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Meta-Analysis of Genetic Polymorphisms in Granulomatosis With Polyangiitis (Wegener's) Reveals Shared Susceptibility Loci With Rheumatoid Arthritis

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Objective. **To examine the association of previously identified autoimmune disease susceptibility loci with granulomatosis with polyangiitis (Wegener's) (GPA), and to determine whether the genetic susceptibility profiles of other autoimmune diseases are associated with those of GPA.**

Methods. **Genetic data from 2 cohorts were meta-analyzed. Genotypes for 168 previously identified single-nucleotide polymorphisms (SNPs) associated with susceptibility to different autoimmune diseases were ascertained in a total of 880 patients with GPA and 1,969 control subjects of European descent. Single-marker associations were identified using additive logistic regression models. Associations of multiple SNPs with GPA were assessed using genetic risk scores based on susceptibility loci for Crohn's disease, type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis (RA), 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 (odds ratio [OR] 0.79, 95% confidence interval [95% CI] 0.70–0.89, $P = 9.8 \times 10^{-5}$). The genetic risk score for RA susceptibility markers was significantly associated with GPA (OR 1.05 per 1-unit increase in genetic risk score, 95% CI 1.02–1.08, $P = 5.1 \times 10^{-5}$).**

Conclusion. **RA 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 significantly associated with GPA in this study.**

Granulomatosis with polyangiitis (Wegener's) (GPA) is a severe, multisystem inflammatory disease with a prevalence of ~1 in 10,000–40,000 persons of

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European ancestry (1). GPA is thought to be an autoimmune disease because it is highly associated with autoantibodies to proteinase 3, which are rare in the general population (2–4). It is unclear to what extent genetics contribute to the risk of GPA. Results of family studies have suggested a slight increase in risk (estimated at 1.5- to 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 consideration of GPA as fundamentally an autoimmune disease. The other is a null allele in α_1-antitrypsin (*A1AT*, or *SERPINA*) (8–10). However, because these null alleles are uncommon, haploinsufficiency of *A1AT* accounts for only ~7% of cases of GPA (8). Many other polymorphisms have been investigated on the basis of existing knowledge of the role of the associated gene in immunity, but only 2 associations (in *CD226* and *FCGR3B*) have been confirmed in >1 cohort (11,12).

The contribution of many common genetic variants to the risk of more common autoimmune diseases, such as rheumatoid arthritis (RA), type 1 diabetes, and inflammatory bowel disease, has been established through genome-wide association studies (GWAS) and meta-analyses of the data from these studies (13–27). Some polymorphisms appear to confer risk in multiple autoimmune diseases. Although candidate gene studies in GPA have often investigated genes related to immunity, they have usually examined 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 2 sources. First, studies of familial associations between GPA and other autoimmune diseases have concluded that first-degree relatives of individuals with GPA have a modest increase in the risk of common autoimmune diseases in general (relative risk 1.32), and of RA, multiple sclerosis (MS), psoriatic arthritis, and Sjögren's syndrome in particular (6,30). Calculated associations with lupus, inflammatory bowel disease, and ankylosing spondylitis (AS) 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 the risk of GPA in 1 or 2 cohorts have also been associated with other autoimmune diseases (11,12,28,29,31,32).

We performed a candidate gene study in GPA, in which we assessed 168 single-nucleotide polymorphisms (SNPs) found to be associated with ≥1 autoimmune disease. Our goals were 1) to identify individual SNPs associated with GPA using a case–control study design in 2 cohorts, and 2) to test associations of multiple SNPs in models of genetic risk (using the genetic risk score [GRS]), which were developed to investigate individual autoimmune diseases for their ability to predict an increased risk of GPA, regardless of the statistical significance of the component SNPs. This 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. Data from 2 cohorts were analyzed independently and then combined for study in a meta-analysis. All patients were enrolled using protocols approved by the Institutional Review/Ethics Boards at the participating sites.

In the first cohort, 431 patients with GPA and 391 healthy control subjects who were enrolled in the Wegener's Granulomatosis Genetics Repository (WGGER) (8) and who were of self-identified European descent were genotyped. Subjects were recruited at 8 US centers between 2001 and 2005, and clinical data from the patients were recorded using a standardized form. These data were reviewed to ensure that all GPA cases met the American College of Rheumatology (ACR) 1990 classification criteria for GPA (33). Controls were individuals who were not related to the patients and who did not have a personal or family history of autoimmune inflammatory diseases. Demographic data collected from the case and control groups included age, sex, and race/ethnicity. In this sample, 47% of the patients with GPA and 60% of the control subjects were female, and the mean age was 53.1 years (range 18–87 years) among cases and 49.5 years (range 18–85 years) among controls.

To increase the statistical power of this initial cohort, 82 individuals of northern and western European ancestry, whose genotypes are recorded in the Centre d'Etude du Polymorphisme Humain (CEPH) data collection from the International HapMap Project (http://www.hapmap.org), were included as additional controls in this study. Thus, the total sample size for this cohort was 431 GPA cases and 473 controls.

A second cohort of 464 patients with GPA was assembled in Toronto between 2001 and 2010 from multiple sites (50% from the US, 40% from Canada, 10% from Europe, and <1% from other locations), through physician contacts and online advertisement. Information about symptoms, organ involvement, and antineutrophil cytoplasmic antibody levels was garnered from physician records, and all cases met the 1990 modified ACR criteria for GPA. The mean age of the

patients in this cohort was 52.8 years (range 14–85 years), and 55% of the patients were female.

Controls for the Toronto cohort (n = 1,503) were derived from 2 sources: 380 volunteers from the Toronto metropolitan area (mean age 40 years, range 23–91 years, 82% female), and 1,123 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). None of these control subjects had a history of autoimmune disease, and all cases and controls were of European descent, as ascertained by self-report.

SNP selection. A custom set of 384 SNPs, including 192 associated with autoimmune diseases and 192 AIMs (34–36), was chosen for genotyping all subjects in the WGGER cohort. All autoimmune disease–associated SNPs were outside of the HLA region. After application of quality control filters and imputation of SNPs not determined in the Toronto cohort (as detailed below), 168 SNPs associated with autoimmune diseases remained for analysis (for a complete list, see Supplementary Table 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131). These included 58 SNPs associated with Crohn's disease (13,14,23,27,37,38), 32 associated with type 1 diabetes (15,16,39–42), 23 associated with systemic lupus erythematosus (SLE) (17–21,43–47), 24 associated with RA (22,36,48–50), 12 associated with ulcerative colitis (UC) (23–25,27,38,51), 8 associated with psoriasis (26,52), 15 associated with celiac disease (53–55), 2 associated with MS (56–58), 2 associated with AS (59), and 1 associated with primary biliary cirrhosis (60). Some of these SNPs have been found to be associated with more than 1 of the listed diseases, which is the reason that the numbers of SNPs associated with individual diseases add up to >168. The AIMs genotyped in the subjects in the WGGER cohort (see Supplementary Table 1, on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131) are informative for both continental and intra-European ancestry.

Genotyping, data quality filters, and imputation analyses. Genotyping of the WGGER samples was performed at the Broad Institute (Cambridge, MA) using the BeadXpress platform from Illumina. Genotypes of the autoimmunity-associated SNPs in the Toronto cohort were determined using data from a GWAS that had been performed previously (K. Siminovitch KA, et al: unpublished observations). Genotypes were determined using the Illumina HumanCNV370-quad version 3 platform (464 cases and 380 controls) and the HumanHap370 BeadChip (1,123 controls).

The following data quality filters were applied separately to the WGGER and Toronto cohorts. SNPs were removed from analysis if they had >10% missing genotypes, a minor allele frequency of <1%, or evidence of deviation from Hardy-Weinberg equilibrium in the controls ($P < 0.0001$). Subjects were removed from the analysis if their overall genotyping rate was <90% or if population outliers were observed on principal components analysis (defined as values >6 SD from the mean for any of the first 10 principal components). Duplicate samples were identified using identity-by-state measures, calculated using Plink software (http://pngu.mgh.harvard.edu/purcell/plink/) version 1.07 (61), in which all of the samples in this study were assessed using the 218 genotyped SNPs that overlapped between the WGGER and Toronto cohorts. 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 whose genotyped SNPs had 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 $\approx$ 1.0) and 6 subjects whose data were genetic outliers on principal components analysis were removed from the Toronto cohort, leaving 456 cases and 1,500 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), utilizing, as reference, the 283 European samples from phase I of the 1000 Genomes Project (sequence index 2010.08.04). After filtering the data according to an info score of >0.80, 76 of the 95 SNPs were successfully imputed. Thus, 168 autoimmunity-associated SNPs were identified for further assessment in the final analysis.

Analysis of population substructure. Principal components analysis was performed in the WGGER cohort using the EigenStrat program (63) (http://genepath.med.harvard.edu/~reich/Software.htm) and using data from all 187 AIMs. No genetic outliers were identified. Visualization of the first 2 principal components showed that all 424 cases and 387 control subjects who self-identified as being of non-Hispanic European descent were clustered in the same group as the 82 European subjects included in the study from the CEPH/HapMap phase 3 database.

Principal components analysis 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 principal components using EigenStrat. Six cases were removed as genetic outliers (defined as values >6 SD from the mean of any of the first 10 principal components).

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. These analyses were carried out using Plink version 1.07. The first 2 principal components specific to each cohort were included in all logistic regression models to adjust for population substructure. For SNPs that had been imputed in the Toronto cohort, associations with GPA were assessed using the score method in SNPTest (version 2.2.0). For these analyses, probabilistic genotypes were utilized, assuming additive genetic models, in logistic regression analyses, which also included the first 2 principal components to adjust for population substructure.

To produce an overall estimate of the association of each marker with GPA in the 2 cohorts, a meta-analysis combining the results for each SNP was performed using Plink

Table 1. Single-nucleotide polymorphisms (SNPs) associated with granulomatosis with polyangiitis (Wegener's)*

					WGGER cohort		Toronto cohort			Meta-analysis	
Chromosome	SNP	Disease†	Gene	Risk allele	OR (95% CI)	*P*	OR (95% CI)	*P*	Source of genotype	OR (95% CI)	*P*‡
2	rs3087243	RA, type 1 diabetes	*CTLA4*	A	0.80 (0.66–0.97)	0.03	0.78 (0.67–0.91)	0.001	Imputed	0.79 (0.70–0.89)	9.83×10^{-5}
2	rs231735	RA	*CTLA4*	G	0.84 (0.69–1.02)	0.08	0.81 (0.70–0.94)	0.005	Genotyped	0.82 (0.73–0.92)	0.001
1	rs2476601	Crohn's disease, psoriasis, RA, SLE, type 1 diabetes	*PTPN22*	A	1.24 (0.92–1.69)	0.16	1.41 (1.12–1.79)	0.004	Genotyped	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	Imputed	0.81 (0.70–0.92)	0.002
1	rs3766606	Celiac disease	*PARK7, DJ-1*	T	0.79 (0.61–1.02)	0.07	0.80 (0.66–0.98)	0.03	Imputed	0.80 (0.68–0.94)	0.005
16	rs4788084	Type 1 diabetes	*IL27*	T	1.13 (0.94–1.37)	0.19	1.21 (1.04–1.41)	0.01	Genotyped	1.18 (1.05–1.33)	0.006
16	rs151181	Crohn's disease	*IL27, others*	C	1.16 (0.96–1.40)	0.12	1.20 (1.02–1.41)	0.03	Imputed	1.18 (1.05–1.34)	0.007
10	rs6584283	Crohn's disease, UC	*NKX2-3*	T	0.83 (0.69–1.00)	0.05	0.87 (0.75–1.01)	0.07	Imputed	0.86 (0.76–0.96)	0.009
1	rs12727642	Celiac disease	*PARK7, TNFRSF9*	A	0.81 (0.64–1.05)	0.11	0.81 (0.66–1.00)	0.05	Genotyped	0.81 (0.69–0.95)	0.01
10	rs11190140	Crohn's disease, UC	*NKX2-3*	T	0.85 (0.71–1.02)	0.08	0.87 (0.75–1.01)	0.07	Genotyped	0.86 (0.77–0.97)	0.01
13	rs9585056	Type 1 diabetes	*IDIN*	C	0.77 (0.62–0.96)	0.02	0.91 (0.76–1.09)	0.33	Imputed	0.85 (0.74–0.98)	0.03
15	rs17574546	Type 1 diabetes	*RASGRP1*	C	1.15 (0.92–1.44)	0.21	1.20 (0.99–1.44)	0.06	Imputed	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	Genotyped	0.87 (0.77–0.99)	0.03
6	rs11755527	Type 1 diabetes	*BACH2*	G	1.17 (0.97–1.42)	0.10	1.12 (0.96–1.30)	0.16	Imputed	1.14 (1.01–1.28)	0.03
9	rs10758669	Crohn's disease	*JAK2*	C	1.16 (0.95–1.41)	0.15	1.13 (0.97–1.32)	0.12	Genotyped	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	Imputed	1.13 (1.00–1.27)	0.05

* SNPs are listed in order of *P* value. WGGER = Wegener's Granulomatosis Genetics Repository; OR = odds ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; UC = ulcerative colitis.
† Diseases listed are those previously associated with each SNP included in the calculation of the genetic risk scores.
‡ Unadjusted *P* values are shown. Only the top-ranked SNP listed had a *P* value less than 0.05 after adjustment for the false discovery rate ($P \times 168$/rank).

version 1.07. The results from 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 in the meta-analysis results was observed.

P values were adjusted for the false discovery rate (FDR) (64), based on the ranked *P* values of 168 simultaneous tests. Adjusted *P* values less than 0.05 were interpreted as statistically significant.

Calculation of the GRS. For each subject, separate GRS scores for Crohn's disease (57 SNPs), type 1 diabetes (32 SNPs), SLE (22 SNPs), RA (23 SNPs), celiac disease (14 SNPs), and UC (11 SNPs) were calculated using the SNPs that were genotyped or imputed in this study and that have been previously associated with those diseases (see details in Supplementary Table 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131). 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 that showed an association with the same disease (e.g., rs2070197 and rs10488631 in *IRF5*, which are both associated with SLE; $r^2 = 0.93$), 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 score as a continuous variable and the first 2 principal components as the predictor variables, and case/control status as the outcome variable. The WGGER and Toronto cohorts were first analyzed separately and then combined in the meta-analysis. Fixed-effects and random-effects models yielded identical results. All GRS analyses were performed using Stata statistical software (release 9.0).

RESULTS

Autoimmunity-associated SNPs in GPA. After implementing data quality measures, 168 SNPs in at least 141 candidate genes (see Supplementary Table 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131) were studied in a total of 880 GPA cases and 1,969 controls of European descent in the WGGER cohort (424 cases and 469 controls) and Toronto cohort (456 cases and 1,500 controls).

In the WGGER cohort, 12 markers showed nominal evidence of association with GPA ($P_{\text{unadjusted}} < 0.05$), but none of the associations was significant after correction for the FDR. The most statistically significant association was with rs11618775 (odds ratio [OR] 1.34, 95% confidence interval [95% CI] 1.08–1.66, $P_{\text{unadjusted}} = 0.0073$), 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.

Of the 168 SNPs analyzed in the Toronto cohort, 11 SNPs showed nominal evidence of association with GPA ($P_{\text{unadjusted}} < 0.05$). An imputed SNP, rs3087243 (in *CTLA4*), was the most strongly associated with GPA (OR 0.78, 95% CI 0.67–0.91, $P_{\text{unadjusted}} = 0.0014$). 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 significantly associated with GPA after correction for the FDR.

Our meta-analysis yielded a statistically significant association with GPA for rs3087243 in *CTLA4*, with 15 additional SNPs showing unadjusted *P* values of less than 0.05 (Table 1). Three additional SNPs, in *CTLA4*, *PTPN22*, and *CD40*, narrowly missed the prespecified cutoff for a significant association, and the next 6 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*).

Disease-specific GRS associations with GPA. As shown in Table 2, the GRS score derived for susceptibility loci in RA was slightly, but significantly, higher in GPA patients than in controls in both the WGGER and Toronto cohorts individually and in the meta-analysis (OR 1.05 per 1-unit increase in GRS, 95% CI 1.02–1.08, $P = 5.1 \times 10^{-5}$). Having a GRS score for RA that was higher than the median was associated with 37% greater odds of having GPA when compared to having a GRS score for RA that was below the median (OR 1.37, 95% CI 1.16–1.62, $P = 2.6 \times 10^{-6}$). After the 3 top-ranked SNPs (in *CTLA4* and *PTPN22*, all of which are associated with RA) were excluded from the study, the GRS scores for RA susceptibility loci remained slightly higher in GPA cases than in controls (meta-analysis OR per 1-unit increase in GRS 1.04, 95% CI 1.01–1.07, $P = 0.017$), indicating that these 2 genes did not account completely for the GRS result.

GRS scores derived for type 1 diabetes were higher in GPA cases than in controls in the Toronto cohort, but not in the WGGER cohort. Given the substantial heterogeneity of the findings from patients with type 1 diabetes, a meta-analysis of these data was not considered appropriate. Therefore, analyses of the type 1 diabetes–specific GRS scores were inconclusive.

GRS scores derived for celiac disease, Crohn's disease, SLE, and UC did not differ significantly between either the GPA case cohort or control cohort separately, and also did not differ by meta-analysis. Moreover, GRS scores for smaller numbers of risk SNPs (n = 2–8) associated with AS, MS, or psoriasis did

Table 2. Genetic risk scores (GRS) derived from different autoimmune diseases in patients with granulomatosis with polyangiitis (Wegener's) (GPA) compared to controls*

Disease, cohort	Number of risk alleles in GRS†	GRS, mean ± SD (range)‡		Separate cohorts		Meta-analysis	
		GPA cases	Controls	OR (95% CI)§	*P*	OR (95% CI)§	*P*
Celiac disease	14					1.02 (0.99–1.06)	0.20
WGGER		11.4 ± 2.23 (5–19)	11.3 ± 2.42 (5–18)	1.02 (0.96–1.08)	0.54		
Toronto		10.9 ± 2.39 (4–21)	10.8 ± 2.43 (4–19)	1.03 (0.98–1.07)	0.25		
Crohn's disease	57					1.00 (0.99–1.02)	0.63
WGGER		50.2 ± 4.74 (37–62)	50.2 ± 4.84 (36–67)	1.00 (0.98–1.03)	0.83		
Toronto		49.3 ± 4.57 (35–64)	49.2 ± 4.71 (35–66)	1.01 (0.98–1.03)	0.66		
RA	23					1.05 (1.02–1.08)	5.1×10^{-5}
WGGER		21.1 ± 3.00 (13–31)	20.7 ± 3.08 (12–32)	1.05 (1.01–1.10)	0.025		
Toronto		21.0 ± 2.89 (11–30)	20.6 ± 3.06 (12–31)	1.05 (1.02–1.09)	0.005		
SLE	22					1.03 (1.00–1.06)	0.07
WGGER		17.7 ± 3.03 (9–26)	17.5 ± 2.99 (9–28)	1.02 (0.98–1.07)	0.32		
Toronto		17.0 ± 2.83 (9–24)	16.7 ± 2.86 (8–26)	1.03 (0.99–1.07)	0.11		
Type 1 diabetes	32					ND	ND
WGGER		31.2 ± 3.55 (23–41)	31.2 ± 3.84 (22–44)	1.00 (0.97–1.04)	0.95		
Toronto		29.4 ± 3.54 (19–39)	28.5 ± 3.52 (18–41)	1.07 (1.04–1.11)	<0.001		
UC	11					1.00 (0.96–1.04)	0.95
WGGER		11.4 ± 2.21 (5–17)	11.4 ± 2.15 (6–18)	0.98 (0.93–1.06)	0.85		
Toronto		11.4 ± 2.21 (5–19)	11.4 ± 2.20 (4–20)	1.00 (0.96–1.06)	0.94		

* GRS scores were calculated separately for each listed disease. ND = not determined (see Table 1 for other definitions).
† For the disease-specific GRS scores, the number of risk alleles within each independent single-nucleotide polymorphism found in GPA cases and controls was added in an unweighted manner; the maximum possible GRS score is twice this number, since homozygous risk alleles are counted twice.
‡ GRS scores were calculated among 424 cases and 469 controls (including Centre d'Etude du Polymorphisme Humain/HapMap controls) in the WGGER cohort and 456 cases and 1,500 controls in the Toronto cohort.
§ ORs indicate the increase in odds of having GPA associated with a 1-unit increase in the GRS, as determined by logistic regression, with inclusion of the first 2 principal components as independent variables.

not differ significantly between the cohorts or by meta-analysis (results not shown).

Analysis of the distribution of ORs for all risk alleles used in the GRS score calculations did not provide any additional evidence of skewing of autoimmunity-associated SNPs toward an association with GPA. The mean OR of 1.01 (SD 0.09) for all risk alleles 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 for GPA with those for other autoimmune diseases by examining single-marker associations as well as composite GRS 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 type 1 diabetes (39,49,65). SNP rs3087243 does not appear to be significantly linked to previously identified GPA-associated *CTLA4* polymorphisms (rs5742909 [−319C/T] or rs231775 [+49A/G]; $r^2 < 0.1$), but rs231735 has been shown to have 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. SNP rs3087243 has been suggested to influence *CTLA4* messenger RNA 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 found to be associated with GPA (28) and with multiple other autoimmune diseases (13,15,21, 65,68). This nonsynonymous polymorphism induces an amino acid change from arginine to tryptophan at codon 620, and is thought to increase its degradation, leading to lymphocyte hyperresponsiveness (69).

Our findings also suggest that GPA and RA share a common genetic background, which was not observed for Crohn's disease, SLE, type 1 diabetes, or UC. This finding is supported by the findings from a previous epidemiologic study showing an increased frequency of

RA among offspring of patients with GPA (30). This finding is not intuitive, since the pulmonary and renal manifestations of GPA are not commonly observed 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 2 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 that in other candidate gene studies for GPA, which improved the statistical power to test a relatively large number of candidate genes. However, this study still had limited power to detect associations with modest effect sizes, and thus there may be additional associations that have not been identified. Another strength of our study 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, there may be other loci that are shared between GPA and SLE, type 1 diabetes, Crohn's disease, and/or UC, and the genetic background of these diseases may be more similar to that of GPA than has been demonstrated in the present study.

Further delineation of the genetic contribution to risk of GPA will likely require a combination of GWAS results 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 that may be derived from 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 represent a more generic disruption of immune homeostasis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Monach had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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