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Meta-analysis in granulomatosis with polyangiitis reveals shared susceptibility loci with rheumatoid arthritis

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Abstract

Objectives—To examine the association of previously identified autoimmune disease susceptibility loci with granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), and determine whether genetic susceptibility profiles of other autoimmune diseases are associated with GPA

Methods—Genetic data from two cohorts were meta-analyzed. Genotypes for 168 previously identified single nucleotide polymorphisms (SNPs) associated with susceptibility to different autoimmune diseases were ascertained for a total of 880 GPA cases and 1969 controls of

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European descent. Single marker associations were identified using additive logistic regression models. Multi-SNP associations with GPA were assessed using genetic risk scores based on susceptibility loci for Crohn's disease, type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, celiac disease, and ulcerative colitis. Adjustment for population substructure was performed in all analyses using ancestry informative markers and principal components analysis.

Results—Genetic polymorphisms in *CTLA4* were significantly associated with GPA in the single-marker meta-analysis (OR 0.79. 95% CI 0.70–0.89, $p=9.8\times10^{-5}$). A genetic risk score based on rheumatoid arthritis susceptibility markers was significantly associated with GPA (OR 1.05 per 1-unit increase in genetic risk score, 95% CI 1.02–1.08, $p=5.1\times10^{-5}$).

Conclusions—Rheumatoid arthritis and GPA may arise from a similar genetic predisposition. Aside from *CTLA4*, other loci previously found to be associated with common autoimmune diseases were not statistically associated with GPA in this study.

Keywords

genetics; vasculitis; granulomatosis with polyangiitis; rheumatoid arthritis; *CTLA4*

INTRODUCTION

Granulomatosis with polyangiitis (GPA, Wegener's) is a severe, multi-system inflammatory disease with a prevalence of about 1 in 10,000–40,000 persons of European ancestry (1). GPA is thought to be an autoimmune disease, since it is highly associated with autoantibodies to proteinase-3 (PR3), which are rare in the general population (2–4). It is unclear to what extent genetics contributes to risk of GPA. Family studies suggest a slight increase in risk (estimated at 1.5 – 3-fold) among close relatives, but this estimate is imprecise due to the rarity of the disease (5, 6).

Two genetic associations with GPA are well-established. One is in the HLA region, specifically *HLA-DPB1* (7), and this finding provides further support for considering GPA to be fundamentally an autoimmune disease. The other is a null allele in alpha-1-antitrypsin (*A1AT* or *SERPINA*) (8–10). However, because these null alleles are uncommon, haploinsufficiency of *A1AT* accounts for only about 7% of cases of GPA (8). Many other polymorphisms have been investigated on the basis of knowledge of the role of the associated gene in immunity, but only two associations (in *CD226* and *FCGR3B*) have been confirmed in more than one cohort (11, 12).

The contribution of many common genetic variants to risk for more common autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes, and inflammatory bowel disease, has been established through genome-wide association studies (GWAS) and meta-analyses thereof (13–27). Some polymorphisms appear to confer risk to multiple autoimmune diseases. Although candidate gene studies in GPA have often investigated genes related to immunity, they have usually followed hypotheses about the functions of particular genes of interest rather than focusing on polymorphisms that have already been shown to predispose to other diseases, with few exceptions (28, 29).

Support for pursuing the hypothesis that genes that predispose to other autoimmune diseases are also risk alleles for GPA comes from two sources. First, studies of familial associations between GPA and other autoimmune diseases have concluded that first-degree relatives of persons with GPA have a modest increase in risk of common autoimmune diseases in general (relative risk 1.32), and of rheumatoid arthritis, multiple sclerosis, psoriatic arthritis, and Sjogren's syndrome in particular (6, 30). Calculated associations with lupus, inflammatory bowel disease, and ankylosing spondylitis were of similar magnitude but did

not reach statistical significance, since these diseases were less common in the cohort (6). Second, several polymorphisms that have each been associated with risk of GPA in 1–2 cohorts have also been associated with other autoimmune diseases (11, 12, 28, 29, 31, 32).

We performed a candidate gene study in GPA of 168 single-nucleotide polymorphisms (SNPs) associated with one or more autoimmune diseases, with two goals: i) identify individual SNPs associated with GPA using a case-control design in two cohorts, and ii) test multi-SNP models of genetic risk (genetic risk scores, GRSs) developed for individual autoimmune diseases for their ability to predict increased risk of GPA, regardless of the statistical significance of the component SNPs. The study was more rigorous than most candidate gene studies, because we utilized ancestry-informative markers (AIMs) and principal components analysis to control for population stratification.

PATIENTS AND METHODS

Study Subjects

Two cohorts were analyzed independently and then together by meta-analysis. All patients were enrolled using protocols approved by Institutional Review/Ethics Boards at the participating sites.

In the first cohort, 431 GPA cases and 392 healthy controls enrolled in the Wegener's Granulomatosis Genetics Repository (WGGER) (8) and of self-identified European descent were genotyped. Subjects were recruited at 8 US centers between 2001 and 2005, and clinical data from cases were recorded using a standardized form. These data were reviewed to ensure that all cases met American College of Rheumatology (ACR) 1990 classification criteria for GPA (33). Controls were unrelated to cases and denied a personal or family history of autoimmune inflammatory diseases. Demographic data collected from cases and controls included age, sex, and race/ethnicity. In this sample, 47% of cases and 60% of controls were female, and mean age was 53.1 years (range 18–87) in cases and 49.5 (range 18–85) in controls. To increase the statistical power of this initial cohort, 82 individuals with northern and western European ancestry genotyped in the International HapMap Project (www.hapmap.org) from the CEPH (Centre d'Etude du Polymorphisme Humain) collection were included with the healthy controls in this study (see below). Thus, the total sample size for this cohort was 431 GPA cases and 473 controls.

A second cohort of 464 GPA cases was assembled in Toronto between 2001 and 2010 from multiple sites (50% US, 40% Canada, 10% Europe, less than 1% other locations), through physician contacts and online advertisement. Information about symptoms, organ involvement, and c-ANCA levels was garnered from physician records, and all cases met modified 1990 ACR criteria for GPA. Mean age was 52.8 years (range 14–85), and 55% of cases were female.

Controls for the Toronto cohort (n=1503) were derived from two sources: 380 volunteers from the Toronto metropolitan area (mean age 40 years, range 23–91, 82% female), and 1123 healthy persons recruited into the M.D. Anderson Cancer Center Lung Cancer Study (ongoing since 1999) from the Kelsey-Seibold Clinics in the Houston metropolitan area (mean age 61.1 years, 43% female). Controls reported no history of autoimmune disease, and all cases and controls were of European descent by self-report.

SNP Selection

A custom set of 384 SNPs, including 192 associated with autoimmune diseases and 192 ancestry informative markers (AIMs) (34–36) was chosen for genotyping the WGGER cohort. All autoimmune disease-associated SNPs were outside of the HLA region. After

application of quality-control filters and imputation of SNPs missing in the Toronto cohort (see below), 168 SNPs associated with autoimmune diseases remained (Supplementary Table 1): 58 with Crohn's disease (13, 14, 23, 27, 37, 38), 32 with type I diabetes (15, 16, 39–42), 23 with systemic lupus erythematosus (17–21, 43–47), 24 with rheumatoid arthritis (22, 36, 48–50), 12 with ulcerative colitis (23–25, 27, 38, 51), 8 with psoriasis (26, 52), 15 with celiac disease (53–55), 2 with multiple sclerosis (56–58), 2 with ankylosing spondylitis (59), and 1 with primary biliary cirrhosis (60). Some of these SNPs have been associated with more than one of the listed diseases, explaining why the numbers associated with individual diseases add to more than 168. The AIMs genotyped for the subjects in WGGER are informative for both continental and intra-European ancestry (Supplementary Table 1).

Genotyping, Data Quality Filters, and Imputation

Genotyping of the WGGER samples was performed at the Broad Institute (Cambridge, MA) using the BeadXpress platform from Illumina (San Diego, CA). Genotypes of the autoimmunity-associated SNPs in the Toronto cohort were determined using data from a genome-wide association study (GWAS) that had been performed previously using the Illumina HumanCNV370-quad v3 (464 cases and 380 controls) and HumanHap370 BeadChip (1123 controls) platforms (K. Siminovitch et al., submitted).

The following data quality filters were applied separately to the WGGER and Toronto cohorts: SNPs were removed from analysis if they had greater than 10% missing genotypes, a minor allele frequency less than 1%, or evidence of deviation from Hardy Weinberg equilibrium (HWE) in the controls ($p<0.0001$). Subjects were removed from analysis if their overall genotyping rate was < 90% or were population outliers (more than 6 standard deviations from the mean along any of the first 10 principal components, see below). Duplicate individuals were identified using identity-by-state measures calculated in PLINK v1.07 (61) (http://pngu.mgh.harvard.edu/purcell/plink/) between all of the samples in this study using the 218 genotyped SNPs that overlapped between the WGGER and Toronto cohorts, and individuals who were enrolled in both studies were retained in the WGGER cohort.

Ten SNPs were removed from the WGGER cohort for failing the data quality filters described above. Thus, 374 SNPs (187 autoimmunity-associated and 187 AIMs) were used in subsequent steps. Eleven samples (7 cases and 4 controls) were excluded on the basis of poor genotyping rates, leaving 424 cases and 469 controls with an average call rate of 99.7%.

In the Toronto cohort, 92 of the 187 candidate SNPs were successfully genotyped. Five duplicate GPA cases were identified (pi_hat≈1.0) and 6 genetic outliers were removed from the Toronto cohort, leaving 456 cases and 1500 controls. The remaining 95 candidate SNPs not genotyped in the Toronto cohort were imputed using Impute version 2 (http://mathgen.stats.ox.ac.uk/impute/impute_v2.html) (62), using the 283 European samples from Phase I of the 1000 Genomes Project (2010.08.04 sequence index) as the reference. After filtering based on an info score of >0.80, 76 of the 95 SNPs were successfully imputed. Thus, 168 autoimmunity-associated SNPs were used for the final analysis.

Analysis for Population Substructure

Principal components analysis (PCA) was performed on the WGGER cohort using EIGENSTRAT (63) (http://genepath.med.harvard.edu/~reich/Software.htm) and data from all 187 AIMs. No genetic outliers were identified. Visualization of the first 2 principal components (PCs) showed that all 424 cases and 387 controls self-identified as non-

Hispanic European descent clustered with the 82 European (CEPH) subjects in HapMap Phase 3 included in the study.

PCA was also used to assess for population substructure for the Toronto cohort. After removal of SNPs in regions with extensive linkage disequilibrium on chromosomes 5 (44–51.5 Mb), 6 (25–33.5 Mb), 8 (8–12 Mb),11 (45–57 Mb), and 17 (40–43 Mb), all remaining SNPs on the genome-wide genotyping platform were used to calculate PCs using EIGENSTRAT. Six cases were removed as genetic outliers (more than 6 standard deviations from the mean of any of the first 10 PCs).

Association Study and Meta-Analysis

For the WGGER cohort and for candidate SNPs that had been genotyped in the Toronto cohort, association of each SNP genotype with GPA disease status was assessed separately in each cohort using logistic regression assuming additive genetic models using PLINK v1.07. The first two PCs specific to each cohort were included in all logistic regression models to adjust for population substructure. For SNPs imputed in the Toronto cohort, association with GPA was assessed using the score method in SNPTEST (v2.2.0). For these analyses, probabilistic genotypes were utilized assuming additive genetic models in logistic regression analyses, which also included the first two PCs to adjust for population substructure.

To produce an overall estimate of the association for each marker in the two cohorts, meta-analysis combining the results for each SNP was performed using PLINK v1.07. Results of fixed-effects models are reported, but random-effects models were also generated and produced identical results for the 10 SNPs with the lowest P-values. No significant heterogeneity was observed in the meta-analysis results.

P-values were adjusted for the false discovery rate (FDR) (64) based on the ranked P-values of 168 simultaneous tests, and an adjusted P-value < 0.05 was interpreted as significant.

Genetic Risk Scores (GRS)

For each subject, separate genetic risk scores for Crohn's disease (CD, 57 SNPs), type 1 diabetes (T1D, 32 SNPs), systemic lupus erythematosus (SLE, 22 SNPs), rheumatoid arthritis (RA, 23 SNPs), celiac disease (14 SNPs), and ulcerative colitis (UC, 11 SNPs) were calculated using the SNPs genotyped or imputed in this study that have previously been associated with those diseases (Supplementary Table 1). For each disease-specific GRS, the numbers of risk alleles present in each GPA case or control were added in an unweighted manner, and homozygous risk alleles were counted twice. Each missing genotype was replaced with the mean risk allele frequency for a given SNP among cases or controls. Probabilistic genotypes were utilized for imputed SNPs. For SNPs in linkage disequilibrium associated with the same disease (e.g., rs2070197 and rs10488631 (r^2=0.93) in *IRF5* which are both associated with SLE), the SNP with the most statistically significant association with GPA was retained in the GRS calculations. The distributions of GRS scores among cases and controls were compared by logistic regression, with the disease-specific GRS (as a continuous variable) and the first two PCs as the predictor variables and case/control status as the outcome variable. The WGGER and Toronto cohorts were analyzed separately and then combined in meta-analysis as above. Fixed- and random-effects models yielded identical results. All GRS analyses were performed using STATA 9.0/SE (College Station, TX, USA).

RESULTS

After implementing data quality measures, 168 SNPs in at least 141 candidate genes (Supplementary Table 1) were studied in a total of 880 GPA cases and 1969 controls of European descent between the WGGER (424 cases and 469 controls) and Toronto cohorts (456 cases and 1500 controls).

Association Study of Autoimmunity-Associated SNPs with GPA

In the WGGER cohort, twelve markers showed nominal evidence of association ($p_{unadjusted}$ <0.05), but none of the associations was significant after FDR correction. The most statistically significant association was with rs11618775 (OR 1.34, 95% CI 1.08–1.66, $p_{unadjusted}$=0.0073), which does not have a known gene within 100 kb upstream or downstream. This SNP was poorly imputed in the Toronto cohort, and thus was not included in further analyses. Out of the 168 SNPs analyzed in the Toronto cohort, 11 SNPs showed nominal evidence of association ($p_{unadjusted}$ <0.05). An imputed SNP, rs3087243 (*CTLA4*), was the most strongly associated with GPA (OR 0.78, 95% CI 0.67–0.91, $p_{unadjusted}$=0.0014). The most strongly associated genotyped SNP was rs2476601 in *PTPN22* (OR 1.41, 95% CI 1.12–1.79, p=0.0042). Neither marker was statistically significant after FDR correction.

Meta-analysis yielded a statistically significant association with GPA for rs3087243 in *CTLA4*, with 15 additional SNPs showing unadjusted p<0.05 (Table 1 and Supplementary Table 2). Three additional SNPs, in *CTLA4*, *PTPN22*, and *CD40*, narrowly missed the pre-specified significance cut-off, and the next six SNPs in order of significance were notable for involving pairs of SNPs in moderate to strong linkage disequilibrium in 3 regions (in or near *PARK7*, *IL27*, or *NKX2-3*).

Genetic Risk Scores Associated with GPA

As shown in Table 2, the GRS score derived from RA was slightly but significantly higher in GPA patients than in controls in both the WGGER and Toronto cohorts individually, and by meta-analysis (OR 1.05 per 1-unit increase in GRS, 95% CI 1.02–1.08, p=5.1E-05). Having an RA GRS score greater than the median was associated with a 37% greater odds of having GPA, compared to having a GRS below the median (OR 1.37 (95% CI 1.16–1.62, p=2.6E-06). After exclusion of the 3 top-ranked SNPs in the study (all of which are associated with RA, in *CTLA4* and *PTPN22*), GRS scores for RA remained slightly higher in cases than controls (OR from meta-analysis 1.04 per 1-unit increase in GRS, 95% CI 1.01–1.07, p=0.017), indicating that these two genes did not account completely for the GRS result. GRS scores for T1D were higher in GPA cases than controls in the Toronto cohort but not WGGER. Given the substantial heterogeneity of the T1D findings, meta-analysis was not felt to be appropriate; thus, results for the T1D GRS were inconclusive. GRSs derived from celiac disease, CD, SLE, and UC did not differ significantly in either cohort separately nor by meta-analysis, nor did scores comprised of the smaller numbers of risk SNPs (n=2–8) associated with the AS, MS, or psoriasis (data not shown).

Analysis of the distribution of OR's for all risk alleles used in the GRSs did not provide any additional evidence of skewing of autoimmunity-associated SNPs toward association with GPA: the mean OR of 1.01 (SD 0.09) was not significantly different from the null distribution.

DISCUSSION

In this study, one of the largest genetic studies of GPA to date, we investigated the comparability of genetic risk factors of GPA with other autoimmune diseases by examining

single-marker associations as well as composite genetic risk scores of previously identified autoimmune disease susceptibility loci.

In single marker analyses, we confirmed an association of GPA with genetic variation in *CTLA4*. The 2 SNPs in this gene found to be associated with GPA in this study, rs3087243 and rs231735, have been previously associated with RA and T1D (39, 49, 65). rs3087243 does not appear to be significantly linked to previously identified GPA-associated *CTLA4* polymorphisms rs5742909 (−319C/T) or rs231775 (+49A/G), with $r^2<0.1$, but rs231735 shows moderate linkage with rs231775 ($r^2=0.6$) (29, 66, 67). These findings suggest that *CTLA4* may harbor multiple genetic variants contributing to disease risk. rs3087243 has been suggested to influence *CTLA4* mRNA stability, since it is located ~300 bp downstream from the major 3′ poly-A tail, while rs231735 is located ~40 kb upstream of *CTLA4* and does not have a known functional effect. The *PTPN22* polymorphism that showed some evidence of association in this study, rs2476601, has been previously associated with GPA (28) and with multiple other autoimmune diseases (13, 15, 21, 65, 68). This non-synonymous polymorphism induces an amino acid change from arginine to tryptophan at codon 620, and is thought to increase its degradation leading to lymphocyte hyper-responsiveness (69).

Our findings also suggest that the risk of GPA and RA share a common genetic background, which was not observed for CD, SLE, T1D, or UC. This finding is supported by a previous epidemiologic study showing an increase in RA among offspring of patients with GPA (30). This finding is not intuitive, since the pulmonary and renal manifestations of GPA are not common in RA, and inflammatory arthritis, the hallmark of RA, is not present in all patients with GPA and is rarely destructive. Having a similar genetic background implies that the two diseases may share similar pathogenic mechanisms, and the shared association with alleles in *CTLA4* and *PTPN22* suggests that this mechanism involves the threshold for activation or deactivation of autoreactive T cells.

The major strength of this analysis is the relatively large sample size represented by the meta-analysis when compared to other candidate gene studies for GPA, which improved statistical power to test a relative large number of candidate genes. However, this study still had limited power to detect associations of modest effect sizes, and thus, there may be additional associations that have not been identified. Another strength is that careful adjustment for population stratification was performed, which is not always accounted for in candidate gene studies. Finally, not all of the associated loci for these autoimmune diseases were genotyped. Therefore, other loci may be shared between GPA and SLE, T1D, CD, and/or UC, and the genetic background for these diseases may be more similar to GPA than what was found in this study.

Further delineation of the genetic contribution to risk of GPA will likely require a combination of GWAS studies and an ongoing hypothesis-driven search for rare variants (such as null alleles in *A1AT/SERPINA*) that would be missed by such screens. A prediction of the current study might be that outside of *HLA-DPB1*, *CTLA4*, and perhaps a few other polymorphisms associated with multiple autoimmune diseases, most genes found to predispose to GPA will reflect the unique pathophysiology of this disease rather than more generic disruption of immune homeostasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

SNPs associated with GPA, listed in order of P-value.

					WGGER		Toronto			Meta-analysis	
Chr	**SNP**	**Disease(s)***	**Gene(s)**	**A**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**S**	**OR (95% CI)**	**P†**
2	rs3087243	RA,T1D	*CTLA4*	A	0.80 (0.66–0.97)	0.03	0.78 (0.67–0.91)	0.001	I	0.79 (0.70–0.89)	9.83E-05†
2	rs231735	RA	*CTLA4*	G	0.84 (0.69–1.02)	0.08	0.81 (0.70–0.94)	0.005	G	0.82 (0.73–0.92)	0.001
1	rs2476601	CD,Ps,RA,SLE,T1D	*PTPN22*	A	1.24 (0.92–1.69)	0.16	1.41 (1.12–1.79)	0.004	G	1.35 (1.12–1.62)	0.002
20	rs4810485	RA	*CD40*	T	0.80 (0.64–1.01)	0.05	0.81 (0.68–0.96)	0.02	I	0.81 (0.70–0.92)	0.002
1	rs3766606	Celiac	*PARK7,DJ-1*	T	0.79 (0.61–1.02)	0.07	0.80 (0.66–0.98)	0.03	I	0.80 (0.68–0.94)	0.005
16	rs4788084	T1D	*IL27*	T	1.13 (0.94–1.37)	0.19	1.21 (1.04–1.41)	0.01	G	1.18 (1.05–1.33)	0.006
16	rs151181	CD	*IL27,others*	C	1.16 (0.96–1.40)	0.12	1.20 (1.02–1.41)	0.03	I	1.18 (1.05–1.34)	0.007
10	rs6584283	CD,UC	*NKX2-3*	T	0.83 (0.69–1.00)	0.05	0.87 (0.75–1.01)	0.07	I	0.86 (0.76–0.96)	0.009
1	rs12727642	Celiac	*PARK7,TNFRSF9*	A	0.81 (0.64–1.05)	0.11	0.81 (0.66–1.00)	0.05	G	0.81 (0.69–0.95)	0.01
10	rs11190140	CD,UC	*NKX2-3*	T	0.85 (0.71–1.02)	0.08	0.87 (0.75–1.01)	0.07	G	0.86 (0.77–0.97)	0.01
13	rs9585056	T1D	*IDIN*	C	0.77 (0.62–0.96)	0.02	0.91 (0.76–1.09)	0.33	I	0.85 (0.74–0.98)	0.03
15	rs17574546	T1D	*RASGRP1*	C	1.15 (0.92–1.44)	0.21	1.20 (0.99–1.44)	0.06	I	1.18 (1.02–1.36)	0.03
11	rs4963128	SLE	*PHRF1,KIAA1542*	T	0.79 (0.64–0.97	0.02	0.92 (0.79–1.08)	0.32	G	0.87 (0.77–0.99)	0.03
6	rs11755527	T1D	*BACH2*	G	1.17 (0.97–1.42)	0.10	1.12 (0.96–1.30)	0.16	I	1.14 (1.01–1.28)	0.03
9	rs10758669	CD	*JAK2*	C	1.16 (0.95–1.41)	0.15	1.13 (0.97–1.32)	0.12	G	1.14 (1.01–1.29)	0.03
10	rs706778	RA	*IL2RA*	T	1.11 (0.92–1.33)	0.29	1.14 (0.98–1.33)	0.09	I	1.13 (1.00–1.27)	0.05

Abbreviations: Chr = chromosome; SNP = single nucleotide polymorphism designation; RA = rheumatoid arthritis; T1D = type 1 diabetes; CD = Crohn's disease; Ps = psoriasis; SLE = systemic lupus erythematosus; UC = ulcerative colitis; A (in column heading) = allele used to calculate odds ratio; OR = odds ratio; CI = confidence interval; S = source of genotype in Toronto cohort (I = imputed, G = genotyped).

* SNPs were included in genetic risk scores for the diseases listed.

† Unadjusted P-values are shown. Only the top-ranked SNP had a P-value still <0.05 after adjustment for the false discovery rate (P*168/rank).

Table 2

Genetic risk scores derived from different autoimmune diseases, in patients with GPA compared to controls.

Disease*	Number of Risk Alleles in GRS†	Cohort	GRS in GPA cases Mean ± SD (Range)‡	GRS in Controls Mean ± SD (Range)‡	Separate Cohorts		Meta-analysis	
					Odds Ratio (95% CI) §	P	Odds Ratio (95% CI) §	P
Celiac	14	W	11.4 ± 2.23 (5–19)	11.3 ± 2.42 (5–18)	1.02 (0.96–1.08)	0.54	1.02 (0.99–1.06)	0.20
		T	10.9 ± 2.39 (4–21)	10.8 ± 2.43 (4–19)	1.03 (0.98–1.07)	0.25		
CD	57	W	50.2 ± 4.74 (37–62)	50.2 ± 4.84 (36–67)	1.00 (0.98–1.03)	0.83	1.00 (0.99–1.02)	0.63
		T	49.3 ± 4.57 (35–64)	49.2 ± 4.71 (35–66)	1.01 (0.98–1.03)	0.66		
RA	23	W	21.1 ± 3.00 (13–31)	20.7 ± 3.08 (12–32)	1.05 (1.01–1.10)	0.025	1.05 (1.02–1.08)	5.1E-05
		T	21.0 ± 2.89 (11–30)	20.6 ± 3.06 (12–31)	1.05 (1.02–1.09)	0.005		
SLE	22	W	17.7 ± 3.03 (9–26)	17.5 ± 2.99 (9–28)	1.02 (0.98–1.07)	0.32	1.03 (1.00–1.06)	0.07
		T	17.0 ± 2.83 (9–24)	16.7 ± 2.86 (8–26)	1.03 (0.99–1.07)	0.11		
T1D	32	W	31.2 ± 3.55 (23–41)	31.2 ± 3.84 (22–44)	1.00 (0.97–1.04)	0.95	ND	
		T	29.4 ± 3.54 (19–39)	28.5 ± 3.52 (18–41)	1.07 (1.04–1.11)	<0.001		
UC	11	W	11.4 ± 2.21 (5–17)	11.4 ± 2.15 (6–18)	0.98 (0.93–1.06)	0.85	1.00 (0.96–1.04)	0.95
		T	11.4 ± 2.21 (5–19)	11.4 ± 2.20 (4–20)	1.00 (0.96–1.06)	0.94		

*Genetic risk scores (GRSs) were calculated separately for each listed disease. CD = Crohn's disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; T1D = Type 1 diabetes; UC = ulcerative colitis.

†The number of independent SNPs in the GRS is shown; the maximum possible GRS is twice this number, since homozygous risk alleles are counted twice.

‡Among 424 cases and 469 controls in WGGER (including CEU controls), or 456 cases and 1500 controls in Toronto.

§Odds ratio indicates the increase in odds of having GPA associated with a 1-unit increase in GRS, determined by logistic regression with inclusion of the first two principal components as independent variables. CI = confidence interval.