table 1

Characteristics of the dermatomyositis cases, controls and SNP data included in the study

Population	Cases				Controls		No. of successfully genotyped SNPs	Covariate	Genomic inflation factor (λ)
	Adult dermatomyositis		Juvenile dermatomyositis						
	Sample size	Female (%)	Sample size	Female (%)	Sample size	Female (%)			
Czech/Hungarian	178	70.8%	23	78.3%	256	57.4%	242530	Population structure	1.01
Spanish	43	81.4%	4	50.0%	259	65.6%	242871	Population structure	1.009
Swedish/Dutch	48	68.8%	4	75.0%	642	72.4%	242644	Population structure	1.021
UK	149	65.8%	159	70.4%	2415	47.8%	236039	None	1
USA	287	76.0%	283	69.6%	1152	70.8%	237155	Population structure	1.073
Meta-analysis	705	72.4%	473	70.2%	4724	58.2%	241502	None	1.043

Table 2

Overlap of published genome-wide association study single nucleotide polymorphisms for autoimmune diseases with those for dermatomyositis*

Gene Name	SNP Marker	Original SNP/LD	Chr: Position	OR (CI)	*P*	FDR	SNP Disease Source [ref]
PLCL1	rs7572733	rs6738825/0.979	2: 198929806	0.80 (0.72–0.88)	6.18E-06	0.00089	SLE [17]
PLCL1	rs1518364	rs6738825/0.958	2: 198809975	1.22 (1.11–1.35)	5.11E-05	0.0037	SLE [17]
PLCL1	rs938929	rs6738825/0.958	2: 198780860	1.22 (1.10–1.34)	0.00008322	0.0030	SLE [17]
BLK	rs2736340		8: 11343973	1.25 (1.12–1.40)	0.0000653	0.0031	RA [14]
CCL21	rs2492358	rs951005/1.0	9: 34737828	0.77 (0.67–0.88)	0.0002093	0.0060	RA [14]
CCL21	rs951005		9: 34743681	0.77 (0.67–0.89)	0.000317	0.0076	RA [14]

*Only SNPs with FDR < 0.05 are listed; SNP marker = directly genotyped single nucleotide polymorphism (SNP) by genome-wide association studies; Original SNP = original SNPs among 141 SNPs associated with autoimmune diseases, if not directly genotyped; LD = linkage disequilibrium in r^2 with the directly genotyped SNP on Illumina arrays; Chr = chromosome; Position = base pair in hg19/build37 coordinate; OR = odds ratio; CI = 95% confidence interval; *P* = fixed effect *P* value in meta-analysis; FDR = false discovery rate; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis.