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Identification of functional and expression polymorphisms associated with risk for anti-neutrophil cytoplasmic autoantibody-associated vasculitis

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ABSTRACT

Objective: To identify risk alleles relevant to the cause and biology of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods: We conducted a genome-wide association and subsequent replication study including 1986 cases of AAV [granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)] and 4723 controls. Meta-analysis of these datasets and functional annotation of identified risk loci were performed and candidate disease variants with unknown functional effects investigated for impact on gene expression and/or protein function.

Results: Among the genome-wide significant associations identified, the largest effect on risk came from rs141530235 and rs1042169 SNP variants at the *HLA-DPB1* locus (odds ratios = 2.99 and 2.82, respectively) which, together with a third (rs386699872) variant, constitute a triallelic risk haplotype associated with reduced *HLA-DPB1* gene and HLA-DP protein expression in B cells and monocytes and with increased frequency of complementary proteinase-3-reactive T cells relative to levels in protective haplotype carriers. Significant associations were also observed at the *SERPINA1* and *PTPN22* loci, the peak signals arising from functionally-relevant missense variants, and at *PRTN3*, where the top-scoring variant correlated with increased *PRTN3* expression in neutrophils. Effects of individual loci on risk differed in patients with GPA versus MPA or proteinase-3 versus myeloperoxidase-ANCA, but the collective population attributable fraction for these variants was substantive (77%).

Conclusion: This study reveals the association of GPA and MPA susceptibility with functional gene variants that explain much of the genetic etiology of AAV, influence and possibly predict clinical presentation, and alter immune cell proteins and responses likely key to disease etiopathogenesis.

INTRODUCTION

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are life-threating necrotizing vasculitides strongly associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA) reactive to proteinase-3 (PR3) or myeloperoxidase (MPO). Although often considered a single disease, GPA and MPA diverge in important respects, such as the extent of their association with PR3-reactive versus MPO-reactive ANCA, risk of relapsing disease, and GPA association with granulomatosis inflammation. The etiology of AAV remains unknown; however, genome-wide association studies (GWAS) performed in a North American GPA cohort and a European GPA/MPA cohort confirmed candidate gene analyses identifying strong association of these diseases with MHC class II region alleles (1, 2). A genome-significant association at the *SERPINA1* locus was also identified in the European study, with this and several MHC associations differentially detected in patient subsets defined by presence of PR3 or MPO-ANCA (2). These findings have not yet been replicated and knowledge remains rudimentary regarding the non-MHC loci and specific disease-causal variants predisposing to GPA and/or MPA. Therefore, we sought to further define the genetic variation underpinning GPA and MPA susceptibility by conducting a new GWAS and validation study of a larger, independently-ascertained North American-based cohort of GPA/MPA patients and healthy controls and using functional annotation of the risk loci to identify candidate disease-causal alleles.

METHODS

Subjects

All study subjects were of self-reported European ancestry, with the diagnosis of AAV and GPA or MPA based on modified ACR criteria for classifying vasculitis (3). The discovery cohort included: 779 cases recruited via 13 centers from the Vasculitis Clinical Research Consortium (VCRC), which conducts studies involving vasculitis patients followed in the USA, Canada and elsewhere; 438 cases recruited via the Wegener's Granulomatosis Genetic Repository (WGGER), a study conducted at 8 centers in the USA from 2001 to 2005; and 378 cases from the University of North Carolina Kidney Center. Key clinical and serological features for the cases are provided in Supplementary Table 3. The controls included 202 healthy subjects recruited via WGGER and 3121 historic controls whose genotype data were obtained from the Resource for Genetic Epidemiology Research on Aging study (4, 5). The replication cohort included 505 AAV cases and 1477 healthy controls recruited independently from Canada and the USA via a Toronto-based AAV study and 114 independent cases recruited via the VCRC. Demographic data, peripheral blood cells and/or saliva samples were obtained with written informed consent as approved by the local institutional review board.

Genotyping methods

For the GWAS, 1615 cases of AAV and 202 controls were genotyped at the Mount Sinai Hospital Clinical Genomics Centre and 3121 "historic" controls were genotyped at Affymetrix (Santa Cruz, CA) using the Axiom Biobank 1 Genotyping array. This array tests 628,679 SNPs, including 246,000 (36.5%) genome-wide association markers, 265,000 (39.3%) non-synonymous coding SNPs, 70,000 (10.4%) loss-of-function SNPs, 23,000 (3.4%) eQTL SNPs,

2,000 (0.3%) pharmacogenetic markers, and 27,679 "custom" markers. Genotypes were called and processed using Affymetrix Genotyping Console™ 4.2 and SNPolisher software. Quality control filtering was performed using Golden Helix SVS 8.3.4 software and genotype call rate > 95%, individual sample call rate > 97% and exclusion of SNPs with Hardy-Weinberg equilibrium (HWE) p-value < 10^{-5}. After filtering, genotypes derived from SNP markers common to both datasets were merged in a single file containing 1528 cases, 3309 controls and 333,040 SNPs. A set of LD-pruned SNPs with MAF > 5% was used to estimate identity by descent (IBD) and ancestry. For each pair of individuals with an estimated IBD of > 0.25, the sample with the lower call rate was removed. Principal-component analysis (PCA) was used to exclude samples of non-European ancestry (6). In total, 1371 cases, 3258 controls, and 333,035 SNPs passed quality control filters (Supplementary Figure 1).

For the replication study, 8 SNPs in 6 gene loci were genotyped in 619 AAV cases and 1477 controls using Sequenom iPLEX assays. One other SNP (rs62132293) at the *PRTN3* locus was genotyped using Taqman (Applied Biosystems). After quality control filtering, 615 cases, 1465 controls, and 9 SNPs were retained for analysis. For the replication study of the MPO-ANCA/perinuclear ANCA (designated here as MPO-ANCA) subgroup, three additional SNPs (rs3998159, rs7454108 and rs1049072) at the *HLA-DQA2* and *-DQB1* loci were genotyped on the same platform. GWAS and replication datasets were then combined for meta-analysis.

Statistical methods

Association and meta-analyses. For the discovery dataset, case-control association tests were conducted using logistic regression with principal components differing between cases and

controls included as covariates to adjust for population stratification. Calculation of the genomic control factor using EIGENSTRAT showed minimal inflation, 1.012 and 0.991, respectively, before and after adjustment for the top three eigenvectors (Supplementary Figure 2). An analysis of all the nonzero eigenvalues established that 221,341 independent tests were conducted from 280,677 autosomal markers which, with Bonferroni correction, established the p value for genome-wide significance as $< 2.2x10^{-7}$. Meta-analysis of the data from the GWAS and replication logistic regression analyses was conducted using the basic meta-analysis function in PLINK v1.9 (6, 7). Differences between GPA and MPA and PR3-ANCA/cytoplasmic ANCA (hereinafter PR3-ANCA) and MPO-ANCA case groups were studied using this approach. Between-study heterogeneity was tested by the χ^2-based Cochrane's Q statistic. Heritability was estimated using GCTA as described by Lee et al (8) and assuming an AAV prevalence of 1/10,000. Prior to analysis we excluded sex chromosome data, SNPs with MAFs <0.05 and missing rates >0.01, individuals whose missing SNP rates were>0.01, SNPs with an HWE p-value <0.05 or markers with a significant difference in missingess between cases and controls.

Imputation. Genome-wide imputation for the 4629 samples in the discovery cohort was performed using 1000 Genomes Project Phase 3 data as the reference (release date October 2014) for the autosomes and Phase 1 data (release date August 2012) for the X chromosome. Following removal of SNPs with call rates <95%, MAF <0.001 and HWE p values $< 10^{-5}$, SHAPEIT (shapeit.v2.r790.Ubuntu_12.04.4.static) was used to derive phased genotypes and the phased data imputed using IMPUTEv2 (impute_v2.3.2_x86_64_static) to assess ~5Mb non-overlapping intervals (9). Imputation within defined regions was performed using IMPUTEv2 without prephasing.

Conditional Analysis. To test for multiple independent effects within the HLA region, a logistic regression framework was used to assess individual HLA alleles for association, including the top 3 principal components as covariates to account for population stratification. After identifying the most significant marker, we tested for additional independent effects by including the dosage of the top markers in a joint model. Conditional analysis was performed using the proc logistic module of SAS version 9.2 to obtain odds ratios (ORs) when all top markers were jointly analyzed.

Population Attributable Fraction (PAF). PAF was estimated using ORs from a multivariate logistic regression model incorporating SNPs from multiple loci so that each OR is adjusted for the effects of the other SNPs. PAF for effects from an allele at a single locus was set as:

$$PAF = \frac{RAF(OR-1)}{1+RAF(OR-1)}$$

where OR is the odds ratio associated with the allele genotype and RAF is the allele frequency of the risk variant. For computation over multiple loci, this formula becomes:

$$PAF_{combined} = 1 - (\prod_{1=1}^{nloci} 1 - (PAF_i))$$

Random Forest Analysis. The potential role for combinations of alleles in risk for AAV was evaluated by random forest analysis using classification and regression tree (CART) methodology (10). Data from 11 risk-associated variants were subjected to analysis in which CARTs were repetitively built using two-thirds of the samples and variables and used to classify the remaining one-third of the data. Eight variants that improved the model fit by ≥ 3% were retained to build a CART. The rpart program in R and the Gini index measure were used to

identify optimal splits of the data, with the complexity parameter set to 0.001 and the data then pruned to include only those nodes containing at least 20 observations. This final model had a classification accuracy of 73%. ORs were calculated with: $OR = \frac{\#cases\ in\ node\ i / \#controls\ in\ node\ i}{\#cases\ in\ node\ 1 / \#controls\ in\ node\ 1}$ and used the Woolf approximation to compute standard errors and confidence intervals.

Functional annotation. The online Probabilistic Identification of Causal SNPs (PICS) algorithm (http://www.broadinstitute.org/pubs/finemapping/?q=pics) was used to identify variants at each risk locus with a PICS probability (>0.0275) consistent with that used by Farh et al (11). We then used the Ensembl Variant Effect Predictor web tool to annotate these variants for predicted functional consequences (http://www.ensembl.org/info/docs/tools/vep/index.html) and Genevar (12), seeQTL (http://www.bios.unc.edu/research/genomic_software/seeQTL/) (13) and the University of Chicago eQTL browser (http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl/) to identify expression quantitative trait loci (eQTLs).

Cellular assays

Peripheral blood mononuclear cells (PBMCs) and polymorphonuclear leukocytes were isolated over Ficoll-Hypaque from patients followed at MSH. For quantitative PCR (qPCR), RNA (500ng) was reverse transcribed using random hexamer primer and SuperScriptIII reverse transcriptase (Invitrogen) and qPCR performed using SYBR green and the gene appropriate primer pairs (Supplementary Table 1). Samples were run on an ABI PRISM 7900 HT system (Applied Biosystems) and the fold change in expression of the specific gene relative to the internal control gene (*COX5B* for *PRTN3*; *GAPDH* for *HLA-DPB1*) calculated using the $2^{(\Delta\Delta Ct)}$ method (14).

For flow cytometry, PMBCs stained with phycoerythrin anti-CD19, APC-Cy7-anti-CD14 (BD Biosciences) and/or FITC-HLA-DP (Leinco) antibodies or FITC-conjugated murine IgG (BD Biosciences) were analyzed using the FACS Canto cytometer (BD Biosciences) and FlowJo software.

For ELISPOT experiments, 20mer peptides selected using published data or the NetMHCII 2.2 prediction algorithm (www.cbs.dtu.dk) were synthesized and purified by the manufacturer (Genscript) (Supplementary Table 2).

PBMCs ($2x10^{-5}$) from PR3-ANCA vasculitis patients and healthy controls were suspended in 20% FBS-supplemented RPMI and incubated in 96-well ELISPOT plates (Millipore) pre-coated with anti-human IFN-γ monoclonal antibody (eBioscience). Cells were stimulated for 24 hours at 37°C with 10μg/ml peptide or 1μg/ml ConA (Sigma) and incubated with biotinylated mouse anti-human IFN-γ antibody (eBioscience), avidin-HRP (eBioscience) and AEC solution (BD™ ELISPOT) using the ImmunoSpot reader and software (Cellular Technology) to detect IFN-γ releasing cells.

RESULTS

Identifying GPA/MPA susceptibility loci

After filtering and correction for population substructure, our GWAS discovery dataset included 333,035 SNPs genotyped in 1,371 cases of AAV (GPA and MPA) and 3,258 healthy controls

with no evidence of inflation of the test statistic (λ_{GC}=0.991) (Supplementary: Methods, Figures 1 and 2, and Table 3).

Association analysis of this cohort identified 120 SNPs across the MHC class II locus achieving genome-wide significance levels, the strongest signals emanating from the *DPB1, DPA1, DQA1,* and *DQB1* genes (Table 1 and Supplementary Table 4). Four other SNPs across three non-MHC gene loci also achieved genome-wide significance levels and were taken forward together with five top-scoring SNPs from the MHC region for a replication study in an independent cohort of 615 cases and 1,465 controls (Table 1, Supplementary Figure 1 and Table 3). As all associations tested were replicated ($P \leq 0.05$ threshold), the GWAS and replication datasets were combined for a meta-analysis and the nine associations also explored in patient subgroups defined by GPA or MPA phenotypes or ANCA specificities and/or immunofluorescence patterns (PR3-ANCA or MPO-ANCA).

Results of the meta-analysis confirmed the MHC class II region as the locus most strongly associated with AAV susceptibility (Table 1). The peak association signals arose from two *HLA-DPB1* gene variants, rs141530233 ($P=1.13x10^{-89}$) and rs1042169 ($P=1.12x10^{-84}$), with other significant associations observed in the *HLA-DPA1,DQA1* and *DQB1* genes (Table 1, Supplementary Figures 3 and 4). Associations with *DPA1* and *DPB1* remained strong in the GPA and PR3-ANCA subgroups, but not in the MPA or MPO-ANCA subgroups. Conversely, the *DQB1* association was much stronger in the MPO-ANCA relative to PR3-ANCA subgroup (Table 2A). In view of this divergence, GWAS, replication, and meta-analysis were also performed de novo comparing patients with either PR3-ANCA or MPO-ANCA to controls.

These analyses revealed significant association of the MPO-ANCA phenotype with rs3998159 ($P=5.24x10^{-25}$) and rs7454108 ($P=5.03x10^{-25}$) variants at the *HLA-DQA2* locus (Table 2B, Supplementary Table 6). Neither this nor any other significant associations beyond those detected in the AAV GWAS were detected in the GWAS of PR3-ANCA cases and controls (Supplementary Table 5).

Among the non-MHC associations identified in the AAV GWAS, the strongest signal arose from a SNP (rs28929474) in the *SERPINA1* gene ($P=3.09x10^{-12}$) encoding an α1 anti-trypsin null ("Z") allele implicated previously in GPA by candidate gene analysis (Table 1, Supplementary Figures 3 and 4) (15). This association was limited to the GPA and PR3-ANCA subsets (Table 2A) and is consistent with prior GWAS data showing that a significant association with another *SERPINA1* SNP (rs7151526) depended entirely on concomitant presence of the Z allele (2).

A significant association of AAV ($P = 8.60 \times 10^{-11}$) with rs62132293, a SNP located 2.6kb upstream of the *PRTN3* transcription start site, was also observed and is in keeping with prior associations (albeit with different SNPs) at this locus identified by AAV candidate gene and GWAS analyses (Table 1, Supplementary Figures 3 and 4) (2, 16). This association was limited to the GPA and PR3-ANCA subsets (Table 2A), consistent with pathophysiologic relevance of the *PRTN3*-encoded proteinase 3 serine protease (PR3) to these phenotypes (17).

Significant associations with AAV were observed at the *PTPN22* rs6679677 and rs2476601 loci ($P=1.88x10^{-8}$, $P=1.86x10^{-7}$, respectively) (Table 1, Supplementary Figures 3 and 4). Consistent with their equivalent effect sizes, these variants are in almost complete LD ($r^2=0.99$). However,

the rs2476601 variant encodes an Arg620Trp substitution in the Lyp phosphatase associated with risk for multiple autoimmune diseases, including giant cell arteritis (18, 19). Although variably observed in candidate gene studies (20, 21), this allele's association with GPA/MPA is strongly supported by our data and, unlike most other significant associations, did not differ between subgroups (Table 2A).

Possibly reflecting the analysis of a different case/control cohort, the discovery GWAS of either the entire cohort or the PR3-ANCA subgroup revealed no reliable associations at the *SEMA6A* gene locus. In the current discovery GWAS, there were 189 SNPs in the 1 MB region around *SEMA6A* from which the most significant variant (rs12521259) is ~100kb upstream of *SEMA6A*, with $p=9.11x10^{-3}$ in the full cohort and $p=4.87x10^{-3}$ in the PR3 ANCA subgroup.

Analyses of the associations in patient subgroups defined by presence or absence of lung or kidney disease revealed a modest association ($P=8.15x10^{-3}$) at the *HLA-DPA1* locus restricted to patients with kidney involvement; no significant subgroup differences were apparent at the other risk loci (Supplementary Table 7). A modest restriction of the *HLA-DPB1* and *HLA-DPA1* association to ANCA-positive patients was observed, but may reflect the relatively low numbers of ANCA-negative cases analyzed.

Risk alleles contribute jointly to disease susceptibility

As the strongest associations in all subgroups were with MHC gene SNPs, independence of the individual allele associations was explored by forward logistic regression selection analysis. Beginning with the most significant SNP identified in the total cohort or in the PR3-ANCA or

MPO-ANCA subgroups, additional significant variants were incorporated into the analysis until no variants significant at the $P<5x10^{-8}$ level remained. This analysis (Supplementary Table 8) revealed variants in several of the class II genes studied in each group to be jointly significantly associated with risk.

Results showed the array heritability of AAV was 0.2197 $\pm$ 0.0204, while with the HLA region removed, was 0.138 $\pm$ 0.022. The population attributable fraction (PAF) for the risk loci to disease was also assessed and the collective contribution of these loci to risk for AAV found to be substantive (PAF = 77%), albeit variable (PAFs between 30% and 87%) across different subgroups (Table 3).

The extent to which the risk variants/variant combinations predict disease was also evaluated using random forest and classification and regression tree (CART) methods. These analyses confirmed the strong association of *HLA* class II alleles with risk (Supplementary Figure 6), with homozygosity for the relatively common *DPB1* rs141530233 and *DPA1* rs9277341 risk alleles together with homozygosity or heterozygosity for the rare *SERPINA1* risk variant (rs2829474) identifying a subgroup with an OR > 10 for developing AAV. For HLA alleles, no subsets were defined by heterozygotes and further modeling comparing the goodness-of-fit of additive, dominant and recessive models showed that risk imbued by the *HLA-DPB1, DPA1* and *DQA1* disease-associated variants is recessively inherited, i.e. conferred by carriage of the common homozygous genotypes (Supplementary Table 9). The ORs associated with homozygous risk genotypes were 3.58 for rs141530233, 2.69 for rs9277341 and 1.80 for rs352425282. Similar results were found for the subgroups defined by carriage of PR3- or MPO-ANCA with recessive

models fitting best. These observations suggest the potential for genetic data to inform the distinction of patient subsets within the AAV population and identify an unusual recessive effect for the HLA region loci studied.

The disease-associated *PRTN3* polymorphism is a novel eQTL

To identify candidate causal variants, additional genotypes were imputed and the PICS algorithm applied across each risk locus (11). Although peak association signals at a few loci were stronger for imputed than observed SNPs (Supplementary Table 10), among all variants with PICS probability >0.0275, the index SNPs derived from direct genotyping were consistently associated with the highest PICS values (Supplementary Table 11). PICS values were particularly high for the index SNPs at the *HLA-DPB1, SERPINA1,* and *PTPN22* loci, which are all functional missense variants (15, 22, 23). The candidate causal variants at the other *HLA* gene loci were either synonymous, intronic, or upstream gene variants, but the majority of these noncoding and even several *HLA-DPB1* coding variants have been annotated as expression quantitative trait loci (eQTL) influencing gene expression in immune cell lineages (24).

None of the candidate variants at the *PRTN3* locus were coding or reported eQTL SNPs. Increases in *PRTN3* expression levels have, however, been observed in AAV patient neutrophils and implicated in pathogenicity (17, 25). As knowledge of neutrophil-specific eQTLs remains limited, we evaluated the lead SNP at this locus (rs62132293) for allelic effects on *PRTN3* expression in neutrophils. Results of qPCR analyses revealed cellular *PRTN3* transcript levels to be significantly higher in risk (G) allele homozygotes than in donors with CC or CG genotypes

(Figure 1). These results identify rs62132293 SNP as an eQTL for *PRTN3* and suggest that the causal variant at this locus engenders risk by its association with increased *PRTN3* expression.

The rs141530233 risk variant is associated with altered *HLA-DPB1* expression and T cell responses

Among the candidate causal variants, the *HLA-DPB1* rs141530233 and rs1042169 SNPs had the largest effects on risk, with respective ORs of 2.99 and 2.82 in the primary cohort and 6.19 and 6.09 in the PR3-ANCA subset (Tables 1 and 2A). These SNPs are, respectively, insertion/deletion (-/A) and missense (G/A) polymorphisms that map only two base pairs apart in exon 2 of the *HLA-DPB1* gene, with their risk alleles in complete LD in the control cohort and the reference 1000 Genomes Project datasets. In the latter population, these alleles correlate perfectly with another insertion/deletion polymorphic variant (rs386699872 CA/G) three base pairs downstream of rs141530233, suggesting that these variants comprise a triallelic risk and non-risk *HLA-DPB1* haplotype (Supplementary Figure 5). To confirm the haplotypic relatedness of the three variants, we sequenced this region in 100 study subjects homozygous for the rs141530233 and rs1042169 markers. Our findings confirmed the organization of the three variants in two haplotype blocks (Supplementary Figure 5), in keeping with prior reports of a dimorphic polymorphism (GGPM versus DEAV) at the corresponding amino acid positions (84-87) of the HLA-DPB chain (22, 26, 27).

Effects of the rs141530233 SNP on gene expression have not been reported, but the linked missense rs1042169 G/A SNP has been catalogued as an eQTL with the homozygous GG

genotype correlated to increased *HLA-DPB1* expression in peripheral blood mononuclear cells (PBMCs) (24). These variants are in LD with a SNP variant in the downstream *HLA-DPB1* 3' UTR (rs9277534) for which the homozygous genotype is associated with lower levels of *HLA-DPB1* and HLA-DP expression in immune cells compared to the alternate homozygous genotype (28, 29). We therefore assessed the relationship between the triallelic AAV risk haplotype and *HLA-DPB1*/HLA-DP expression using PBMCs from healthy subjects carrying risk or protective rs1042169 alleles. Results of qPCR analysis revealed *HLA-DPB1* mRNA levels to be significantly lower in rs1042169 GG risk allele homozygotes than in subjects with AA or GA genotypes (Figure 2A). Flow cytometric analyses revealed significantly lower HLA-DP expression on $CD19^+$ B cells and $CD14^+$ monocytes from GG donors than on cells from GA or AA subjects (Figures 2B and 2C). Thus, the triallelic risk haplotype defined by the rs104216 G variant is associated with reduced *HLA-DPB1* transcript and HLA-DP surface expression in immune cells.

The finding that a triallelic haplotype correlated to reduced *HLA-DPB1*/HLA-DP expression and encoding a putative functionally important HLA-DP polymorphism is highly associated with risk for AAV and particularly PR3-ANCA vasculitis strongly suggests that this genetic variation influences HLA-DP-modulated immune responses relevant to susceptibility. Because T cells that respond to PR3 protein or peptides have been identified in patients with PR3-ANCA AAV and the frequency of T cells responding to a "complementary" peptide encoding anti-sense PR3 codons (cPR3) has been correlated with the presence and activity of disease (30-35), we stimulated PBMCs from patients carrying rs1042169 G and/or A alleles with putatively immunogenic cPR3 and PR3 peptides and used an interferon-γ ELISPOT assay to identify

responding T cells. While the PR3 peptides elicited either no or minimal responses (data not shown), in most patients the cPR3 peptide evoked clear reactivity that was completely absent in cells stimulated with an irrelevant (OXY) peptide (Figure 2D) and in cells from healthy controls (data not shown). Frequencies of IFN-γ-producing cells differed strikingly among patients depending on rs1042169 allele status, numbers of responding T cells being significantly higher ($P < 0.020$) in risk allele homozygotes than in individuals having one or two copies of the protective A allele and significantly higher in risk allele homozygotes following cPR3 compared to OXY stimulation ($P < 0.0064$). These findings are in keeping with presence of cPR3-reactive T cells in PR3-ANCA vasculitis patients and the possibility that altered HLA-DP expression and possibly function associated with the *HLA-DPB1* homozygous risk haplotype correlate with increased numbers of autoreactive cells.

DISCUSSION

This study identifies MHC and non-MHC gene variants associated with GPA/MPA susceptibility and altered gene expression and/or function of proteins integral to immune responses. Our data reveal that the largest effect on risk emanates from a triallelic *HLA-DPB1* haplotype underpinning a previously-reported HLA-DPB amino acid polymorphism across positions 84-87 (22-27). Our data also support major roles for the *PRTN3*, *SERPINA1*, and *PTPN22* genes in AAV susceptibility, providing the first evidence for genome-wide significant association with the *PTPN22* rs2476601 functional variant and identifying the top-scoring variant at *SERPINA1* as a null allele and at *PRTN3* as an eQTL allele correlated with increased *PRTN3* expression in neutrophils. Results of CART analysis reveal the potential for these functional variants to identify population subsets at highly elevated risk for GPA/MPA, consistent with their collective

PAF of 77%. The estimated array heritability of 21% is comparable to estimates for inflammatory bowel disease (36).

Among the MHC associations, the *HLA-DPB1* risk haplotype alleles appear particularly significant, having a very strong effect on risk and underpinning a beta chain polymorphism in the HLA-DP antigen-binding pocket that modulates the protein's peptide-binding properties and possibly its effects on T cell allorecognition (22). This haplotype's physiologic significance is also implied by our data linking these risk alleles to decreased *HLA-DPB1* and HLA-DP expression and increased frequency of cPR3 peptide-reactive T cells in patients with anti-PR3 autoantibodies. Although understanding of the autoantigenic epitopes driving T cell responses in AAV is limited, our findings are consistent with prior data correlating alleles at linked *HLA-DPB1* SNP loci to differential *HLA-DPB1*/HLA-DP expression and with the association of such expression changes as well as the HLA-DP GGPM/DEAV variance with differential outcomes of specific immune challenges (28, 29). Further investigation is required to define the extent to which the risk haplotype associated increase in autoreactive T cells reflects the failure to eliminate such cells during thymic selection and/or another mechanistic aberrancy.

Among the non-MHC associations identified, direct causal effects of the *PTPN22* risk variant are strongly suggested by data linking the associated Lyp variant to aberrant increases in lymphocyte antigen receptor signaling and dendritic cell activation (23). Direct contribution of the *SERPINA1* rs28929474 risk variant to pathogenesis is also implied by the established role for alpha 1-antitrypsin in inhibiting PR3 protease activity and, by extension, PR3-induced inflammatory responses (37). Similarly, the most strongly associated *PRTN3* variant increases

neutrophil *PRTN3* expression, an aberrancy found often in PR3-ANCA positive patients and correlated with pathogenic neutrophil activation, suggesting that altered *PRTN3* expression mediated via this or a tightly-linked variant(s) functionally underpins the *PRTN3* association with AAV (17, 38).

Our analyses revealed risk for the various AAV phenotypes to be linked to joint effects of different genes across the HLA class II region. Consistent with a prior report of genetic distinctions between PR3-ANCA and MPO-ANCA vasculitis (2), we detected peak associations with *HLA-DPB1* and *HLA-DPA1* variants in the former, but with *HLA-DQA2* and *HLA-DQB1* variants, in the latter subgroup. Differential effects of these variants also distinguished GPA from MPA patients, suggesting that GPA and PR3-ANCA AAV share a composite of MHC class II risk alleles that is largely distinct from those conferring risk for MPA and MPO-ANCA AAV. Stronger associations at the *PRTN3* and *SERPINA1* loci appear to distinguish the GPA and PR3-ANCA subsets from their counterpart subgroups. By contrast, effects of the *PTPN22* locus on risk seem equivalent across the different subsets, suggesting the genetic disparities between subgroups do not reflect insufficient statistical power and are important determinants of phenotypic heterogeneity in AAV.

In summary, our study has illuminated MHC and non-MHC gene variants that are strongly associated with AAV, differentially associated with key clinical and serological disease subsets, and potentially directly influencing pathogenesis. The extent to which and mechanisms whereby these variants directly cause disease requires more investigation, our data not precluding biologic relevance of other alleles in LD with these variants, particularly at the *HLA-DPB1* and *PRTN3*

loci. Whether sample size constrained analysis of important subsets (such as patients with IgG versus IgA ANCA) or confounded detection of some important associations remains to be determined (39). Nonetheless, our findings identify a set of risk variants that explain much of the genetic risk for GPA/MPA, appear to influence clinical presentation of disease, and represent biologically important alleles with high potential to drive the aberrant immune responses contributing to development of AAV.

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Author contributions

This study was initially conceived and designed by Siminovitch, Merkel, and Amos. The collection and processing of samples for the study were supervised and coordinated by Merkel, Edberg, Falk, and Pagnoux with contributions by Carette, Chung, Ciavatta, Dellaripa, Elder, Forbess, Gewurz-Singer, Hoffman, Khalidi, Koening, Langford, Mahr, McAlear, Monach, Moreland, Qu, Seo, Specks, Spiera, Sreih, St. Clair, Stone, Ytterberg. Siminovitch. Lab work was supervised and/or executed by Siminovitch, Pinder, Zhao, Zhang, Ochi, and Hirano. Statistical analyses of the data were performed by Xie, Ji, Byun, and Qian. The paper was written primarily by Siminovitch, Merkel, Monach, and Amos, and critically reviewed and revised by all of the above authors.

Conflict of Interests

The authors declare no competing financial interests relevant to this work.

Figure Legends

Figure 1. AAV-associated rs62132293 variant is associated with increases in PRTN3 expression. *PRTN3* mRNA levels were detected by qPCR amplification of cDNA from peripheral blood polymorphic nuclear leukocytes of healthy donors with rs62132293 CC (n = 7), rs62132293 CG (n = 9) or rs62132293 GG (n = 6) genotypes. *PRTN3* expression levels relative to the calibrator reference gene *COX5B* are presented as normalized individual data points in box-and-whisker plots. AAV = ANCA-associated vasculitis. The horizontal line within each box indicates the median expression value; vertical lines indicate lowest and highest data points. Data are representative of 3 independent experiments. P value shown for unpaired *t* test.

Figure 2. rs1042169 alleles are associated with differential *HLA-DPB1* expression and T cell responses. (A) *HLA-DPB1* mRNA levels were detected by qPCR amplification of cDNA from PBMCs of healthy donors with *rs1042169 GG* (n=13), *rs1042169 AA* (n=7) or *rs1042169 GA* (n=8) genotypes. *HLA-DPB1* mRNA levels relative to the calibrator reference gene *GAPDH* are shown in box-and-whisker plots; horizontal line indicates median expression value and vertical lines indicate lowest and highest data points. Data are representative of 3 independent experiments. **(B, C)** Surface HLA-DP levels were evaluated in B cells (B) and monocytes (C) by flow cytometric assays of anti-DP and anti-CD19 or anti-CD14 antibody stained PBMCs from *rs1042169 GG* (n=24), *rs1042169 AA* (n=5), or *rs1042169 GA* (n=9) donors. Black bars show average mean fluorescence intensity (MFI) values. **(D)** PBMCs from PR3 ANCA^{+} patients with *rs10421699 GG* (n=21), *AA/AG* (n=8) genotypes were stimulated with anti-sense PR3 cPR3 or OXY control peptide and analyzed for IFNγ-secreting T cells by ELISPOT (data indicate mean fold change of stimulated versus unstimulated cells). Bars show the mean ± SEM. Significant P

values shown for unpaired *t* test (A-C), Mann-Whitney U test (D: *GG* vs *AA/AG* + cPR3^{138}), and Wilcoxon signed-rank test (D: *GG* cPR3^{138} vs *GG* OXY^{271}).

Supplementary Figure 1. Quality Control and Study Design. AAV = ANCA-associated vasculitis; GERA = Genetic Epidemiology Research on Aging; VCRC = Vasculitis Clinical Research Consortium; WGGER = Wegener's Granulomatosis Genetic Repository; UNC = University of North Carolina. Panel A shows the outcomes of genotyping quality control for single nucleotide polymorphisms (SNPs) and genomic DNA from individual subjects. The requirements for SNPs to meet quality control standards were call rates of greater than 95%, $p < 1 \times 10^{-5}$ for test of Hardy-Weinberg equilibrium and >0.01 for test of minor allele frequency. Panel B shows the numbers of cases and controls used in the discovery (GWAS) and replication cohorts and combined to generate a meta-analysis data set.

Supplementary Figure 2. Quantile-Quantile plot of test statistics for the genome-wide association study. The $-\log_{10}(p)$ values from EIGENSTRAT analysis are plotted on the Y axis against the expected $-\log_{10}(p)$ values on the X axis after removing all individuals and SNPs that failed quality control. After genomic control correction, the inflation factor was $\lambda = 0.991$ with and 1.012 without eigenvector adjustment. (A) $-\log_{10}(p)$ values for all GWAS SNPs. (B) $-\log_{10}(p)$ values after removal of the *HLA* region SNPs.

Supplementary Figure 3. Results of the ANCA-associated vasculitis genome-wide association screen. The Y axis shows the $-\log_{10}$P values (from EIGENSTRAT) for each single

nucleotide polymorphism on each chromosome along the X axis. The dashed line indicates the genome-wide significance threshold ($P = 5.0 \times 10^{-7}$).

Supplementary Figure 4. Locus Zoom plots. Showing regional associations across the MHC and non-MHC loci. The $-\log_{10}$P values of single-nucleotide polymorphisms genotyped in the discovery (●) and replication (▲) cohorts and included in the meta-analysis (♦) are plotted against their chromosomal position at each locus. SNPs are coloured depending on their degree of correlation (r^2) with the top SNP (as estimated on the basis of 1000 Genome European haplotypes, 2012) shown in purple. Genes and expressed sequence tags within each region are shown in the lower panels. HLA-DP and DQ regions; PTPN22; PRTN3 and SERPINA1.

Supplementary Figure 5. Confirmation of triallelic *HLA-DPB1* risk and non-risk haplotypes by direct sequencing analysis. Sequence analysis showing the *HLA-DPB1* exon 2 region rs1042169, rs141530233, rs386699872 risk and non-risk haplotypes. A 201 bp segment across *HLA-DPB1* nucleotide positions 3,048,604 to 33,048,804 (GRCh37/hg19) was PCR amplified using primer pairs 5'-GAGTACTGGAACAGCCAGAA and 3'-TAAGGTCCCTTAGGCCAACC and the amplification products then directly Sanger sequenced in individuals identified in the genome-wide association study as having homozygous risk (n = 50) or homozygous non-risk (n = 50) rs1042169 and rs141530233 genotypes. A representative example of the sequence read-out from each subgroup is shown with the nucleotide sequence and corresponding amino acid sequence and position shown below. The polymorphic alleles within each haplotype are circled. The sequence analysis confirmed 100% correlation of rs386699872 CA with the risk and rs386699872 G with the non-risk rs1042169/rs141530233 haplotype.

Supplementary Figure 6. Classification And Regression Tree (CART) model for predicting risk for GPA/MPA vasculitis. The CART analysis incorporated the disease-associated SNPs identified in the initial ANCA-associated vasculitis cohort meta-analysis. The *HLA-DQA2* rs7454108 and *PTPN22* rs6679677 and rs2476601 variants that did not substantially improve classification of cases and controls were removed from further analyses. Eight other variants (*HLA-DPA1* rs9277341, *HLA-DPB1* rs141530233, *HLA-DPB1* rs1042169, *PRTN3* rs62132293, *HLA-DQA1* rs35242582, *SERPINA1* rs28929474, *HLA-DQB1* rs104902, and *HLA-DQA2* rs39981589) all improved the model fit by at least 3% and were retained to build a CART. The three symbols ++, +-, or -- on each split represent minor variant homozygote, heterozygote, or homozygote, respectively. Odds ratios (OR) and confidence intervals (bracketed numbers) are shown for each node with the effects of specific variants on risk shown for each sequentially subclassified patient subset.

Table 1. Results of GWAS, replication, and combined association analyses

					GWAS (N=1371 cases. 3258 controls)				Replication (N = 615 cases, 1465 controls)				Combined analysis (N = 1986 cases, 4723 controls)	
					RAF				RAF					
SNP	Locus	Position	Gene	Risk allele	Cases	Controls	*P*[a]	OR (95% CI)[c]	Cases	Controls	*P*[b]	OR (95% CI)	*P*[c]	OR (95% CI)
rs141530233	6p21.32	33048688	*HLA-DPB1*	A del[d]	0.86	0.70	5.93×10^{-56}	2.76 (2.44 - 3.13)	0.90	0.69	2.45×10^{-39}	4.00 (3.23 - 5.00)	1.13×10^{-89}	2.99 (2.69 - 3.33)
rs1042169	6p21.32	33048686	*HLA-DPB1*	G	0.86	0.70	4.41×10^{-52}	2.57 (2.27 - 2.94)	0.90	0.68	1.94×10^{-39}	4.00 (3.23 - 5.00)	1.12×10^{-84}	2.82 (2.54 - 3.13)
rs9277341	6p21.32	33039625	*HLA-DPA1*	T	0.84	0.70	1.62×10^{-40}	2.21 (1.96 - 2.50)	0.87	0.66	3.58×10^{-34}	3.13 (2.63 - 3.70)	6.09×10^{-71}	2.44 (2.21 - 2.69)
rs35242582	6p21.32	32600057	*HLA-DQA1*	A	0.82	0.74	3.34×10^{-16}	1.61 (1.43 - 1.79)	0.82	0.74	3.59×10^{-8}	1.59 (1.35 - 1.89)	6.34×10^{-23}	1.60 (1.46 - 1.76)
rs1049072	6p21.32	32634355	*HLA-DQB1*	A	0.23	0.17	4.23×10^{-10}	1.43 (1.28 - 1.59)	0.21	0.17	1.69×10^{-3}	1.30 (1.10 - 1.54)	6.46×10^{-13}	1.40 (1.28 - 1.53)
rs6679677	1p13.2	114303808	*PTPN22*	A	0.13	0.09	2.40×10^{-8}	1.49 (1.30 - 1.72)	0.11	0.09	4.57×10^{-2}	1.25 (1.00 - 1.55)	1.88×10^{-8}	1.40 (1.25 - 1.57)
rs62132293	19p13.3	838178	*PRTN3*	G	0.37	0.31	5.55×10^{-8}	1.30 (1.18 - 1.43)	0.37	0.31	6.81×10^{-5}	1.33 (1.15 - 1.52)	8.60×10^{-11}	1.29 (1.19 - 1.39)
rs28929474	14q32.13	94844947	*SERPINA1*	T	0.04	0.02	8.26×10^{-8}	2.09 (1.59 - 2.73)	0.04	0.02	6.72×10^{-5}	2.18 (1.49 - 3.20)	3.09×10^{-12}	2.18 (1.75 - 2.71)
rs2476601	1p13.2	114377568	*PTPN22 (R620W)*	A	0.13	0.10	3.03×10^{-7}	1.45 (1.26 - 1.66)	0.11	0.09	5.38×10^{-2}	1.24 (1.00 - 1.53)	1.86×10^{-7}	1.36 (1.21 - 1.53)

Legend: CI, confidence interval; A del, adenosine deletion; OR, odds ratio; RAF, risk allele frequency.

[a] Eigenstrat Pvalue, [b] PLINK Pvalues, [c] Pvalues for the combined GWAS and replication datasets calculated using the Cochran-Mantel-Haenszel method of combining allele frequency counts.

[d] rs141530233 is an insertion/deletion (indel) polymorphism, the risk genotype lacking and the non-risk genotype containing an adenosine residue at nucleotide position 33048688.

Table 2. Effects of clinical and serologic status on the MHC and non-MHC associations with ANCA-associated vasculitis.

A. Subgroup comparisons

						Clinical syndrome						ANCA specificity					
				Overall analysis of combined cohort (N = 1986 cases, 4723 controls)		GPA (N = 1556) vs Controls (N = 4723)		MPA (N = 236) vs Controls (N = 4723)		GPA (N = 1556) vs MPA (N = 236)		PR3/cANCA (N = 1361) vs Controls (N = 4723)		MPO/pANCA (N = 378) vs Controls (N = 4723)		PR3/cANCA (N = 1361) vs MPO/pANCA (N = 378)	
SNP	Locus	Gene	Risk allele	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR
rs141530233	6p21.32	*HLA-DPB1*	A del	1.13×10^{-89}	2.99	3.80×10^{-93}	3.82	9.45×10^{-5}	1.58	1.45×10^{-9}	2.04	1.33×10^{-106}	6.19	1.50×10^{-2}	1.24	3.53×10^{-32}	3.93
rs1042169	6p21.32	*HLA-DPB1*	G	1.12×10^{-84}	2.82	1.09×10^{-90}	3.66	2.22×10^{-3}	1.40	9.50×10^{-12}	2.18	6.53×10^{-106}	6.09	1.27×10^{-1}	1.14	3.44×10^{-36}	4.27
rs9277341	6p21.32	*HLA-DPA1*	T	6.09×10^{-71}	2.44	2.78×10^{-73}	2.86	9.40×10^{-4}	1.45	4.96×10^{-7}	1.79	4.52×10^{-84}	3.69	3.61×10^{-3}	1.29	4.55×10^{-20}	2.61
rs35242582	6p21.32	*HLA-DQA1*	A	6.34×10^{-23}	1.60	1.60×10^{-20}	1.63	8.91×10^{-3}	1.36	1.36×10^{-1}	1.20	5.78×10^{-18}	1.62	2.34×10^{-7}	1.68	7.67×10^{-1}	1.03
rs1049072	6p21.32	*HLA-DQB1*	A	6.46×10^{-13}	1.40	1.40×10^{-7}	1.31	4.16×10^{-9}	1.89	2.99×10^{-3}	1.39	3.82×10^{-3}	1.17	2.13×10^{-24}	2.37	7.53×10^{-13}	1.94
rs6679677	1p13.2	*PTPN22*	A	1.88×10^{-8}	1.40	2.38×10^{-7}	1.40	8.96×10^{-4}	1.58	5.48×10^{-1}	1.09	7.89×10^{-6}	1.36	8.83×10^{-7}	1.71	1.08×10^{-1}	1.21
rs62132293	19p13.3	*PRTN3*	G	8.60×10^{-11}	1.29	7.06×10^{-11}	1.32	1.12×10^{-1}	1.17	2.70×10^{-1}	1.12	3.59×10^{-13}	1.39	5.66×10^{-1}	1.05	3.22×10^{-5}	1.45
rs28929474	14q32.13	*SERPINA1*	T	3.09×10^{-12}	2.18	3.53×10^{-13}	2.35	2.06×10^{-2}	1.88	3.86×10^{-1}	1.26	1.29×10^{-13}	2.43	4.96×10^{-3}	1.87	1.92×10^{-1}	1.34
rs2476601	1p13.2	*PTPN22 (R620W)*	A	1.86×10^{-7}	1.36	1.77×10^{-6}	1.36	1.31×10^{-3}	1.56	4.95×10^{-1}	1.10	3.19×10^{-5}	1.33	5.85×10^{-6}	1.64	1.40×10^{-1}	1.19

Legend: ANCA = Anti-neutrophil cytoplasmic autoantibody; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; cANCA = cytoplasmic ANCA; pANCA = perinuclar ANCA; MPO = myeloperoxidase; PR3 = proteinase 3;

N = numbers of subjects; OR = odds ratio; P = Eigenstrat P value.

Table 2. Effects of clinical and serologic status on the MHC and non-MHC associations with ANCA-associated vasculitis

B. GWAS, replication and combined analysis of MPO/pANCA subgroup

					GWAS N = 324 MPO/pANCA, 3258 controls				Replication N = 54 MPO/pANCA, 1465 controls				Combined N = 378 MPO/pANCA, 4723 controls		Analysis in combined PR3/cANCA patients N = 1361 PR3/cANCA, 4723 controls	
					RAF				RAF							
SNP	Locus	Position	Gene	Risk allele	Cases	Controls	*P*	OR (95% CI)	Cases	Controls	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
rs3998159	6p21.32	32682019	*HLA-DQA2*	C	0.23	0.10	3.47×10^{-19}	2.61 (2.12 - 3.22)	0.25	0.09	7.11×10^{-7}	3.25 (2.04 - 5.18)	5.24×10^{-25}	2.72 (2.24 - 3.22)	5.18×10^{-1}	1.05 (0.91 - 1.20)
rs7454108	6p21.32	32681483	*HLA-DQA2*	C	0.23	0.10	3.90×10^{-19}	2.61 (2.12 - 3.23)	0.25	0.09	4.78×10^{-7}	3.34 (2.09 - 5.33)	5.03×10^{-25}	2.73 (2.25 - 3.24)	5.48×10^{-1}	1.04 (0.90 - 1.20)
rs1049072	6p21.32	32634355	*HLA-DQB1*	A	0.32	0.17	1.63×10^{-18}	2.27 (1.89 - 2.72)	0.35	0.17	3.16×10^{-6}	2.60 (1.74 -3.88)	2.13×10^{-24}	2.37 (2.01 - 2.78)	3.82×10^{-3}	1.17 (1.06 - 1.31)

Legend: ANCA = Anti-neutrophil cytoplasmic autoantibody; MPO = myeloperoxidase; pANCA = perinuclear ANCA; GWAS = genome-wide association screen; OR = odds ratios; RAF = risk allele frequency; PR3 = proteinase 3; P = Eigenstrat P values.

Table 3. Population-Attributable Fraction for Disease-Associated SNPs at the MHC and non-MHC loci.

			AAV		GPA		MPA		PR3/cANCA		MPO/pANCA	
Gene	SNP	RAF	OR	PAF	OR	PAF	OR	PAF	OR	PAF	OR	PAF
HLA-DPB1	rs141530233	0.70	2.36	0.49	3.01	0.58	1.64	0.31	3.98	0.68	1.01	0.00
HLA-DPA1	rs9277341	0.70	1.62	0.30	1.81	0.36	1.26	0.00	1.84	0.37	1.03	0.00
HLA-DQA1	rs35242582	0.74	1.39	0.22	1.46	0.26	1.06	0.00	1.27	0.17	1.02	0.00
HLA-DQB1	rs1049072	0.17	1.33	0.05	1.19	0.00	1.91	0.13	1.16	0.00	2.64	0.22
PRTN3	rs62132293	0.31	1.27	0.08	1.30	0.09	1.18	0.00	1.59	0.16	1.10	0.00
SERPINA1	rs28929474	0.02	2.13	0.02	2.43	0.02	1.98	0.00	3.64	0.04	2.98	0.00
PTPN22 (R620W)	rs2476601	0.10	1.45	0.04	1.47	0.04	1.62	0.06	1.71	0.06	2.18	0.10
Combined				0.77		0.83		0.43		0.87		0.30

Legend: Population-attributable fraction (PAF) were calculated from the combined overall ANCA-associated vasculitis (AAV) and from clinically and serologically defined subgroups. GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; PR3 = proteinase 3; MPO = myeloperoxidase; RAF = risk allele frequency in healthy controls; OR = odds ratio.

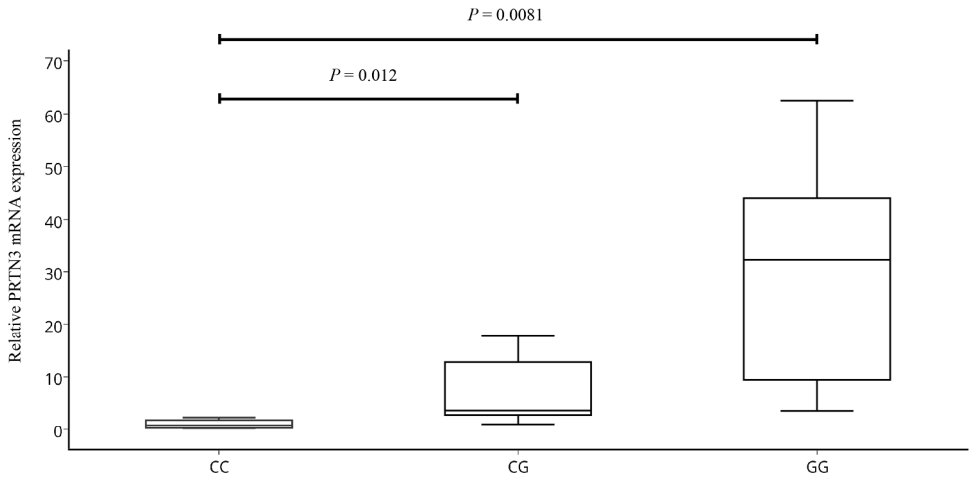


Figure 1. AAV-associated rs62132293 variant is associated with increases in PRTN3 expression.

245x136mm (300 x 300 DPI)

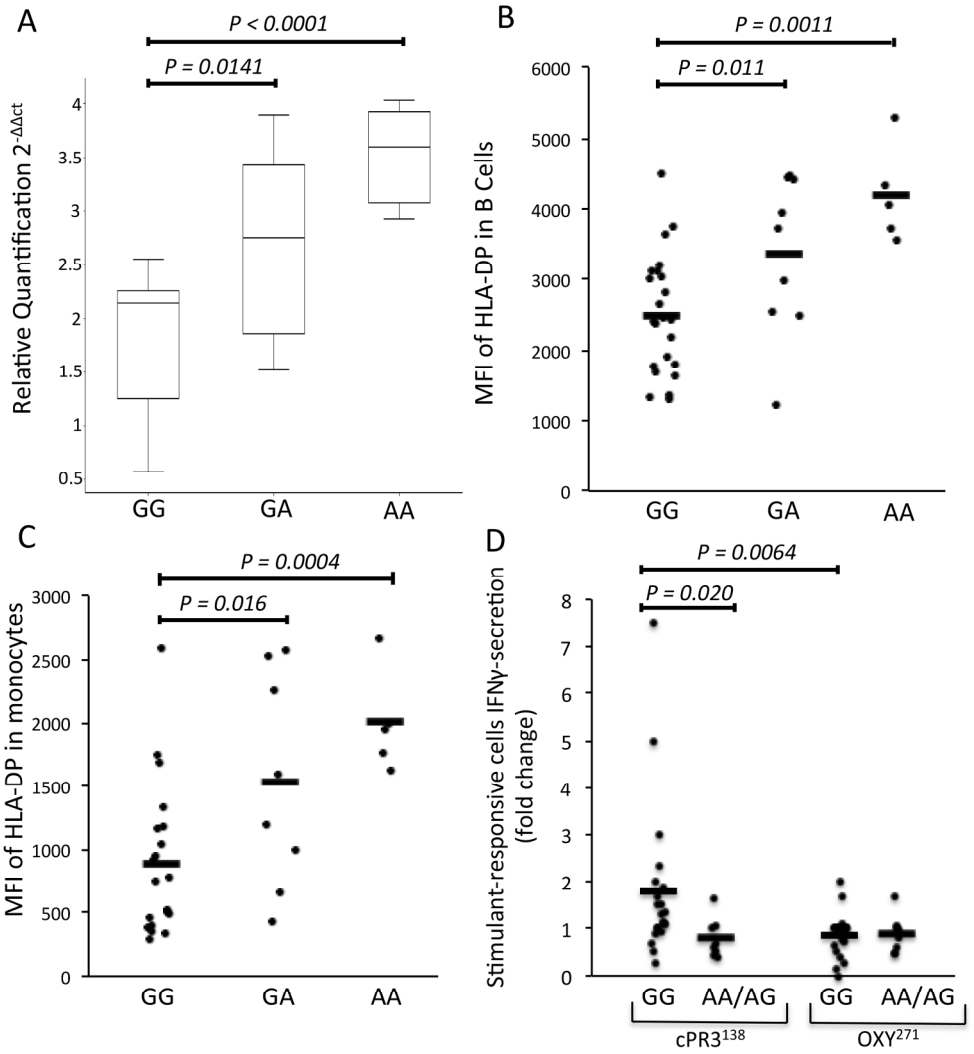


Figure 2. rs1042169 alleles are associated with differential HLA-DPB1 expression and T cell responses.

181x207mm (300 x 300 DPI)

Supplementary Table 1. Sequences of primer pairs used in quantitative PCR analyses.

Gene	Forward	Reverse
PRTN3	ACAACTACGACGCGGAGAAC	ACGGAGGCACTGAGGTTG
COX5B	ACTGGGTTGGAGAGGGAGAT	TGGAGATGGAGGGGACTAAA
HLA-DPB1	CAGCCTGGATAGTCCTGTCA	ATGCCCACTCCACAGATGAT
GAPDH	ATGTTCGTCATGGGTGTGAA	GGTGCTAAGCAGTTGGTGGT

Supplementary Table 2. Sequences of 20mer peptides used to evaluate T cell responses.

Peptide Name	Peptide Sequence
cPR3133	$_{152}$ALGAVGHWLVLLWQLDCGDG$_{133}$
cPR3138	$_{157}$PAHGQALGAVGHWLVLLWQL$_{138}$
PR3091	$_{091}$RTQEPTQQHFSVAQVFLNNYDA$_{112}$
PR3217	$_{217}$DSFVIWGCATRLFPDFFTRV$_{236}$
PR3222	$_{222}$WGCATRLFPDFFTRVALYVD$_{241}$
PR3227	$_{227}$RLFPDFFTRVALYVDWIRST$_{246}$
PR3232	$_{232}$FFTRVALYVDWIRSTLRRVE$_{251}$
PR3237	$_{237}$ALYVDWIRSTLRRVEAKGRP$_{256}$
Oxy271 control peptide	$_{271}$EKKYFAATQFEPLAARL$_{287}$

Supplementary Table 3. Summary of patient demographics, clinical data and quality controls outcomes by cohort

Cohort	Centre	Subject numbers		Clinical features of cases				ANCA specificity of cases[4]	
				Diagnosis (%)		Organ Involvement (%)		Number (%)	
Discovery[1]		Genotyped	Post QC	GPA	MPA	Kidney	Lung[3]	PR3-ANCA	MPO-ANCA
Cases									
	WGGER	438	377	360 (95.5)	0	208 (55.2)	203 (53.9)	298 (79.1)	25 (0.07)
	VCRC	779	668	564 (84.4)	76 (11.4)	405 (60.6)	481 (72.0)	446 (66.8)	152 (22.8)
	UNC Kidney Center	378	326	91 (27.9)	130 (39.9)	218 (66.9)	144 (44.2)	138 (42.3)	147 (45.1)
	Total	1615	1371	1015 (74.0)	206 (15)	831 (60.6)	828 (60.4)	882 (64.3)	324 (23.6)
	Age at diagnosis (Mean ± SD)		51 ± 17						
	Female (%)		51						
Controls									
	WGGER	202	184						
	GERA historic controls	3121	3074						
	Total	3323	3258						
	Age at recruitment (Mean ± SD)		43 ± 18						
	Female (%)		58						
Replication[2]									
Cases									
	Toronto	505	501	459 (91.6)	3 (0.6)	265 (52.9)	307 (61.3)	413 (82.4)	20 (4.0)
	VCRC	114	114	82 (71.9)	27 (23.7)	75 (65.8)	65 (57.0)	66 (57.9)	34 (29.8)
	Total	619	615	541 (88.0)	30 (4.9)	340 (55.3)	372 (60.5)	479 (77.9)	54 (8.8)
	Age at diagnosis (Mean ± SD)		47 ± 17						
	Female (%)		54						
Controls									
	Toronto	1477	1465						
	Age at recruitment (Mean ± SD)		33 ± 16						
	Female (%)		74						
Overall	Cases		1986	1556	236	1171	1200	1361	378
	Controls		4723						

Legend: ANCA = anti-neutrophil cytoplasmic autoantibody; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; GERA = Genetic Epidemiology Research on Aging
PR3 = proteinase-3; MPO = myeloperoxidase; VCRC = Vasculitis Clinical Research Consortium; WGGER = Wegener's Granulomatosis Genetic Repository; UNC = University of North Carolina
Post-QC refers to subjects in whom genotyping passed all quality control measures and principal component analysis.

[1] The WGGER and VCRC cases and WGGER controls included in the discovery GWAS were also included in a prior replication association analysis specifically testing association of 5 candidate loci with GPA (1)

[2] The "Toronto" cases (505) and 380 of the "Toronto" controls included in the replication analysis were previously studied in a prior GWAS on GPA conducted by our group (1)

[3] Diagnosis of lung involvement was based on reported pleuritis/pleural effusion, nodules or cavities, endobronchial involvement, alveolar hemorrhage or other pulmonary infiltrat

[4] ANCA specificity defined by PR3 or MPO-ANCA specificity and/or by non-antigen specific immunofluorescence ANCA assays

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs141530233	6p21.32	33048688	HLA-DPB1	-	5.93E-56	2.76
rs1042169	6p21.32	33048686	HLA-DPB1	G	4.41E-52	2.57
rs9277554	6p21.32	33055538	HLA-DPB1	C	4.97E-48	2.52
rs1071597	6p21.32	33052986	HLA-DPB1	T	1.08E-47	2.49
rs9277410	6p21.32	33051640	HLA-DPB1	G	1.90E-47	2.48
rs9277424	6p21.32	33051865	HLA-DPB1	A	3.11E-47	2.48
rs9277546	6p21.32	33055346	HLA-DPB1	T	5.72E-47	2.47
rs9277514	6p21.32	33054235	HLA-DPB1	T	5.80E-47	2.47
rs9277498	6p21.32	33054141	HLA-DPB1	T	6.33E-47	2.46
rs9277471	6p21.32	33053682	HLA-DPB1	G	7.62E-47	2.46
rs2064476	6p21.32	33073322	HLA-DPB1	A	9.30E-47	2.46
rs1042335	6p21.32	33052958	HLA-DPB1	C	9.66E-46	2.44
rs1431403	6p21.32	33047031	HLA-DPB1	T	1.38E-43	2.41
rs2144014	6p21.32	33065813	HLA-DPB1	G	2.34E-41	2.47
rs9277341	6p21.32	33039625	HLA-DPA1	T	1.62E-40	2.21
rs3117223	6p21.32	33060064	HLA-DPB1	G	7.69E-40	2.42
rs2395314	6p21.32	33062673	HLA-DPB1	G	1.04E-39	2.42
rs3128917	6p21.32	33059996	HLA-DPB1	T	1.26E-39	2.42
rs3128921	6p21.32	33070749	HLA-DPB1	C	2.11E-39	2.44
rs1042153	6p21.32	33048663	HLA-DPB1	G	4.31E-39	2.67
rs9277535	6p21.32	33054861	HLA-DPB1	A	4.74E-39	2.43
rs3128927	6p21.32	33074288	HLA-DPB1	C	6.44E-39	2.30
rs9277464	6p21.32	33053352	HLA-DPB1	C	7.11E-39	2.42
rs3135024	6p21.32	33047466	HLA-DPB1	T	7.44E-39	2.45
rs3130190	6p21.32	33061690	HLA-DPB1	T	1.04E-38	2.39
rs9277489	6p21.32	33053942	HLA-DPB1	T	1.42E-38	2.40
rs3117231	6p21.32	33074908	HLA-DPB1	A	1.23E-37	2.37
rs1042151	6p21.32	33048661	HLA-DPB1	A	2.85E-35	2.75
rs1126513	6p21.32	33048467	HLA-DPB1	G	9.27E-34	2.35
rs2179920	6p21.32	33058874	HLA-DPB1	C	5.71E-32	2.30
rs9277567	6p21.32	33057013	HLA-DPB1	A	1.48E-31	2.36
rs2064474	6p21.32	33073463	HLA-DPB1	G	1.53E-31	2.24
rs2064478	6p21.32	33072266	HLA-DPB1	C	1.63E-31	2.27
rs3117230	6p21.32	33075635	HLA-DPB1	A	2.12E-31	2.26
rs1042434	6p21.32	33036505	HLA-DPA1	G	3.13E-31	2.62
rs3077	6p21.32	33033022	HLA-DPA1	A	9.84E-31	2.60
Affx-28512827	6p21.32	33037424	HLA-DPA1	T	2.15E-30	2.59
rs2308911	6p21.32	33037580	HLA-DPA1	T	2.48E-30	2.59
Affx-28512796	6p21.32	33036853	HLA-DPA1	A	4.25E-30	2.57
rs17214533	6p21.32	33032272	HLA-DOA	C	7.68E-30	2.57
rs10214910	6p21.32	33037675	HLA-DPA1	C	7.88E-30	2.56

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs1431399	6p21.32	33041034	HLA-DPA1	A	1.37E-29	2.54
rs910320	6p21.32	33075443	HLA-DPB1	C	1.27E-28	2.18
rs1126769	6p21.32	33036435	HLA-DPA1	T	1.04E-27	2.49
rs2071352	6p21.32	33044188	HLA-DPB1	T	3.22E-27	3.01
rs439205	6p21.32	33173842	HSD17B8	G	6.32E-27	2.00
rs1042190	6p21.32	33036999	HLA-DPA1	T	7.03E-27	2.53
rs2071025	6p21.32	33143756	COL11A2	A	2.02E-26	1.99
rs2076310	6p21.32	33166034	RXRB	A	7.10E-26	1.96
rs2281389	6p21.32	33059796	HLA-DPB1	A	1.02E-24	2.24
rs2858458	6p21.32	33003065	HLA-DOA	T	6.23E-24	1.85
rs3097671	6p21.32	33047612	HLA-DPB1	G	8.27E-24	2.24
rs421446	6p21.32	33174783	HSD17B8	A	2.80E-23	1.77
rs213209	6p21.32	33176958	RING1	C	3.23E-23	1.79
rs1126543	6p21.32	33037419	HLA-DPA1	G	1.14E-22	2.16
rs987870	6p21.32	33042880	HLA-DPA1	A	3.38E-22	2.37
rs9277935	6p21.32	33160425	COL11A2	G	1.13E-21	1.91
rs3117016	6p21.32	33095516	HLA-DPB2	G	3.57E-20	1.58
rs986521	6p21.32	33136145	COL11A2	G	2.04E-18	1.56
rs439121	6p21.32	33192867	RING1	A	1.12E-16	1.64
rs213212	6p21.32	33185918	RING1	C	1.30E-16	1.51
rs213194	6p21.32	33195604	RING1	A	1.80E-16	1.50
rs213213	6p21.32	33183730	RING1	T	2.54E-16	1.48
rs3130161	6p21.32	33125858	COL11A2	A	2.65E-16	2.04
rs2855442	6p21.32	33137403	COL11A2	C	3.27E-16	1.49
rs35242582	6p21.32	32600057	HLA-DQA1	A	3.34E-16	1.61
rs2855425	6p21.32	33144373	COL11A2	G	3.92E-16	1.49
rs3116994	6p21.32	33098797	COL11A2	G	7.30E-16	1.46
rs6531	6p21.32	33163451	RXRB	G	9.30E-16	1.48
rs2744512	6p21.32	33141920	COL11A2	G	1.13E-15	1.50
rs3129270	6p21.32	33097423	COL11A2	C	1.23E-13	1.96
rs7772134	6p21.32	33049726	HLA-DPB1	G	1.90E-13	2.17
rs3129207	6p21.32	33125312	COL11A2	G	2.47E-13	1.40
rs2855437	6p21.32	33138955	COL11A2	G	2.83E-13	1.43
rs3117008	6p21.32	33096274	HLA-DPB2	G	3.20E-13	1.40
rs1883414	6p21.32	33086448	HLA-DPB2	G	5.43E-13	1.46
rs9277946	6p21.32	33194717	RING1	C	5.62E-13	1.78
rs3129294	6p21.32	33084671	HLA-DPB2	A	6.57E-13	1.43
rs2855459	6p21.32	33154656	COL11A2	G	8.59E-13	1.77
rs3129274	6p21.32	33094869	HLA-DPB2	C	1.27E-12	1.41
rs3129267	6p21.32	33098896	COL11A2	C	1.37E-12	1.41
rs660895	6p21.32	32577380	HLA-DRB1	G	1.70E-12	1.47
rs28584179	6p21.32	32626119	HLA-DQA1	C	1.78E-12	1.94
rs116518618	6p21.32	32594998	HLA-DRB1	C	1.80E-12	1.94

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs9271897	6p21.32	32595954	HLA-DRB1	G	3.68E-12	1.38
rs3116999	6p21.32	33097166	COL11A2	G	1.22E-11	1.61
rs1882	6p21.33	31382911	MICA	A	1.94E-11	1.38
rs3097669	6p21.32	33023792	HLA-DOA	A	2.94E-11	1.47
rs3130176	6p21.32	33017457	HLA-DOA	A	3.19E-11	1.36
rs9271824	6p21.32	32594916	HLA-DRB1	A	3.47E-11	1.36
rs3134926	6p21.32	32200147	NOTCH4	C	4.60E-11	1.42
rs2294479	6p21.32	33098389	COL11A2	G	5.44E-11	1.40
Affx-52341735	6p21.32	33138955	COL11A2	G	2.19E-10	1.36
rs2254287	6p21.32	33143948	COL11A2	C	2.57E-10	1.36
rs726599	6p21.32	33121678	COL11A2	C	3.85E-10	1.35
rs1049072	6p21.32	32634355	HLA-DQB1	A	4.23E-10	1.43
rs2855448	6p21.32	33136575	COL11A2	C	1.05E-09	1.34
rs9272105	6p21.32	32599999	HLA-DRB1	G	1.08E-09	1.32
rs2257126	6p21.32	33131734	COL11A2	A	1.16E-09	1.34
rs2596530	6p21.33	31387373	MICA	G	1.37E-09	1.34
rs9273088	6p21.32	32612488	HLA-DQA1	C	1.41E-09	1.33
rs2395175	6p21.32	32405026	HLA-DRA	A	2.08E-09	1.42
rs9296068	6p21.32	32988695	HLA-DOA	T	2.55E-09	1.35
rs1130399	6p21.32	32629755	HLA-DQB1	A	2.94E-09	1.40
rs2256183	6p21.33	31380529	MICA	A	3.05E-09	1.33
rs1810472	6p21.32	33083121	HLA-DPB2	T	3.37E-09	1.37
rs213210	6p21.32	33175824	RING1	A	4.30E-09	1.99
rs9272116	6p21.32	32600404	HLA-DQA1	T	6.01E-09	1.31
rs9368758	6p21.32	33138021	COL11A2	G	6.60E-09	1.98
rs75549913	6p21.33	31390139	MICA	-	6.65E-09	1.33
rs9273215	6p21.32	32613712	HLA-DQA1	G	6.75E-09	1.31
rs438999	6p21.33	31928306	SKIV2L	A	7.46E-09	1.73
rs541862	6p21.33	31916951	CFB	T	7.90E-09	1.73
rs763469	6p21.32	33004387	HLA-DOA	A	8.02E-09	1.41
rs9274552	6p21.32	32634838	HLA-DQB1	C	9.40E-09	1.31
rs6936620	6p21.32	32984451	HLA-DOA	A	1.18E-08	1.31
rs3096702	6p21.32	32192331	NOTCH4	A	1.38E-08	1.31
rs3130604	6p21.32	32985052	HLA-DOA	G	1.76E-08	1.40
rs2068204	6p21.32	33058718	HLA-DPB1	G	1.87E-08	2.82
rs1063355	6p21.32	32627714	HLA-DQB1	G	1.89E-08	1.30
rs17612576	6p21.32	32615458	HLA-DQA1	A	1.92E-08	1.30
rs382259	6p21.32	32209027	NOTCH4	T	2.07E-08	1.36
rs2070600	6p21.32	32151443	AGER	T	2.10E-08	1.71
rs199556640	6p21.32	32609299	HLA-DQA1	-	2.27E-08	1.30
rs6679677	1p13.2	114303808	PTPN22	A	2.40E-08	1.49
rs3129304	6p21.32	32973743	HLA-DOA	C	2.66E-08	1.39
rs429608	6p21.33	31930462	SKIV2L	G	2.98E-08	1.49

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs17843619	6p21.32	32620775	HLA-DQA1	A	3.47E-08	1.29
rs3132454	6p21.33	31489644	MCCD1	A	3.93E-08	1.32
rs9272346	6p21.32	32604372	HLA-DQA1	A	4.89E-08	1.29
rs62132293	19p13.3	838178	PRTN3	G	5.55E-08	1.30
rs9468925	6p21.33	31258837	HLA-C	G	6.28E-08	1.30
rs429916	6p21.32	32978587	HLA-DOA	C	7.41E-08	1.79
rs6910071	6p21.32	32282854	C6orf10	G	7.87E-08	1.35
rs3793127	6p21.32	32371915	BTNL2	T	7.96E-08	1.33
rs28929474	14q32.13	94844947	SERPINA1	T	8.26E-08	2.09
rs2844514	6p21.33	31380340	MICA	C	8.29E-08	1.29
rs1129808	6p21.32	32609312	HLA-DQA1	C	8.40E-08	1.28
rs389512	6p21.33	31947594	STK19	G	8.57E-08	1.52
rs2857107	6p21.32	32785515	HLA-DOB	C	8.63E-08	1.55
rs1894411	6p21.32	32792973	TAP2	T	9.43E-08	1.55
rs34892006	6p22.1	29012712	OR2W1	C	9.47E-08	13.46
rs387608	6p21.33	31941557	STK19	G	1.01E-07	1.52
Affx-28465058	6p21.33	31936679	SKIV2L	C	1.01E-07	1.52
rs2844513	6p21.33	31388214	MICA	G	1.06E-07	1.29
Affx-28513472	6p21.32	33053577	HLA-DPB1	G	1.08E-07	2.16
rs206762	6p21.32	32970450	BRD2	G	1.15E-07	1.28
rs9263873	6p21.33	31170713	HCG27	T	1.21E-07	1.29
rs2517424	6p21.33	30949996	MUC21	T	1.30E-07	1.48
rs2524040	6p21.33	31257625	HLA-C	T	1.36E-07	1.29
rs805284	6p21.33	31682029	LY6G6D	A	1.38E-07	1.69
rs1143260	6p21.32	32359227	HCG23	A	1.46E-07	1.52
rs3873386	6p21.33	31273745	HLA-C	T	1.59E-07	1.29
rs9380343	6p21.32	33079166	HLA-DPB1	C	1.66E-07	2.51
rs2395163	6p21.32	32387809	HLA-DRA	C	1.79E-07	1.32
rs17843606	6p21.32	32620399	HLA-DQA1	T	1.84E-07	1.28
rs444921	6p21.33	31932177	SKIV2L	C	1.88E-07	1.51
rs213226	6p21.32	33209310	RING1	A	2.04E-07	1.27
rs3130257	6p21.32	33256471	WDR46	T	2.16E-07	1.42
rs2857605	6p21.33	31524851	NFKBIL1	C	2.63E-07	1.32
rs2476601	1p13.2	114377568	PTPN22 (R620W)	A	3.03E-07	1.45
rs211449	6p21.32	33333916	DAXX	G	3.05E-07	1.29
rs4713447	6p21.33	31162963	PSORS1C3	A	3.27E-07	1.28
rs2228396	6p21.32	32797809	TAP2	T	3.36E-07	1.48
rs3097648	6p21.32	32990970	HLA-DOA	A	3.67E-07	1.50
rs34252386	6p21.32	32546912	HLA-DRB1	G	4.03E-07	1.28
rs6457374	6p21.33	31272261	HLA-C	C	4.24E-07	1.30
rs9277348	6p21.32	33048538	HLA-DPB1	T	4.37E-07	3.07
rs67523850	6p21.32	33054014	HLA-DPB1	A	5.48E-07	2.12
rs1130368	6p21.32	32632818	HLA-DQB1	T	5.71E-07	1.39

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs511294	6p21.33	31888869	C2	T	5.86E-07	1.75
Affx-28512853	6p21.32	33037640	HLA-DPA1	C	6.46E-07	2.59
rs3132680	6p22.1	30073195	TRIM31	A	6.48E-07	1.28
rs3094672	6p21.33	30993377	MUC22	T	6.57E-07	1.29
rs6928399	6p21.33	31195218	HLA-C	C	6.71E-07	1.29
rs9348906	6p21.32	33080360	HLA-DPB2	T	7.08E-07	2.89
rs6928482	6p21.32	32626249	HLA-DQA1	C	7.11E-07	1.26
rs605203	6p21.33	31847012	EHMT2	C	7.22E-07	1.27
rs486416	6p21.33	31856070	EHMT2	G	7.96E-07	1.27
rs1062481	6p21.32	33037611	HLA-DPA1	C	9.54E-07	2.59
rs6899309	6p21.32	32915823	HLA-DMB	T	1.01E-06	1.86
rs2247056	6p21.33	31265490	HLA-C	T	1.01E-06	1.29
rs659445	6p21.33	31864304	EHMT2	G	1.17E-06	1.26
rs9380345	6p21.32	33080359	HLA-DPB2	C	1.18E-06	2.79
rs35445101	6p21.32	32546879	HLA-DRB1	G	1.20E-06	1.26
rs2240070	6p22.1	30071110	TRIM31	T	1.21E-06	1.27
rs9267873	6p21.32	32199352	NOTCH4	C	1.26E-06	1.26
rs440454	6p21.33	31927342	SKIV2L	A	1.26E-06	1.27
rs423209	6p21.32	32983474	HLA-DOA	G	1.27E-06	2.26
rs638383	6p21.33	31908224	C2	C	1.30E-06	2.02
rs213220	6p21.32	33202640	RING1	C	1.30E-06	1.25
rs7264431	20p13	1716975	SIRPG	C	1.36E-06	1.44
rs2853931	6p21.33	31255007	HLA-C	C	1.37E-06	1.25
rs3905495	6p21.33	31265539	HLA-C	G	1.38E-06	1.27
rs4642516	6p21.32	32657543	HLA-DQA2	T	1.39E-06	1.25
Affx-52368679	6p21.32	32632863	HLA-DQB1	CGGT	1.41E-06	1.26
rs3134996	6p21.32	32636866	HLA-DQB1	T	1.43E-06	1.26
rs7755364	6p21.33	30981715	MUC22	G	1.50E-06	1.43
rs3998159	6p21.32	32682019	HLA-DQA2	C	1.55E-06	1.40
rs7454108	6p21.32	32681483	HLA-DQA2	C	1.56E-06	1.40
rs28366130	6p21.33	31363805	MICA	A	1.61E-06	1.28
rs166325	6p22.1	29993196	ZNRD1-AS1	G	1.64E-06	1.67
rs1269851	6p21.33	32092207	ATF6B	T	1.77E-06	1.98
rs423639	6p21.32	32987774	HLA-DOA	C	1.82E-06	1.62
rs176248	6p21.32	32965942	BRD2	G	1.85E-06	1.30
rs9366814	6p21.32	33080799	HLA-DPB2	T	1.88E-06	2.57
Affx-37072023	6p21.32	32612430	HLA-DQA1	C	1.91E-06	1.25
rs28366302	6p21.32	32560934	HLA-DRB1	C	1.92E-06	1.26
rs41267649	6p21.32	33384473	CUTA	T	2.03E-06	1.91
rs419788	6p21.33	31928799	SKIV2L	T	2.07E-06	1.27
rs365053	6p21.32	32195988	NOTCH4	T	2.14E-06	1.30
rs204890	6p21.33	32085598	ATF6B	C	2.16E-06	2.07
rs2844529	6p21.33	31353593	MICA	G	2.52E-06	1.27

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs3130609	6p21.32	32989521	HLA-DOA	C	2.54E-06	2.32
rs3873444	6p21.32	32682724	HLA-DQA2	C	2.66E-06	1.55
rs2523467	6p21.33	31362930	MICA	C	2.77E-06	1.27
rs2523554	6p21.33	31331829	MICA	C	2.85E-06	1.25
rs1634717	6p21.33	30972589	MUC22	G	2.89E-06	1.24
rs4668338	2q31.1	171733225	GAD1	C	3.04E-06	4.70
rs241438	6p21.32	32797620	TAP2	C	3.19E-06	1.26
rs535586	6p21.33	31860337	EHMT2	T	3.24E-06	1.25
rs3819721	6p21.32	32804798	TAP2	A	3.34E-06	1.27
rs437179	6p21.33	31929014	SKIV2L	A	3.43E-06	1.26
rs115771946	6p22.1	29837127	HLA-G	T	3.70E-06	1.63
rs2844795	6p22.1	30073847	TRIM31	C	4.02E-06	1.24
rs2853933	6p21.33	31254088	HLA-C	T	4.08E-06	1.24
rs2596542	6p21.33	31366595	MICA	C	4.11E-06	1.26
rs2523473	6p21.33	31361897	MICA	A	4.28E-06	1.26
Affx-28507878	6p21.32	32823948	PSMB9	G	4.50E-06	2.59
rs448733	6p21.32	33003687	HLA-DOA	C	4.66E-06	1.83
rs9274697	6p21.32	32637016	HLA-DQB1	G	4.77E-06	1.23
rs2395185	6p21.32	32433167	HLA-DRB5	T	5.07E-06	1.25
rs34182778	6p21.33	31084943	CDSN	-	5.27E-06	1.29
rs2524163	6p21.33	31259579	HLA-C	C	5.81E-06	1.24
rs259937	6p22.1	30007493	ZNRD1-AS1	T	5.97E-06	1.62
rs4412248	6p21.32	33072415	HLA-DPB1	C	6.08E-06	3.25
rs630379	6p21.33	31922254	NELFE	A	6.19E-06	1.25
rs7041467	9q21.32	85865570	FRMD3	G	6.26E-06	5.77
rs389883	6p21.33	31947460	STK19	G	6.48E-06	1.25
rs2524089	6p21.33	31266522	HLA-C	G	6.60E-06	1.23
rs12662501	6p21.33	31190850	HLA-C	C	6.62E-06	1.37
rs9268923	6p21.32	32432835	HLA-DRB5	T	6.68E-06	1.24
rs146599962	18q21.31	55398906	ATP8B1	G	6.69E-06	16.56
rs5024432	6p21.32	32684468	HLA-DQA2	C	6.91E-06	1.44
rs498422	6p21.32	32286761	C6orf10	T	6.97E-06	1.61
rs150018949	1p34.2	40981245	EXO5	G	7.07E-06	1.82
rs204894	6p21.33	32093922	ATF6B	G	7.43E-06	1.80
rs9275184	6p21.32	32654714	HLA-DQA2	C	7.81E-06	1.37
rs4726308	7q36.2	153290520	DPP6	T	7.86E-06	1.24
rs213199	6p21.32	33235755	VPS52	G	8.24E-06	1.24
rs3117034	6p21.32	33087358	HLA-DPB2	T	8.42E-06	1.23
rs411337	6p21.33	32077380	ATF6B	C	8.79E-06	1.55
rs3093983	6p21.33	31496925	MCCD1	G	8.90E-06	1.28
rs10484561	6p21.32	32665420	HLA-DQA2	T	8.91E-06	1.41
rs1619376	6p21.33	30983326	MUC22	A	9.04E-06	1.27
rs6457144	6p22.1	30063368	TRIM31	T	9.05E-06	1.23

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs202081894	11p15.5	824567	PNPLA2	C	9.12E-06	4.40
rs2071285	6p21.32	32180431	NOTCH4	T	9.24E-06	1.47
rs2854050	6p21.32	32185605	NOTCH4	A	9.63E-06	1.47
rs2243868	6p21.33	31261276	HLA-C	A	1.04E-05	1.23
rs1241983	18p11.31	6875693	ARHGAP28	A	1.04E-05	1.22
rs6937034	6p21.32	33079766	HLA-DPB1	A	1.06E-05	2.30
rs6457702	6p21.32	32988049	HLA-DOA	T	1.10E-05	1.23
rs2517421	6p21.33	30951209	MUC21	C	1.17E-05	1.36
rs2249168	6p21.33	30958254	MUC22	C	1.19E-05	1.36
rs3131631	6p21.33	31484683	MCCD1	G	1.19E-05	1.25
rs204888	6p21.33	32089142	ATF6B	G	1.20E-05	1.54
rs2116263	6p21.32	33025493	HLA-DOA	G	1.28E-05	2.82
rs213204	6p21.32	33241076	RPS18	C	1.32E-05	1.24
rs2523915	6p21.33	30973358	MUC22	T	1.34E-05	1.36
rs56291618	7p22.3	164282	FAM20C	A	1.39E-05	1.87
rs2853939	6p21.33	31250642	HLA-C	T	1.41E-05	1.22
rs213202	6p21.32	33232055	VPS52	G	1.44E-05	1.24
rs2517409	6p21.33	30964393	MUC22	T	1.48E-05	1.36
rs59726684	8p21.2	24775457	NEFM	C	1.48E-05	1.96
rs204879	6p21.33	32043157	TNXB	T	1.49E-05	2.03
rs204996	6p21.32	32149883	AGER	C	1.54E-05	1.75
rs9391630	6p22.1	29722515	HCG4	G	1.58E-05	1.26
rs61815115	1q21.3	151783324	RORC	G	1.58E-05	1.40
rs2229784	6p21.32	33136310	COL11A2	G	1.59E-05	2.24
rs2341320	2q37.1	232740108	COPS7B	T	1.62E-05	1.22
rs67529500	6p21.32	32504757	HLA-DRB5	G	1.64E-05	1.22
rs3135195	6p21.32	32999330	HLA-DOA	T	1.65E-05	2.25
rs3132682	6p22.1	30044388	TRIM31	G	1.76E-05	1.22
rs6909253	6p22.1	30055643	TRIM31	G	1.96E-05	1.22
rs1042149	6p21.33	31082960	CDSN	A	1.98E-05	1.22
rs9271709	6p21.32	32593392	HLA-DRB1	G	1.99E-05	1.24
rs2524074	6p21.33	31244021	HLA-C	G	2.01E-05	1.23
rs77637983	6p21.32	32549452	HLA-DRB1	C	2.07E-05	1.22
rs700726	8q12.1	60931328	CA8	T	2.08E-05	1.22
rs2844682	6p21.33	30946148	MUC21	G	2.14E-05	1.35
rs106287	6p21.33	31935750	SKIV2L	G	2.14E-05	2.01
rs2523685	6p21.33	31426256	MICA	G	2.24E-05	1.27
rs2523921	6p21.33	30975090	MUC22	T	2.28E-05	1.35
rs142478577	4p16.3	2994002	GRK4	C	2.41E-05	15.67
rs4713422	6p21.33	30999902	MUC22	G	2.44E-05	1.23
rs2255625	6p21.33	30940705	MUC21	A	2.56E-05	1.35
rs3104401	6p21.32	32687358	HLA-DQA2	A	2.62E-05	1.34
rs169494	6p21.33	32097876	FKBPL	G	2.66E-05	1.51

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs62399430	6p21.33	30993866	MUC22	A	2.66E-05	1.36
rs211450	6p21.32	33333446	DAXX	C	2.71E-05	1.23
rs2517439	6p21.33	30942929	MUC21	G	2.85E-05	1.35
rs653667	1p36.22	12251808	TNFRSF1B	T	2.85E-05	1.23
rs3094212	6p21.33	31085770	CDSN	G	2.90E-05	1.21
rs204885	6p21.33	32029929	TNXB	C	3.00E-05	1.94
rs241436	6p21.32	32797876	TAP2	A	3.11E-05	1.22
rs261945	6p22.1	30272417	HCG18	C	3.12E-05	1.22
rs2596501	6p21.33	31321211	HLA-C	C	3.12E-05	1.21
rs9261485	6p22.1	30108751	TRIM40	A	3.14E-05	1.25
rs213203	6p21.32	33238404	VPS52	A	3.15E-05	1.21
rs5027459	6p21.32	32719028	HLA-DQB2	G	3.25E-05	1.24
rs73727981	6p21.32	32511791	HLA-DRB5	A	3.38E-05	1.21
rs3132554	6p21.33	31084163	CDSN	A	3.42E-05	1.21
rs4713438	6p21.33	31146846	PSORS1C3	G	3.43E-05	1.30
rs10947121	6p21.33	30999997	MUC22	T	3.48E-05	1.23
rs2516472	6p21.33	31394700	MICA	A	3.63E-05	1.51
rs15574	6p21.33	31686497	LY6G6C	G	3.67E-05	1.28
rs2844463	6p21.33	31615167	BAG6	G	3.80E-05	1.35
rs4807840	19p13.3	6156483	ACSBG2	C	3.81E-05	1.23
rs34411532	6p21.32	32592294	HLA-DRB1	G	3.94E-05	1.31
rs1562284	13q12.12	25297674	ATP12A	T	3.98E-05	1.36
rs3129264	6p21.32	33101602	COL11A2	A	4.02E-05	1.26
rs2239707	6p21.33	31525319	NFKBIL1	C	4.11E-05	1.22
rs201458058	1q32.3	212142051	INTS7	-	4.12E-05	1.70
rs480092	6p21.33	31764899	VARS	T	4.12E-05	1.31
Affx-52368556	6p21.33	31084936	CDSN	-	4.18E-05	1.25
rs3129878	6p21.32	32408735	HLA-DRA	A	4.46E-05	1.23
rs79192891	3q12.3	102470556	ZPLD1	T	4.54E-05	1.80
rs2596480	6p21.33	31425985	MICA	C	4.59E-05	1.50
rs78374723	12q13.13	53096894	KRT77	T	4.63E-05	13.35
rs2508016	6p21.33	30969527	MUC22	C	4.63E-05	1.32
rs35157068	1q43	242762202	PLD5	T	4.65E-05	1.21
rs3129234	6p21.32	33111347	COL11A2	C	4.67E-05	1.26
rs1264708	6p22.1	30057154	TRIM31	A	4.79E-05	1.26
rs34976040	2q37.3	241401673	GPC1	A	4.80E-05	1.72
rs723872	20p13	1707027	SIRPG	C	4.82E-05	1.34
rs1051790	6p21.33	31378956	MICA	C	4.90E-05	1.32
rs2596460	6p21.33	31417510	MICA	A	4.95E-05	1.50
Affx-28441669	6p21.33	31084075	CDSN	G	5.07E-05	1.21
rs17015501	2p22.3	34906388	LINC01320	C	5.23E-05	1.26
rs3132499	6p21.33	31207920	HLA-C	C	5.23E-05	1.28
Affx-80220121	2q37.3	242051776	PASK	A	5.26E-05	1.35

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs756440	6p21.32	33122331	COL11A2	A	5.27E-05	1.26
rs422640	6p22.1	29943005	HCG9	G	5.33E-05	1.31
rs3117294	6p22.1	29653329	HLA-F	T	5.37E-05	1.22
rs3807031	6p22.1	30033884	PPP1R11	A	5.39E-05	1.25
rs743400	6p21.33	31607111	BAG6	A	5.53E-05	1.59
rs11933083	4q13.2	68114997	LOC101927237	G	5.64E-05	1.41
rs492899	6p21.33	31933518	SKIV2L	T	5.64E-05	1.44
rs241455	6p21.32	32796019	TAP2	C	5.64E-05	1.24
rs9287104	1q32.1	199631525	NR5A2	G	5.66E-05	1.45
rs61748840	21q22.13	38563686	TTC3	G	5.70E-05	1.76
rs9276436	6p21.32	32714083	HLA-DQA2	T	5.98E-05	1.52
rs3130013	6p21.32	33313427	DAXX	A	6.00E-05	1.33
rs4389802	6p21.32	32328237	C6orf10	A	6.01E-05	1.28
rs10796745	9q13	68242821	ANKRD20A3	C	6.06E-05	1.35
rs1130838	6p21.33	31237124	HLA-C	T	6.19E-05	1.21
rs17088339	18q22.3	71476133	FBXO15	T	6.23E-05	1.41
rs150865922	12q13.11	48381394	COL2A1	A	6.36E-05	12.66
rs2239526	6p21.33	31509432	DDX39B	G	6.40E-05	1.23
rs7744593	6p21.32	32704326	HLA-DQA2	A	6.47E-05	1.24
rs241439	6p21.32	32797537	TAP2	T	6.50E-05	1.21
rs86567	6p21.32	32976759	HLA-DOA	G	6.53E-05	1.20
rs62132300	19p13.3	862355	CFD	C	6.58E-05	1.23
rs3134931	6p21.32	32190620	NOTCH4	T	6.68E-05	1.23
rs56203327	8q12.1	60775976	CA8	G	6.71E-05	1.21
rs66485631	6p21.33	31083798	CDSN	CTT	6.78E-05	1.20
rs7774954	6p21.32	32724189	HLA-DQB2	C	6.80E-05	1.52
rs3128955	6p21.32	33021192	HLA-DOA	A	6.83E-05	1.24
rs2524276	6p21.33	31408265	MICA	C	6.87E-05	1.54
rs202032329	17q23.2	60522293	METTL2A	A	6.90E-05	1.53
rs174220	6p22.1	30017756	ZNRD1-AS1	A	6.97E-05	1.52
rs259942	6p22.1	30015167	ZNRD1-AS1	C	7.16E-05	1.30
rs3115537	6p21.33	31497835	MCCD1	G	7.48E-05	1.25
rs3129252	6p21.32	33108848	COL11A2	T	7.49E-05	1.25
rs1047099	20q13.33	61288038	SLCO4A1	G	7.50E-05	1.23
rs3130666	6p21.33	30740160	IER3	G	7.61E-05	1.85
rs7759909	6p21.33	31158689	PSORS1C3	G	7.88E-05	1.37
rs73605945	8p11.22	39468128	ADAM18	T	7.93E-05	19.18
rs3134782	6p21.33	31197633	HLA-C	G	8.02E-05	1.27
rs3094216	6p21.33	31084048	CDSN	G	8.07E-05	1.24
rs74268183	2q14.1	117105789	DPP10	C	8.17E-05	1.43
rs2075798	6p21.33	31846741	SLC44A4	C	8.24E-05	1.50
rs928822	6p22.1	30275246	HCG18	G	8.33E-05	1.20
rs1267481	6p23	14559080	JARID2	C	8.43E-05	1.25

Supplementary Table 4. Results of genome-wide association analysis for ANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs3131628	6p21.33	31502767	DDX39B	C	8.64E-05	1.24
rs117131055	19p13.2	12780204	WDR83	C	8.80E-05	1.76
rs757262	6p22.1	30114955	TRIM40	T	8.85E-05	1.23
rs12722018	6p21.32	33048532	HLA-DPB1	G	8.91E-05	2.01
rs241437	6p21.32	32797684	TAP2	A	8.94E-05	1.21
rs2230103	7q22.1	101921289	CUX1	A	8.97E-05	1.68
rs10206572	2p25.3	3113710	LINC01250	C	9.05E-05	1.32
rs4337378	18q12.1	25393317	CHST9	C	9.07E-05	1.20
rs3097657	6p21.32	33006252	HLA-DOA	T	9.07E-05	2.16
rs12142107	1p36.22	11097867	MASP2	T	9.10E-05	1.78
rs241447	6p21.32	32796751	TAP2	T	9.20E-05	1.24
rs13121311	4q34.1	172204876	GALNTL6	A	9.26E-05	1.24
rs72927046	6q16.1	96656753	FUT9	T	9.33E-05	1.60
rs707926	6p21.33	31748820	VARS	G	9.47E-05	1.30
rs2309753	2q11.2	100775920	AFF3	C	9.53E-05	1.21
rs12003547	9p13.3	35891996	OR13J1	A	9.53E-05	1.23
rs241449	6p21.32	32796653	TAP2	C	9.57E-05	1.24
rs79523068	2p12	77051328	LRRTM4	T	9.57E-05	1.61
rs34785870	9q22.33	101555336	ANKS6	C	9.67E-05	1.36
rs7282216	21q22.3	47471324	COL6A1	A	9.70E-05	1.20
rs4480926	19p13.3	6127253	RFX2	C	9.73E-05	1.21
rs28587839	10q26.13	125849315	CHST15	T	9.78E-05	1.21
rs67605123	13q21.33	71486708	LINC00348	G	9.85E-05	1.23
rs3093978	6p21.33	31498497	DDX39B	C	9.89E-05	1.24
rs77239684	5p15.2	14265029	TRIO	T	9.90E-05	1.39
rs6111080	20p13	1689231	SIRPG	T	9.92E-05	1.30

Legend: Association data are shown for all SNPs achieving Eigenstrat P values < 1.0×10^{-4}.

Affymetrix SNP IDs are provided for SNPs with no available rs ID.

ANCA = anti-neutrophil cyctoplasmic antibody; OR = odds ratio.

Supplementary Table 5. Results of genome-wide association analysis for PR3-ANCA/cANCA-associated vasculitis.

Supplementary Table 5. Results of genome-wide association analysis for PR3-ANCA/cANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs141530233	6p21.32	33048688	HLA-DPB1	-	1.69E-68	6.06
rs1042169	6p21.32	33048686	HLA-DPB1	G	1.94E-68	5.98
rs1071597	6p21.32	33052986	HLA-DPB1	T	3.75E-65	6.14
rs9277554	6p21.32	33055538	HLA-DPB1	C	9.46E-65	6.06
rs9277498	6p21.32	33054141	HLA-DPB1	T	1.13E-64	5.92
rs9277546	6p21.32	33055346	HLA-DPB1	T	1.24E-64	5.92
rs9277410	6p21.32	33051640	HLA-DPB1	G	1.35E-64	5.92
rs2064476	6p21.32	33073322	HLA-DPB1	A	1.47E-64	5.87
rs9277471	6p21.32	33053682	HLA-DPB1	G	1.48E-64	5.91
rs9277424	6p21.32	33051865	HLA-DPB1	A	1.53E-64	5.91
rs9277514	6p21.32	33054235	HLA-DPB1	T	2.21E-64	5.90
rs1042335	6p21.32	33052958	HLA-DPB1	C	9.74E-64	5.86
rs1431403	6p21.32	33047031	HLA-DPB1	T	9.83E-61	5.83
rs2144014	6p21.32	33065813	HLA-DPB1	G	1.81E-57	6.64
rs3128927	6p21.32	33074288	HLA-DPB1	C	2.25E-56	5.44
rs3117223	6p21.32	33060064	HLA-DPB1	G	2.62E-56	6.62
rs2395314	6p21.32	33062673	HLA-DPB1	G	3.32E-56	6.68
rs3128917	6p21.32	33059996	HLA-DPB1	T	3.33E-56	6.61
rs3130190	6p21.32	33061690	HLA-DPB1	T	1.57E-55	6.41
rs3117231	6p21.32	33074908	HLA-DPB1	A	1.30E-54	6.56
rs3128921	6p21.32	33070749	HLA-DPB1	C	3.42E-54	6.37
rs9277464	6p21.32	33053352	HLA-DPB1	C	2.21E-52	5.39
rs9277535	6p21.32	33054861	HLA-DPB1	A	2.55E-52	5.38
rs9277489	6p21.32	33053942	HLA-DPB1	T	5.99E-52	5.26
rs9277341	6p21.32	33039625	HLA-DPA1	T	3.91E-50	3.44
rs3135024	6p21.32	33047466	HLA-DPB1	T	7.08E-50	5.18
rs2179920	6p21.32	33058874	HLA-DPB1	C	2.29E-47	6.42
rs2064474	6p21.32	33073463	HLA-DPB1	G	3.24E-47	5.89
rs3117230	6p21.32	33075635	HLA-DPB1	A	8.39E-47	5.98
rs2064478	6p21.32	33072266	HLA-DPB1	C	1.03E-46	5.97
rs1042153	6p21.32	33048663	HLA-DPB1	G	2.34E-46	6.59
rs910320	6p21.32	33075443	HLA-DPB1	C	7.28E-45	5.83
rs9277567	6p21.32	33057013	HLA-DPB1	A	3.89E-44	6.10
rs1126513	6p21.32	33048467	HLA-DPB1	G	4.03E-44	4.81
rs1042151	6p21.32	33048661	HLA-DPB1	A	2.10E-40	7.44
rs2281389	6p21.32	33059796	HLA-DPB1	A	2.59E-36	5.90
rs2071025	6p21.32	33143756	COL11A2	A	5.95E-36	3.12
rs439205	6p21.32	33173842	HSD17B8	G	8.69E-36	3.12
rs1042434	6p21.32	33036505	HLA-DPA1	G	3.05E-35	4.93
rs2076310	6p21.32	33166034	RXRB	A	3.40E-35	3.04
rs3077	6p21.32	33033022	HLA-DPA1	A	7.99E-35	4.88
Affx-28512827	6p21.32	33037424	HLA-DPA1	T	1.44E-34	4.84
rs3097671	6p21.32	33047612	HLA-DPB1	G	1.56E-34	5.79
rs10214910	6p21.32	33037675	HLA-DPA1	C	1.87E-34	4.84
Affx-28512796	6p21.32	33036853	HLA-DPA1	A	2.50E-34	4.77
rs2308911	6p21.32	33037580	HLA-DPA1	T	2.70E-34	4.82
rs17214533	6p21.32	33032272	HLA-DOA	C	3.18E-34	4.86
rs1431399	6p21.32	33041034	HLA-DPA1	A	4.03E-34	4.63
rs9277935	6p21.32	33160425	COL11A2	G	5.76E-32	3.15
rs213209	6p21.32	33176958	RING1	C	6.26E-32	2.50
rs421446	6p21.32	33174783	HSD17B8	A	1.36E-31	2.43
rs1126769	6p21.32	33036435	HLA-DPA1	T	2.03E-31	4.25

Supplementary Table 5. Results of genome-wide association analysis for PR3-ANCA/cANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs1042190	6p21.32	33036999	HLA-DPA1	T	7.05E-30	4.51
rs2858458	6p21.32	33003065	HLA-DOA	T	1.20E-28	2.40
rs3117016	6p21.32	33095516	HLA-DPB2	G	2.97E-28	1.98
rs1126543	6p21.32	33037419	HLA-DPA1	G	6.97E-28	3.44
rs3130161	6p21.32	33125858	COL11A2	A	3.94E-26	5.07
rs987870	6p21.32	33042880	HLA-DPA1	A	4.40E-26	4.22
rs2071352	6p21.32	33044188	HLA-DPB1	T	5.40E-26	5.05
rs439121	6p21.32	33192867	RING1	A	1.19E-24	2.19
rs3129270	6p21.32	33097423	COL11A2	C	5.23E-23	4.60
rs986521	6p21.32	33136145	COL11A2	G	6.32E-23	1.77
rs2855459	6p21.32	33154656	COL11A2	G	4.07E-22	3.26
rs213212	6p21.32	33185918	RING1	C	8.67E-22	1.75
rs213213	6p21.32	33183730	RING1	T	1.14E-21	1.71
rs9277946	6p21.32	33194717	RING1	C	1.91E-21	3.12
rs2855442	6p21.32	33137403	COL11A2	C	2.38E-21	1.71
rs213194	6p21.32	33195604	RING1	A	3.44E-21	1.72
rs2855425	6p21.32	33144373	COL11A2	G	3.81E-21	1.71
rs6531	6p21.32	33163451	RXRB	G	7.84E-21	1.71
rs3116994	6p21.32	33098797	COL11A2	G	3.07E-20	1.67
rs2744512	6p21.32	33141920	COL11A2	G	4.16E-20	1.71
rs3116999	6p21.32	33097166	COL11A2	G	7.31E-20	2.42
rs3129207	6p21.32	33125312	COL11A2	G	5.67E-19	1.64
rs1883414	6p21.32	33086448	HLA-DPB2	G	7.80E-19	1.79
rs3129294	6p21.32	33084671	HLA-DPB2	A	5.31E-18	1.69
Affx-52341735	6p21.32	33138955	COL11A2	G	6.65E-18	1.63
rs3117008	6p21.32	33096274	HLA-DPB2	G	7.02E-18	1.61
rs7772134	6p21.32	33049726	HLA-DPB1	G	3.53E-17	4.07
rs2294479	6p21.32	33098389	COL11A2	G	6.15E-17	1.71
rs2855437	6p21.32	33138955	COL11A2	G	4.69E-15	1.55
rs3097669	6p21.32	33023792	HLA-DOA	A	5.11E-15	1.77
rs3129274	6p21.32	33094869	HLA-DPB2	C	2.31E-14	1.54
rs3129267	6p21.32	33098896	COL11A2	C	2.80E-14	1.53
rs2855448	6p21.32	33136575	COL11A2	C	2.39E-12	1.47
rs35242582	6p21.32	32600057	HLA-DQA1	A	2.43E-12	1.63
rs2254287	6p21.32	33143948	COL11A2	C	3.27E-12	1.50
rs726599	6p21.32	33121678	COL11A2	C	9.60E-12	1.46
rs429916	6p21.32	32978587	HLA-DOA	C	2.01E-11	2.88
rs2257126	6p21.32	33131734	COL11A2	A	2.32E-11	1.45
rs763469	6p21.32	33004387	HLA-DOA	A	3.10E-11	1.57
Affx-28513472	6p21.32	33053577	HLA-DPB1	G	5.68E-11	6.98
rs3130604	6p21.32	32985052	HLA-DOA	G	6.20E-11	1.56
rs62132293	19p13.3	838178	PRTN3	G	7.92E-10	1.41
rs3129304	6p21.32	32973743	HLA-DOA	C	9.10E-10	1.51
rs28584179	6p21.32	32626119	HLA-DQA1	C	1.00E-09	2.01
rs116518618	6p21.32	32594998	HLA-DRB1	C	1.26E-09	2.00
rs3130176	6p21.32	33017457	HLA-DOA	A	1.88E-09	1.38
rs1810472	6p21.32	33083121	HLA-DPB2	T	2.46E-09	1.46
rs211449	6p21.32	33333916	DAXX	G	3.20E-09	1.42
rs213210	6p21.32	33175824	RING1	A	3.91E-09	2.49
rs9468925	6p21.33	31258837	HLA-C	G	4.41E-09	1.41
rs423639	6p21.32	32987774	HLA-DOA	C	6.46E-09	2.24
rs3129264	6p21.32	33101602	COL11A2	A	6.51E-09	1.51
rs28929474	14q32.13	94844947	SERPINA1	T	6.82E-09	2.38
rs206762	6p21.32	32970450	BRD2	G	7.04E-09	1.37

Supplementary Table 5. Results of genome-wide association analysis for PR3-ANCA/cANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs2068204	6p21.32	33058718	HLA-DPB1	G	9.13E-09	7.14
rs9368758	6p21.32	33138021	COL11A2	G	9.20E-09	2.42
rs1882	6p21.33	31382911	MICA	A	9.78E-09	1.38
rs3097648	6p21.32	32990970	HLA-DOA	A	1.17E-08	1.78
rs3129234	6p21.32	33111347	COL11A2	C	1.29E-08	1.50
rs756440	6p21.32	33122331	COL11A2	A	1.33E-08	1.49
rs3117034	6p21.32	33087358	HLA-DPB2	T	1.45E-08	1.38
rs3094672	6p21.33	30993377	MUC22	T	1.72E-08	1.40
rs3129258	6p21.32	33105469	COL11A2	G	1.80E-08	1.49
rs3130257	6p21.32	33256471	WDR46	T	2.03E-08	1.55
rs605203	6p21.33	31847012	EHMT2	C	2.22E-08	1.37
rs3129252	6p21.32	33108848	COL11A2	T	2.32E-08	1.48
rs486416	6p21.33	31856070	EHMT2	G	3.20E-08	1.36
rs9380343	6p21.32	33079166	HLA-DPB1	C	3.44E-08	4.89
rs3873386	6p21.33	31273745	HLA-C	T	3.69E-08	1.38
rs2281390	6p21.32	33059669	HLA-DPB1	T	3.71E-08	1.43
rs2596530	6p21.33	31387373	MICA	G	4.73E-08	1.36
rs2524040	6p21.33	31257625	HLA-C	T	4.86E-08	1.36
rs2256183	6p21.33	31380529	MICA	A	5.68E-08	1.36
rs659445	6p21.33	31864304	EHMT2	G	5.85E-08	1.36
rs535586	6p21.33	31860337	EHMT2	T	9.60E-08	1.35
rs9296068	6p21.32	32988695	HLA-DOA	T	1.06E-07	1.38
rs440454	6p21.33	31927342	SKIV2L	A	1.08E-07	1.36
Affx-28512853	6p21.32	33037640	HLA-DPA1	C	1.43E-07	5.57
rs3132454	6p21.33	31489644	MCCD1	A	1.60E-07	1.37
rs419788	6p21.33	31928799	SKIV2L	T	1.68E-07	1.35
rs6936620	6p21.32	32984451	HLA-DOA	A	1.69E-07	1.33
rs176248	6p21.32	32965942	BRD2	G	1.81E-07	1.42
rs3905495	6p21.33	31265539	HLA-C	G	1.86E-07	1.37
rs805284	6p21.33	31682029	LY6G6D	A	2.23E-07	1.79
rs448733	6p21.32	33003687	HLA-DOA	C	2.32E-07	2.52
rs1062481	6p21.32	33037611	HLA-DPA1	C	2.41E-07	5.41
rs213226	6p21.32	33209310	RING1	A	2.79E-07	1.32
rs437179	6p21.33	31929014	SKIV2L	A	3.03E-07	1.35
rs2247056	6p21.33	31265490	HLA-C	T	3.16E-07	1.37
rs630379	6p21.33	31922254	NELFE	A	3.25E-07	1.35
rs6457374	6p21.33	31272261	HLA-C	C	4.49E-07	1.35
rs211450	6p21.32	33333446	DAXX	C	5.06E-07	1.34
rs6899309	6p21.32	32915823	HLA-DMB	T	6.17E-07	2.27
rs2853931	6p21.33	31255007	HLA-C	C	6.48E-07	1.31
rs3129299	6p21.32	32900787	HLA-DMB	C	6.57E-07	1.52
rs67523850	6p21.32	33054014	HLA-DPB1	A	6.90E-07	2.71
rs6937034	6p21.32	33079766	HLA-DPB1	A	7.22E-07	5.05
rs75549913	6p21.33	31390139	MICA	-	7.22E-07	1.33
rs389883	6p21.33	31947460	STK19	G	7.42E-07	1.33
rs3130609	6p21.32	32989521	HLA-DOA	C	7.81E-07	3.67
rs423209	6p21.32	32983474	HLA-DOA	G	8.00E-07	3.21
rs9263873	6p21.33	31170713	HCG27	T	8.94E-07	1.32
rs3873444	6p21.32	32682724	HLA-DQA2	C	1.04E-06	1.67
rs7264431	20p13	1716975	SIRPG	C	1.09E-06	1.52
rs9277348	6p21.32	33048538	HLA-DPB1	T	1.13E-06	7.56
rs1049526	6p21.32	32948804	BRD2	C	1.18E-06	1.51
rs429608	6p21.33	31930462	SKIV2L	G	1.21E-06	1.51
rs1042149	6p21.33	31082960	CDSN	A	1.22E-06	1.31

Supplementary Table 5. Results of genome-wide association analysis for PR3-ANCA/cANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs1050391	6p21.32	32917857	HLA-DMA	A	1.35E-06	1.51
rs9366814	6p21.32	33080799	HLA-DPB2	T	1.37E-06	4.28
rs6928399	6p21.33	31195218	HLA-C	C	1.41E-06	1.34
rs9348906	6p21.32	33080360	HLA-DPB2	T	1.43E-06	4.87
rs3094212	6p21.33	31085770	CDSN	G	1.47E-06	1.31
rs3130320	6p21.32	32223258	NOTCH4	T	1.49E-06	1.31
rs4713447	6p21.33	31162963	PSORS1C3	A	1.51E-06	1.31
rs3135029	6p21.32	32921774	BRD2	T	1.60E-06	1.50
rs3132554	6p21.33	31084163	CDSN	A	1.63E-06	1.31
rs213220	6p21.32	33202640	RING1	C	1.71E-06	1.30
rs9277193	6p21.32	33023880	HLA-DOA	T	1.89E-06	1.30
rs4713422	6p21.33	30999902	MUC22	G	1.96E-06	1.32
rs3129287	6p21.32	33089104	HLA-DPB2	G	1.96E-06	1.37
rs2853933	6p21.33	31254088	HLA-C	T	2.02E-06	1.30
rs3134926	6p21.32	32200147	NOTCH4	C	2.27E-06	1.35
rs9380345	6p21.32	33080359	HLA-DPB2	C	2.28E-06	4.42
rs10947121	6p21.33	30999997	MUC22	T	2.62E-06	1.32
Affx-28441669	6p21.33	31084075	CDSN	G	2.65E-06	1.30
rs3129305	6p21.32	32959180	BRD2	G	2.74E-06	1.49
rs2524163	6p21.33	31259579	HLA-C	C	2.88E-06	1.29
rs3130597	6p21.32	32941191	BRD2	T	3.12E-06	1.49
rs3129297	6p21.32	32927969	BRD2	A	3.16E-06	1.49
rs3097644	6p21.32	32945530	BRD2	G	3.49E-06	1.50
rs2070600	6p21.32	32151443	AGER	T	3.53E-06	1.67
rs2524089	6p21.33	31266522	HLA-C	G	3.55E-06	1.29
rs2844514	6p21.33	31380340	MICA	C	3.57E-06	1.30
rs2243868	6p21.33	31261276	HLA-C	A	3.75E-06	1.29
rs9271897	6p21.32	32595954	HLA-DRB1	G	3.95E-06	1.28
rs12664430	6p21.32	33272677	TAPBP	T	3.95E-06	1.54
rs6936204	6p21.32	32217092	NOTCH4	T	4.07E-06	1.30
rs2844513	6p21.33	31388214	MICA	G	4.11E-06	1.30
rs66485631	6p21.33	31083798	CDSN	CTT	4.26E-06	1.29
rs34892006	6p22.1	29012712	OR2W1	C	4.66E-06	10.85
rs9273088	6p21.32	32612488	HLA-DQA1	C	5.15E-06	1.29
rs541862	6p21.33	31916951	CFB	T	6.14E-06	1.66
rs6679677	1p13.2	114303808	PTPN22	A	6.16E-06	1.46
rs117131055	19p13.2	12780204	WDR83	C	6.20E-06	2.04
rs1130838	6p21.33	31237124	HLA-C	T	6.32E-06	1.29
rs12722018	6p21.32	33048532	HLA-DPB1	G	6.65E-06	3.40
rs3132680	6p22.1	30073195	TRIM31	A	6.66E-06	1.30
rs2853939	6p21.33	31250642	HLA-C	T	6.86E-06	1.27
rs2230693	21q22.3	46913477	COL18A1	C	7.90E-06	4.83
rs16935391	10q21.1	54680402	MBL2	A	8.51E-06	1.48
rs2116263	6p21.32	33025493	HLA-DOA	G	8.56E-06	7.66
rs213199	6p21.32	33235755	VPS52	G	8.59E-06	1.29
rs206018	6p21.32	32177880	NOTCH4	C	9.28E-06	1.42
rs3128955	6p21.32	33021192	HLA-DOA	A	9.38E-06	1.32
rs438999	6p21.33	31928306	SKIV2L	A	9.50E-06	1.63
rs3115572	6p21.32	32220484	NOTCH4	C	9.61E-06	1.28
rs1130368	6p21.32	32632818	HLA-DQB1	T	9.78E-06	1.42
rs3134931	6p21.32	32190620	NOTCH4	T	1.04E-05	1.31
rs3132499	6p21.33	31207920	HLA-C	C	1.05E-05	1.37
rs2524074	6p21.33	31244021	HLA-C	G	1.05E-05	1.29
rs3135195	6p21.32	32999330	HLA-DOA	T	1.14E-05	3.19

Supplementary Table 5. Results of genome-wide association analysis for PR3-ANCA/cANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs146599962	18q21.31	55398906	ATP8B1	G	1.17E-05	16.91
rs3130171	6p21.32	32998729	HLA-DOA	T	1.19E-05	1.29
rs1634717	6p21.33	30972589	MUC22	G	1.23E-05	1.27
rs213202	6p21.32	33232055	VPS52	G	1.29E-05	1.29
rs213204	6p21.32	33241076	RPS18	C	1.32E-05	1.29
rs805287	6p21.33	31678730	LY6G6F	A	1.41E-05	1.31
rs12003547	9p13.3	35891996	OR13J1	A	1.42E-05	1.31
rs34877619	5q15	97466217	RGMB	G	1.65E-05	1.31
rs2394734	6p22.1	30046246	TRIM31	G	1.67E-05	1.39
rs3129883	6p21.32	32410137	HLA-DRA	T	1.67E-05	1.29
rs7720359	5q15	97440378	RGMB	G	1.72E-05	1.31
rs9262549	6p21.33	30997692	MUC22	G	1.82E-05	1.28
rs9271824	6p21.32	32594916	HLA-DRB1	A	1.83E-05	1.26
rs2272592	6p21.33	31698352	CLIC1	T	1.90E-05	1.32
rs382259	6p21.32	32209027	NOTCH4	T	1.95E-05	1.32
rs12722027	6p21.32	33048641	HLA-DPB1	A	2.03E-05	3.08
rs9273215	6p21.32	32613712	HLA-DQA1	A	2.06E-05	1.27
rs389512	6p21.33	31947594	STK19	G	2.13E-05	1.48
rs3130013	6p21.32	33313427	DAXX	A	2.15E-05	1.42
rs2233385	2q37.1	233897503	NEU2	A	2.17E-05	3.17
rs3134604	6p21.32	32122386	PPT2	C	2.23E-05	1.36
rs9274552	6p21.32	32634838	HLA-DQB1	C	2.24E-05	1.27
rs4807840	19p13.3	6156483	ACSBG2	C	2.27E-05	1.29
rs4412248	6p21.32	33072415	HLA-DPB1	C	2.33E-05	11.91
rs7382297	6p21.33	31247067	HLA-C	T	2.38E-05	1.35
rs1143260	6p21.32	32359227	HCG23	A	2.40E-05	1.49
rs2523644	6p21.33	31342484	MICA	C	2.40E-05	1.33
rs78374723	12q13.13	53096894	KRT77	T	2.44E-05	15.79
rs117566511	19p13.2	12805424	FBXW9	T	2.44E-05	1.94
rs411337	6p21.33	32077380	ATF6B	C	2.46E-05	1.67
rs3134782	6p21.33	31197633	HLA-C	G	2.53E-05	1.34
rs3130952	6p21.33	31177915	HLA-C	G	2.70E-05	1.35
rs3094609	6p21.33	31165566	HCG27	T	2.72E-05	1.34
rs4248153	6p21.33	31002527	MUC22	A	2.80E-05	1.27
rs9267649	6p21.33	31824828	NEU1	A	2.81E-05	1.32
rs3130933	6p21.33	31132085	TCF19	T	2.83E-05	1.36
rs3117294	6p22.1	29653329	HLA-F	T	2.84E-05	1.28
rs3873379	6p21.33	31262169	HLA-C	T	2.85E-05	1.30
rs7041467	9q21.32	85865570	FRMD3	G	2.85E-05	5.93
rs2476601	1p13.2	114377568	PTPN22 (R620W)	A	2.92E-05	1.42
rs34182778	6p21.33	31084943	CDSN	-	2.95E-05	1.32
rs9274407	6p21.32	32632832	HLA-DQB1	A	2.99E-05	1.33
rs2517424	6p21.33	30949996	MUC21	T	3.06E-05	1.43
rs28367630	6p21.33	31267934	HLA-C	A	3.17E-05	1.29
rs453590	6p21.32	33403422	SYNGAP1	C	3.22E-05	1.26
rs56291618	7p22.3	164282	FAM20C	A	3.25E-05	2.14
rs2844795	6p22.1	30073847	TRIM31	C	3.27E-05	1.26
rs2857107	6p21.32	32785515	HLA-DOB	C	3.28E-05	1.49
rs76416341	1p36.32	3679783	CCDC27	C	3.34E-05	23.77
rs1800454	6p21.32	32800412	TAP2	T	3.34E-05	1.35
rs1894411	6p21.32	32792973	TAP2	T	3.38E-05	1.49
rs2246638	6p22.1	29949497	HCG9	G	3.47E-05	1.36
rs1063355	6p21.32	32627714	HLA-DQB1	G	3.47E-05	1.26
rs2240070	6p22.1	30071110	TRIM31	T	3.53E-05	1.27

Supplementary Table 5. Results of genome-wide association analysis for PR3-ANCA/cANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs17843619	6p21.32	32620775	HLA-DQA1	A	3.74E-05	1.26
rs3097657	6p21.32	33006252	HLA-DOA	T	3.82E-05	3.19
rs1780735	1p31.1	79209403	IFI44	G	3.86E-05	1.35
rs17612576	6p21.32	32615458	HLA-DQA1	A	3.95E-05	1.26
rs3129888	6p21.32	32411726	HLA-DRA	G	4.22E-05	1.30
rs204888	6p21.33	32089142	ATF6B	G	4.59E-05	1.64
rs1051790	6p21.33	31378956	MICA	C	4.67E-05	1.40
rs2596501	6p21.33	31321211	HLA-C	C	4.69E-05	1.25
rs2808096	10p11.22	32128611	ARHGAP12	A	4.70E-05	1.33
Affx-28465058	6p21.33	31936679	SKIV2L	C	4.74E-05	1.45
rs210120	6p21.31	33574413	ITPR3	A	4.75E-05	1.25
rs2596548	6p21.33	31330546	MICA	T	4.87E-05	1.32
rs723872	20p13	1707027	SIRPG	C	4.88E-05	1.40
rs34196598	7q22.1	100636147	MUC12	C	4.96E-05	1.45
rs10190766	2p13.2	72366818	CYP26B1	T	4.97E-05	1.78
rs241438	6p21.32	32797620	TAP2	C	4.99E-05	1.27
rs213203	6p21.32	33238404	VPS52	A	5.03E-05	1.25
Affx-28507878	6p21.32	32823948	PSMB9	G	5.11E-05	2.92
rs139817454	12q13.3	57000083	BAZ2A	T	5.18E-05	15.90
rs3129301	6p21.32	32990060	HLA-DOA	G	5.19E-05	3.13
rs1241983	18p11.31	6875693	ARHGAP28	A	5.21E-05	1.25
rs3130014	6p21.32	33312308	DAXX	A	5.22E-05	1.28
rs3104402	6p21.32	32681676	HLA-DQB1	T	5.25E-05	1.47
rs3093983	6p21.33	31496925	MCCD1	G	5.38E-05	1.30
rs12184990	14q32.13	95253783	DICER1	T	5.40E-05	1.38
rs2228396	6p21.32	32797809	TAP2	T	5.58E-05	1.43
rs29234	6p22.1	29624112	GABBR1	A	5.66E-05	1.84
rs2395296	6p21.32	32911814	HLA-DMB	A	5.77E-05	1.26
rs423808	6p22.1	29949123	HCG9	G	5.81E-05	1.44
rs444921	6p21.33	31932177	SKIV2L	C	5.85E-05	1.45
rs3130118	6p22.1	30365740	HLA-E	C	5.95E-05	1.26
rs61730696	17q21.2	40831684	CCR10	A	5.95E-05	8.64
rs17271707	2q34	213510374	ERBB4	A	5.96E-05	1.29
rs3131283	6p21.32	32119898	PRRT1	T	6.04E-05	1.34
rs387608	6p21.33	31941557	STK19	G	6.20E-05	1.44
rs2693726	7q32.2	129417679	UBE2H	T	6.25E-05	1.25
rs10213293	4p15.2	23123472	GBA3	G	6.25E-05	1.26
rs1265048	6p21.33	31081409	PSORS1C1	T	6.35E-05	1.27
rs1800684	6p21.32	32151994	AGER	A	6.44E-05	1.33
rs4480926	19p13.3	6127253	RFX2	C	6.53E-05	1.26
rs887466	6p21.33	31143511	PSORS1C3	G	6.80E-05	1.26
rs7738815	6p21.32	33020387	HLA-DOA	G	6.80E-05	4.00
rs9261895	6p22.1	30389323	HLA-E	T	6.98E-05	1.33
rs9264643	6p21.33	31238492	HLA-C	C	7.07E-05	1.25
rs1265155	6p21.33	31143694	PSORS1C3	G	7.23E-05	1.26
rs4668338	2q31.1	171733225	GAD1	C	7.23E-05	7.56
rs17260787	5p15.2	13644978	DNAH5	T	7.28E-05	1.54
rs10859638	12q22	94433035	CRADD	G	7.41E-05	1.31
Affx-28452229	6p21.33	31322303	HLA-B	C	7.51E-05	1.26
rs11933083	4q13.2	68114997	LOC101927237	G	7.55E-05	1.47
rs13043804	20q13.31	55375403	BMP7	C	7.65E-05	1.27
rs199556640	6p21.32	32609299	HLA-DQA1	-	7.71E-05	1.24
rs4713668	6p21.31	33690796	IP6K3	T	7.98E-05	1.24
rs700726	8q12.1	60931328	CA8	T	8.00E-05	1.25

Supplementary Table 5. Results of genome-wide association analysis for PR3-ANCA/cANCA-associated vasculitis.

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs2384114	10q21.1	54831767	MBL2	C	8.06E-05	1.29
rs61745073	14q12	24798433	ADCY4	A	8.08E-05	7.29
rs2227956	6p21.33	31778272	HSPA1L	G	8.11E-05	1.29
rs2535260	6p22.1	29628883	MOG	C	8.51E-05	1.32
rs41267649	6p21.32	33384473	CUTA	T	8.90E-05	1.86
rs7573071	2q36.3	228043161	COL4A3	C	8.99E-05	1.42
rs29272	6p22.1	29618366	GABBR1	G	9.04E-05	1.81
rs34229432	20q13.31	55700904	BMP7	G	9.06E-05	1.49
rs10121214	9p24.3	1919789	SMARCA2	C	9.39E-05	1.25
rs1265109	6p21.33	31119589	CCHCR1	G	9.42E-05	1.29
rs3132946	6p21.32	32190028	NOTCH4	A	9.50E-05	1.33
rs3131631	6p21.33	31484683	MCCD1	G	9.61E-05	1.27
rs3132469	6p21.33	31456567	MICB	A	9.73E-05	1.33
rs62640032	17p13.3	902802	TIMM22	A	9.79E-05	1.65
rs7381988	6p21.33	31246703	HLA-C	G	9.80E-05	1.31
rs2523554	6p21.33	31331829	MICA	C	9.89E-05	1.24
rs73605945	8p11.22	39468128	ADAM18	T	9.92E-05	19.85
rs211474	6p21.32	33320613	DAXX	G	9.94E-05	1.26

Legend: Association data are shown for all SNPs achieving Eigenstrat P values < 1.0×10^{-4}.
Affymetrix SNP IDs are provided for SNPs with no available rs ID.
ANCA = anti-neutrophil cytoplasmic antibody; PR3 = proteinase 3; cANCA = cytoplasmic ANCA; OR = odds ratio

Supplementary Table 6. Results of genome-wide association analysis for MPO-ANCA/pANCA-associated vasculitis

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs3998159	6p21.32	32682019	HLA-DQA2	C	3.47E-19	2.61
rs7454108	6p21.32	32681483	HLA-DQA2	C	3.90E-19	2.61
rs1049072	6p21.32	32634355	HLA-DQB1	A	1.63E-18	2.27
rs9275184	6p21.32	32654714	HLA-DQA2	C	2.29E-18	2.55
rs1130399	6p21.32	32629755	HLA-DQB1	A	1.24E-17	2.22
rs660895	6p21.32	32577380	HLA-DRB1	G	1.94E-17	2.18
rs2395175	6p21.32	32405026	HLA-DRA	A	2.17E-14	2.09
rs115360810	6p21.32	32796310	TAP2	G	2.56E-14	3.55
rs6910071	6p21.32	32282854	C6orf10	G	9.12E-12	1.90
rs2395163	6p21.32	32387809	HLA-DRA	C	1.09E-10	1.80
rs3793127	6p21.32	32371915	BTNL2	T	1.40E-10	1.79
rs34252386	6p21.32	32546912	HLA-DRB1	G	3.29E-10	1.71
rs35445101	6p21.32	32546879	HLA-DRB1	G	4.97E-10	1.70
rs9268923	6p21.32	32432835	HLA-DRB5	T	1.72E-09	1.67
rs2395185	6p21.32	32433167	HLA-DRB5	T	4.19E-09	1.66
rs28366302	6p21.32	32560934	HLA-DRB1	C	5.92E-09	1.65
rs9271897	6p21.32	32595954	HLA-DRB1	G	8.81E-09	1.63
rs9271824	6p21.32	32594916	HLA-DRB1	A	1.75E-08	1.62
rs34892006	6p22.1	29012712	OR2W1	C	2.14E-08	21.18
rs9272105	6p21.32	32599999	HLA-DRB1	G	2.81E-08	1.60
rs9275440	6p21.32	32671596	HLA-DQA2	T	5.23E-08	1.64
rs9267954	6p21.32	32213052	NOTCH4	T	5.92E-08	1.64
rs3916765	6p21.32	32685550	HLA-DQA2	A	3.37E-07	1.76
rs4642516	6p21.32	32657543	HLA-DQA2	T	4.00E-07	1.54
rs6679677	1p13.2	114303808	PTPN22	A	4.63E-07	1.81
rs373169384	9q34.3	139943388	ENTPD2	T	4.63E-07	3.96
rs5020946	6p21.32	32450089	HLA-DRB5	T	5.39E-07	1.54
rs28366353	6p21.32	32565004	HLA-DRB1	G	6.70E-07	1.51
rs9272116	6p21.32	32600404	HLA-DQA1	T	8.43E-07	1.51
rs7764856	6p21.32	32680640	HLA-DQA2	A	1.38E-06	1.52
rs6928482	6p21.32	32626249	HLA-DQA1	C	2.52E-06	1.49
rs10796745	9q13	68242821	ANKRD20A3	C	2.69E-06	1.78
rs9274697	6p21.32	32637016	HLA-DQB1	G	2.93E-06	1.47
rs2073044	6p21.32	32338986	C6orf10	T	3.67E-06	1.53
rs2476601	1p13.2	114377568	PTPN22 (R620W)	A	3.76E-06	1.73
rs9273088	6p21.32	32612488	HLA-DQA1	C	3.94E-06	1.50
rs35242582	6p21.32	32600057	HLA-DQA1	A	4.15E-06	1.65
rs3134996	6p21.32	32636866	HLA-DQB1	T	4.30E-06	1.52
rs2857605	6p21.33	31524851	NFKBIL1	C	4.71E-06	1.54
rs5026743	6p21.32	32439964	HLA-DRB5	T	4.71E-06	1.49
rs9268877	6p21.32	32431147	HLA-DRB5	G	4.91E-06	1.48
rs1129808	6p21.32	32609312	HLA-DQA1	C	5.08E-06	1.49
rs9273215	6p21.32	32613712	HLA-DQA1	A	5.11E-06	1.49
rs199556640	6p21.32	32609299	HLA-DQA1	-	5.28E-06	1.49
rs3134926	6p21.32	32200147	NOTCH4	C	5.32E-06	1.58
rs2269475	6p21.33	31583931	AIF1	T	6.20E-06	1.64
rs17612576	6p21.32	32615458	HLA-DQA1	A	6.91E-06	1.48
rs67529500	6p21.32	32504757	HLA-DRB5	G	7.02E-06	1.49
rs3817966	6p21.32	32367847	BTNL2	C	7.02E-06	1.47
rs2075800	6p21.33	31777946	HSPA1L	T	7.15E-06	1.47
rs1063355	6p21.32	32627714	HLA-DQB1	G	7.28E-06	1.48
rs73727981	6p21.32	32511791	HLA-DRB5	A	7.48E-06	1.49

Supplementary Table 6. Results of genome-wide association analysis for MPO-ANCA/pANCA-associated vasculitis

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs11138651	9q21.31	83021572	Intergenic	T	7.89E-06	1.59
rs3096702	6p21.32	32192331	NOTCH4	A	8.15E-06	1.45
rs9274552	6p21.32	32634838	HLA-DQB1	C	8.51E-06	1.48
rs9268839	6p21.32	32428772	HLA-DRB5	G	8.92E-06	1.46
rs77127003	9q22.1	90500189	SPATA31E1	G	9.68E-06	2.15
rs77696001	21q21.2	25412718	LOC101927869	T	9.98E-06	1.79
rs9268480	6p21.32	32363844	BTNL2	T	1.01E-05	1.47
rs143952489	20q13.33	61525253	DIDO1	T	1.01E-05	21.74
rs9272346	6p21.32	32604372	HLA-DQA1	A	1.02E-05	1.46
rs9268428	6p21.32	32344973	C6orf10	T	1.11E-05	1.47
rs2295665	6p21.33	31632686	GPANK1	T	1.12E-05	1.62
rs4800027	18q12.2	36116229	MIR4318	G	1.25E-05	1.94
rs2242657	6p21.33	31602489	PRRC2A	C	1.29E-05	1.61
rs2071295	6p21.33	32038700	TNXB	T	1.29E-05	1.45
rs2077102	6p21.33	31611840	BAG6	A	1.30E-05	1.61
rs1419673	6p22.1	30096717	TRIM40	G	1.33E-05	1.50
rs17843606	6p21.32	32620399	HLA-DQA1	T	1.47E-05	1.46
rs9261485	6p22.1	30108751	TRIM40	A	1.52E-05	1.49
rs9268474	6p21.32	32357165	C6orf10	C	1.57E-05	1.46
rs3749981	6p21.32	32862682	LOC100294145	T	1.57E-05	1.75
rs261946	6p22.1	30271334	HCG18	G	1.57E-05	1.47
rs3763316	6p21.32	32376746	HLA-DRA	T	1.59E-05	1.46
rs76250508	6p21.33	32010272	TNXB	A	1.69E-05	1.45
rs757262	6p22.1	30114955	TRIM40	T	1.72E-05	1.49
rs2242655	6p21.33	31627449	C6orf47	G	1.79E-05	1.60
rs4151657	6p21.33	31917540	CFB	C	1.82E-05	1.44
rs790604	6q15	91105349	MAP3K7	C	1.84E-05	1.93
rs1882	6p21.33	31382911	MICA	A	1.93E-05	1.44
rs10766484	11p15.1	18539930	TSG101	T	1.93E-05	1.50
rs261945	6p22.1	30272417	HCG18	C	1.94E-05	1.44
rs757259	6p22.1	30115542	TRIM40	A	2.06E-05	1.48
rs3807031	6p22.1	30033884	PPP1R11	A	2.08E-05	1.50
rs17843619	6p21.32	32620775	HLA-DQA1	A	2.10E-05	1.45
rs2736428	6p21.33	31843924	SLC44A4	T	2.11E-05	1.44
rs1394363	14q24.3	77596653	CIPC	T	2.13E-05	1.46
rs11849413	14q21.2	45185079	C14orf28	C	2.14E-05	1.97
rs9268645	6p21.32	32408527	HLA-DRA	G	2.31E-05	1.42
rs1419671	6p22.1	30097170	TRIM40	A	2.37E-05	1.48
rs9261468	6p22.1	30104480	TRIM40	G	2.38E-05	1.48
rs6457620	6p21.32	32663999	HLA-DQA2	C	2.47E-05	1.43
rs75059452	5q34	167700090	TENM2	A	2.52E-05	1.63
rs2523685	6p21.33	31426256	MICA	G	2.53E-05	1.61
rs7510817	22q11.22	23281338	IGLL5	C	2.56E-05	1.75
rs7759742	6p21.32	32381736	HLA-DRA	A	2.57E-05	1.43
rs2280800	6p21.33	31646398	LY6G5C	A	2.67E-05	1.60
rs2239689	6p21.33	32030284	TNXB	A	2.69E-05	1.43
rs59726684	8p21.2	24775457	NEFM	C	3.00E-05	2.69
rs60158447	19q13.32	46387792	IRF2BP1	C	3.14E-05	4.24
rs9261535	6p22.1	30127323	TRIM10	A	3.17E-05	1.47
rs77637983	6p21.32	32549452	HLA-DRB1	C	3.23E-05	1.44
rs1557611	6p22.1	30118360	TRIM10	T	3.39E-05	1.47
rs7328468	13q32.1	96135266	CLDN10	A	3.42E-05	1.42
rs1264585	6p22.1	30285650	HCG18	A	3.51E-05	1.46
Affx-37072023	6p21.32	32612430	HLA-DQA1	C	3.66E-05	1.43

Supplementary Table 6. Results of genome-wide association analysis for MPO-ANCA/pANCA-associated vasculitis

SNP	Chromosome	Position	Gene	Risk allele	*P* value	OR
rs2239530	6p22.1	30152115	TRIM26	G	3.66E-05	1.47
rs387608	6p21.33	31941557	STK19	G	3.74E-05	1.93
rs1541267	6p22.1	30103571	TRIM40	G	3.77E-05	1.45
rs149401094	6p21.32	32374906	HLA-DRA	T	3.78E-05	6.82
rs2187818	6p21.32	32395568	HLA-DRA	T	3.81E-05	1.41
Affx-52344168	8p23.1	7681330	DEFB105B	A	3.82E-05	12.51
rs9271709	6p21.32	32593392	HLA-DRB1	G	3.85E-05	1.48
rs2278319	8p21.2	27308961	PTK2B	T	4.01E-05	1.44
rs2523467	6p21.33	31362930	MICA	C	4.09E-05	1.48
rs4711211	6p22.1	30162809	TRIM26	G	4.44E-05	1.46
rs4835669	5q31.2	137473391	NME5	A	4.74E-05	1.41
rs6457617	6p21.32	32663851	HLA-DQA2	T	4.77E-05	1.41
rs2022533	6p21.32	32307260	C6orf10	G	4.86E-05	1.41
rs2844529	6p21.33	31353593	MICA	G	4.94E-05	1.47
Affx-52368679	6p21.32	32632863	HLA-DQB1	CGGT	5.01E-05	1.44
rs2734971	6p22.1	29834449	HLA-G	A	5.19E-05	1.40
Affx-28427568	6p22.1	30313268	TRIM39-RPP21	A	5.40E-05	1.44
rs2523473	6p21.33	31361897	MICA	A	5.48E-05	1.47
rs8090342	18p11.22	9872638	RAB31	G	5.54E-05	1.75
rs56178414	7q32.2	129201085	SMKR1	A	5.63E-05	1.62
rs2071293	6p21.33	32062687	TNXB	A	5.87E-05	1.41
rs148222739	6q16.1	96034467	MANEA	A	5.87E-05	17.55
rs12874536	13q13.3	38332015	TRPC4	T	6.19E-05	1.41
rs928822	6p22.1	30275246	HCG18	G	6.28E-05	1.40
rs56042230	11q24.1	123347461	GRAMD1B	A	6.52E-05	1.63
rs1115928	18q12.1	28208468	DSC3	A	6.67E-05	1.45
rs3020644	6p21.33	31894626	C2	G	6.68E-05	1.40
rs28366130	6p21.33	31363805	MICA	A	6.78E-05	1.47
rs2596542	6p21.33	31366595	MICA	C	6.89E-05	1.46
rs34171662	6p22.1	30285524	HCG18	T	7.09E-05	1.94
rs74356372	1p34.1	44931239	RNF220	G	7.75E-05	1.41
rs6929776	6p21.32	32303511	C6orf10	A	7.79E-05	1.39
rs614549	6p21.33	31840625	SLC44A4	G	7.80E-05	1.39
rs438999	6p21.33	31928306	SKIV2L	A	7.87E-05	2.16
rs3806156	6p21.32	32373698	BTNL2	T	8.02E-05	1.39
Affx-28465058	6p21.33	31936679	SKIV2L	C	8.28E-05	1.86
rs4756952	11p15.1	18589236	UEVLD	C	8.36E-05	1.45
rs61997250	16q21	58001086	CNGB1	T	8.51E-05	2.14
rs9275857	6p21.32	32691308	HLA-DQA2	C	8.54E-05	1.45
rs3819721	6p21.32	32804798	TAP2	A	8.60E-05	1.42
rs7377975	4p16.1	6200070	JAKMIP1	A	8.62E-05	1.45
rs146599962	18q21.31	55398906	ATP8B1	G	8.78E-05	18.49
rs541862	6p21.33	31916951	CFB	T	8.88E-05	2.15
rs115278773	4p16.3	437909	ZNF721	C	9.33E-05	3.26
rs7759909	6p21.33	31158689	PSORS1C3	G	9.37E-05	1.93
rs4729707	7q22.1	101070104	COL26A1	T	9.42E-05	1.39
rs9911245	17q25.3	77327398	RBFOX3	A	9.47E-05	1.39

Legend: Association data are shown for all SNPs achieved Eigenstrat P values < 1.0×10^{-4}.
Affymetrix SNP IDs are provided for SNPs with no available rs ID.
ANCA = anti-neutrophil cytoplasmic antibody; MPO = myeloperoxisase; pANCA = perinuclear ANCA

Supplementary Table 7. Effects of organ involvement and ANCA status on MHC and non-MHC associations with ANCA-associated vasculitis.

				Overall analysis of combined cohort (N = 1986 cases, 4723 controls)		ANCA positive[a] (N = 1739) vs ANCA negative[b] (N = 42)		Organ involvement			
								Lung affected (N = 1200) vs Lung not affected (N = 616)		Kidney affected (N = 1171) vs Kidney not affected (N = 642)	
dbSNP	Chr.	Gene	Risk allele	*P*	OR	*P*	OR	*P*	OR	*P*	OR
rs141530233	6p21.32	*HLA-DPB1*	A del	1.13E-89	2.99	1.47E-03	2.32	5.71E-01	1.06	2.02E-01	1.13
rs1042169	6p21.32	*HLA-DPB1*	G	1.12E-84	2.82	5.55E-05	2.72	2.61E-01	1.11	3.18E-01	1.10
rs9277341	6p21.32	*HLA-DPA1*	T	6.09E-71	2.44	6.09E-03	2.02	1.60E-01	1.14	8.15E-03	1.28
rs35242582	6p21.32	*HLA-DQA1*	A	6.34E-23	1.60	7.39E-01	1.10	2.88E-01	1.10	2.10E-01	1.11
rs1049072	6p21.32	*HLA-DQB1*	A	6.46E-13	1.40	5.02E-01	1.21	9.89E-01	1.00	1.30E-01	1.13
rs6679677	1p13.2	*PTPN22*	A	1.88E-08	1.40	2.34E-01	1.60	8.30E-01	1.02	8.30E-01	1.02
rs62132293	19p13.3	*PRTN3*	G	8.60E-11	1.29	6.32E-01	1.11	7.77E-01	1.02	1.80E-01	1.10
rs28929474	14q32.13	*SERPINA1*	T	3.09E-12	2.18	4.27E-01	1.76	6.81E-01	1.07	1.12E-01	1.33
rs2476601	1p13.2	*PTPN22 (R620W)*	A	1.86E-07	1.36	2.33E-01	1.60	8.02E-01	1.03	9.44E-01	1.01

Legend: ANCA = Anti-neutrophil cytoplasmic autoantibody; PR3 = proteinase 3; MPO = myeloperoxidase; N = numbers of subjects; OR = odds ratio; P = Eigenstrat P value.

ANCA positive[a] = positive for at least one of PR3-ANCA, cANCA, MPO-ANCA, and pANCA.

ANCA negative[b] = negative for all of PR3-ANCA, cANCA, MPO-ANCA, and pANCA.

Supplementary Table 8. Conditional analyses of risk alleles across the HLA locus

Dataset[a]	Gene	SNP[b]	Unconditioned		Conditioned	
			P	OR (95% CI)	*P*	OR (95% CI)
Primary cohort	*HLA-DPB1*	rs141530233	5.93E-56	2.76 (2.44 - 3.13)	9.76E-35	2.31 (2.02 - 2.63)
	HLA-DPA1	rs9277341	1.62E-40	2.21 (1.96 - 2.50)	2.84E-15	1.65 (1.46 - 1.87)
	HLA-DQA1	rs35242582	3.34E-16	1.61 (1.43 - 1.79)	2.74E-12	1.52 (1.35 - 1.71)
PR3-ANCA/cANCA subgroup	*HLA-DPB1*	rs141530233	1.69E-68	6.06 (4.95 - 7.41)	2.73E-50	4.94 (4.00 - 6.09)
	HLA-DPA1	rs9277341	3.91E-50	3.44 (2.92 - 4.05)	1.64E-20	2.24 (1.89 - 2.66)
MPO-ANCA/pANCA subgroup	*HLA-DQA2*	rs3998159	3.47E-19	2.61 (2.12 - 3.22)	2.15E-03	1.65 (1.20 - 2.27)
	HLA-DQB1	rs1049072	1.63E-18	2.27 (1.89 - 2.72)	2.05E-04	1.70 (1.28 - 2.25)

Legend: OR = odds ratio; 95% CI = 95% confidence interval; ANCA = anti-neutrophil cytoplasmic antibody; PR3 = proteinase-3; MPO = myeloperoxidase.

[a] Data are from results of genome-wide association study (GWAS) incorporating total cohort or PR3-ANCA/cANCA or MPO-ANCA/pANCA subgroups

[b] Peak SNP from GWAS

Supplementary Table 9. Evaluation of genetic models for susceptibility for ANCA-associated vasculitis.

SNP	Gene Region	Genetic Model	2* Ln Likelihood	Degrees of freedom	Test statistic (*p* -value)	OR (95% CI)
rs141530233	*HLA-DPB1*	General	5068.76	2		
		Dominiant	5358.73	1	289.97 (5.06×10^{-65})	2.29 (1.71, 3.07)
		Recessive	5068.84	1	0.08 (7.79×10^{-1})	3.59 (3.10, 4.15)
rs9277341	*HLA-DPA1*	General	5318.00	2		
		Dominiant	5488.80	1	170.80 (4.95×10^{-39})	2.44 (1.82, 3.27)
		Recessive	5321.13	1	3.13 (8.00×10^{-2})	2.69 (2.34, 3.08)
rs35242582	*HLA-DQA1*	General	5538.26	2		
		Dominiant	5611.73	1	73.47 (1.02×10^{-17})	1.47 (1.10, 1.98)
		Recessive	5538.26	1	0.001 (9.80×10^{-1})	1.82 (1.60, 2.09)

Legend: Analyses are derived from fitting logistic regression models to data and comparing the log likelihood ratio of a full model with parameters for additive allelic effects and a recessive effect to reduced models that comprised either recessive or dominant models. In all cases, the recessive model was not rejected indicating it is the best fitting model.

Supplementary Table 10. Comparison of peak observed SNPs and peak imputed SNPs at risk loci for (a) ANCA-associated vasculitis, (b) MPO-ANCA/pANCA associated vasculitis.

			Observed			Imputed		
	Locus	Gene	Peak SNP	Location	P value	Peak SNP	Location	P value
a. AAV	1p13.2	*PTPN22*	rs6679677	114303808	2.40E-08	rs6679677	114303808	5.62E-08
	6p21.32	*HLA-DPB1*	rs141530233	33048688	5.93E-56	rs141530233	33048688	1.18E-61
	6p21.32	*HLA-DPA1*	rs9277341	33039625	1.62E-40	rs9277341	33039625	5.83E-46
	6p21.32	*HLA-DQA1*	rs35242582	32600057	3.34E-16	rs114567049	32601719	1.30E-19
	6p21.32	*HLA-DQB1*	rs1049072	32634355	4.23E-10	rs28746835	32633959	4.35E-17
	14q32.13	*SERPINA1*	rs28929474	94844947	8.26E-08	rs28929474	94844947	9.86E-08
	19p13.3	*PRTN3*	rs62132293	838178	5.55E-08	rs138303849	837174	2.84E-10
b. MPO/pANCA	6p21.32	*HLA-DQA2*	rs3998159	32682019	3.47E-19	rs55765078	32647433	1.70E-20
	6p21.32	*HLA-DQB1*	rs1049072	32634355	1.63E-18	rs28746838	32634057	4.10E-20

Legend: ANCA = anti-neutrophil cytoplasmic antibody; AAV = ANCA-associated vasculitis; MPO = myeloperoxidase.

Supplementary Table 11. Most-likely disease causal variants identified by functional annotation.

Locus	Implicated Gene	SNP	Position	r^2 with peak SNP	PICS	Functional consequence	eQTL Gene	eQTL Tissue
1p13.2	PTPN22	rs2476601	114377568	**index**	0.7876	nonsynonymous variant: R620W	-	-
		rs6679677	114303808	0.99	0.2123	upstream gene variant	-	-
6p21.32	HLA-DPB1	rs141530233	33048688	**index**	0.9998	nonsynonymous variant: G85E	HLA-DPB1	-
		rs1042169	33048686	1.00	0.9201	nonsynonymous variant: G84D	HLA-DPB1	LCLs
		rs386699872	33048694	1.00	0.0793	nonsynonymous variant: M87V	HLA-DPB1	LCLs
6p21.32	HLA-DPA1	rs9277341	33039625	**index**	0.9983	intron variant	HLA-DPA1, HLA-DPB1	Monocytes
6p21.32	HLA-DQA1	rs35242582	32600057	**index**	0.8952	upstream gene variant	HLA-DQB1	LCLs
		rs34180045	32600066	0.90	0.0361	upstream gene variant		
6p21.32	HLA-DQB1	rs1049072	32634355	**index**	0.8104	synonymous variant	HLA-DQA1, HLA-DQB1, HLA-DQA2, HLA-DQB1-AS1, HLA-DRB1	PBs
6p21.32	HLA-DQA2	rs3998159	32682019	**index**	0.0997	upstream gene variant	HLA-DQA2	LCLs
		rs7454108	32681483	1.00	0.0997	upstream gene variant	HLA-DQA2	LCLs
		rs3957148	32682137	1.00	0.0997	upstream gene variant	HLA-DQA2	LCLs
		rs3957146	32681530	1.00	0.0997	upstream gene variant	HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DRB6	LCLs
		rs9275583	32680299	0.99	0.0557	upstream gene variant	-	-
		rs9275592	32680620	0.97	0.0431	upstream gene variant	HLA-DQA2	LCLs
		rs4273728	32678491	0.97	0.0431	upstream gene variant	-	-
14q32.13	SERPINA1	rs28929474	94844947	**index**	0.9758	nonsynonymous variant: E366K (Z allele)	-	-
19p13.3	PRTN3	rs62132293	838178	**index**	0.4596	upstream gene variant	-	-
		rs62132296	841100	0.92	0.0816	intron variant	-	-
		rs62132295	840448	0.92	0.0816	upstream gene variant	-	-
		rs3826947	839876	0.91	0.0754	upstream gene variant	-	-
		rs62132294	839298	0.88	0.0470	upstream gene variant	-	-
		rs62132289	837863	0.87	0.0448	upstream gene variant	-	-
		rs2301879	843692	0.85	0.0365	regulatory gene variant	-	-
		rs3729642	839562	0.85	0.0365	upstream gene variant	-	-

Legend: Candidate variants at AAV and MPO-ANCA risk loci with probabilistic identification of causal SNPs (PICS) probability > 0.0275 identified using the online PICS algorithm (http://www.broadinstitute.org/pubs/finemapping/?q=pics). The functional consequence of each variant was predicted using the Ensembl Variant Effect Predictor (VEP) web tool (http://www.ensembl.org/Homo_sapiens/Tools/VEP). Cis eQTLs were identified using the following searchable eQTL browsers and databases: 1) eqtl.uchicago.edu (http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl/), 2) seeQTL (http://www.bios.unc.edu/research/genomic_software/seeQTL) and 3) GTEx Portal (http://www.gtexportal.org/home/eqtls/tissue?tissueName=All). eQTL = expression quantitative trait locus; PBs = peripheral blood cells; SNP = single nucleotide polymorphism; LCL = lymphoblastoid cell lines; MAF = minor allele frequency.

A. Quality Control

Genotype Facility	Mount Sinai Hospital (University of Toronto, Canada)	Affymetrix (Santa Clara, CA, USA)
DNA samples genotyped	1817 subjects (1615 patients with AAV; 202 controls)	3121 subjects (GERA historic controls)
Samples/SNPs passing quality control measures	1716 subjects; 425,782 SNPs	3121 subjects; 412,408 SNPs
Total samples/SNPs post-quality control/measures	4837 subjects (1528 cases; 3309 controls); 333,040 SNPs	
Total samples/SNPs remaining after exclusion of principle component outliers	4629 subjects (1371 cases; 3258 controls); 333,035 SNPs	

B. Study Design

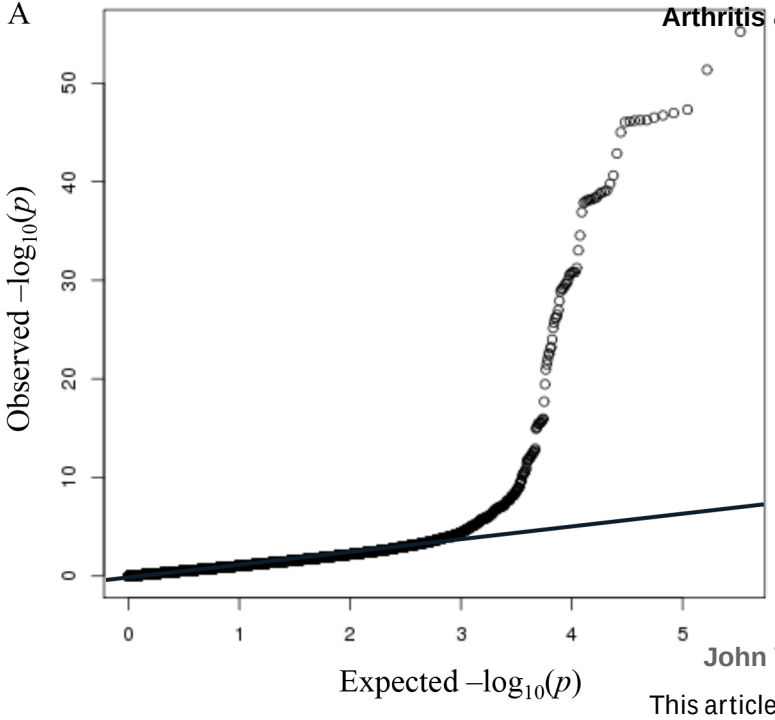
Genome-wide Association Screening
4629 subjects:
1371 patients with AAV — 3258 controls
377 from WGGER — 184 from WGGER
668 from VCRC — 3074 GERA historic controls
326 from UNC Kidney Centre

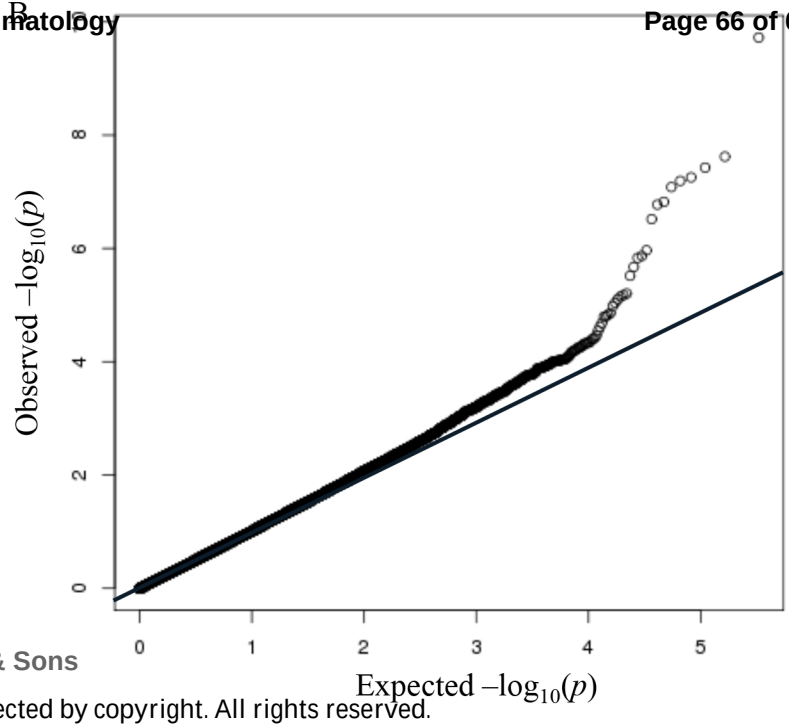
↓

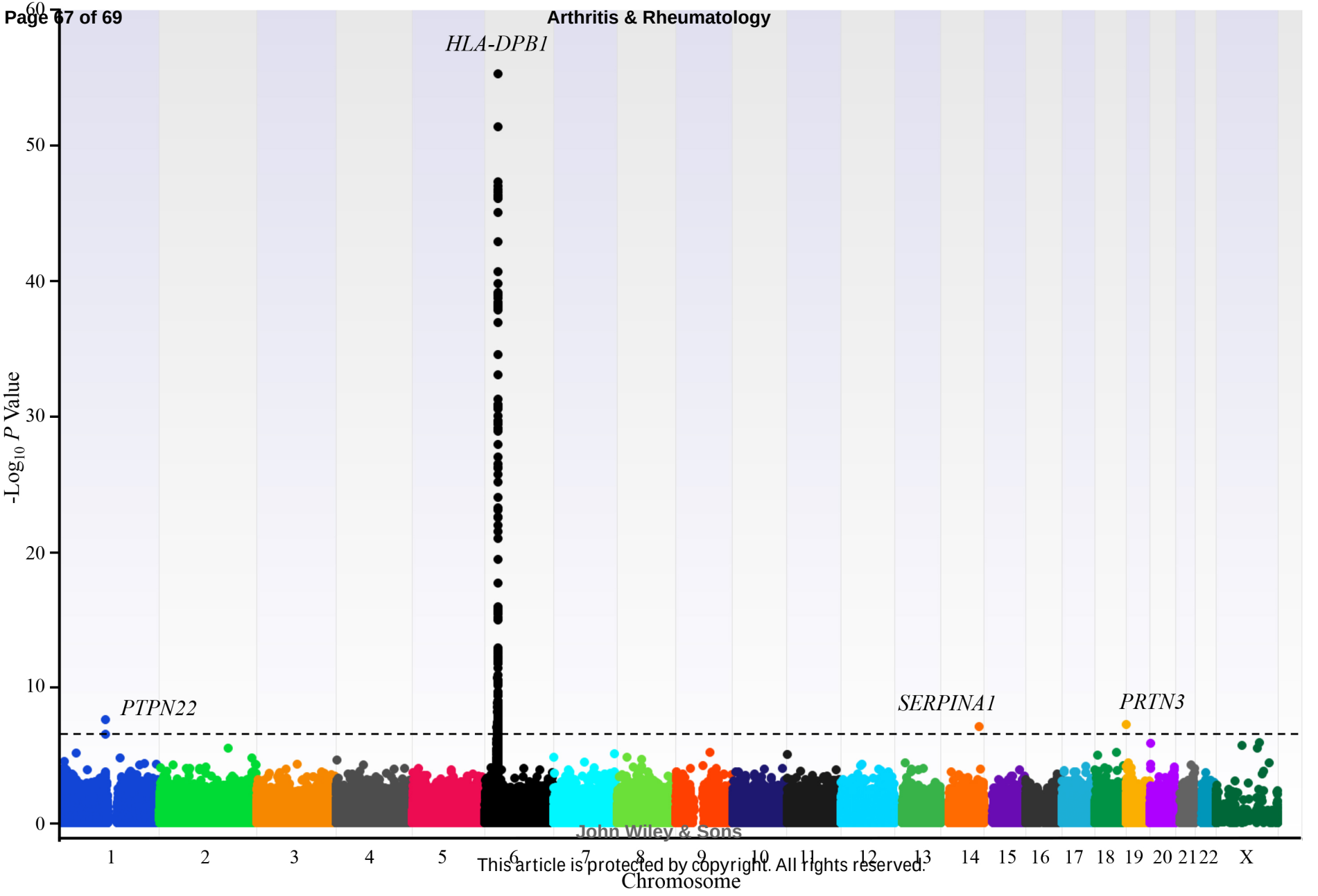
Independent replication
Genotyped 9 top-scoring SNPs in 7 gene regions identified in GWAS.
2080 subjects:
615 patients with AAV — 1465 controls from Toronto
501 from Toronto
114 from VCRC

↓

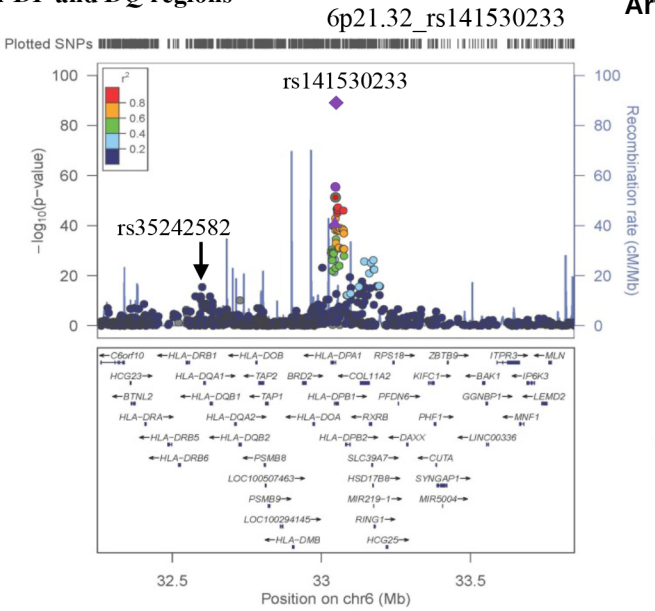
Meta analysis of the combined GWAS and replication data sets
1986 patients with AAV (1371 + 615)
4723 controls (1649 from WGGER and Toronto; 3074 historic controls)



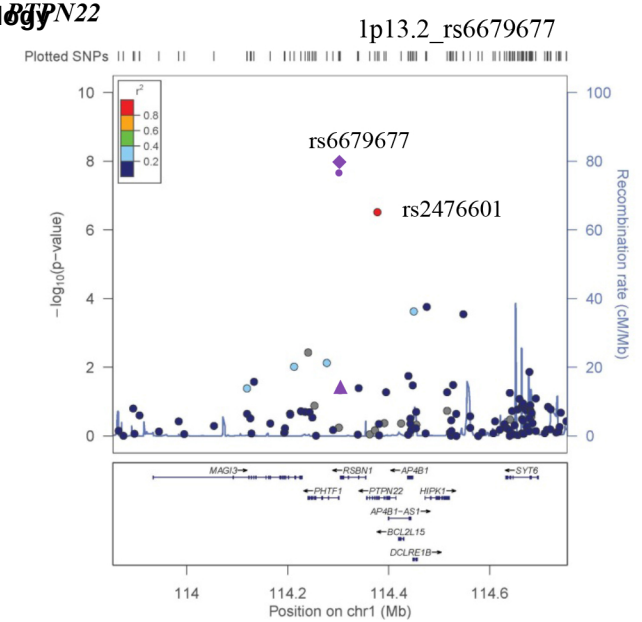




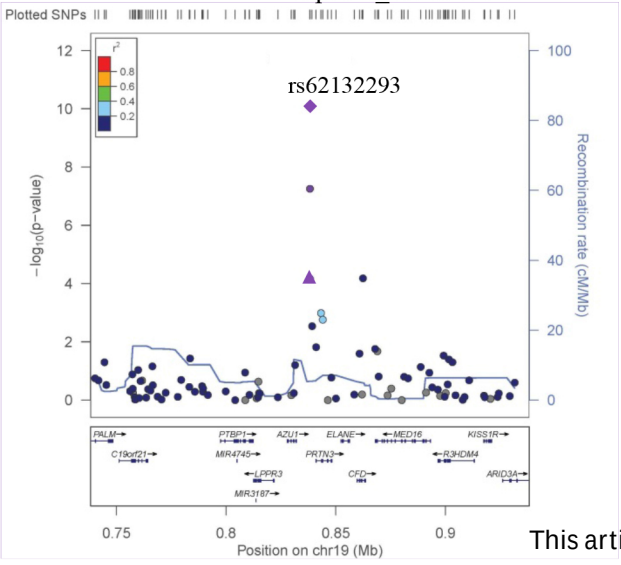
***HLA-DP* and *DQ* regions**



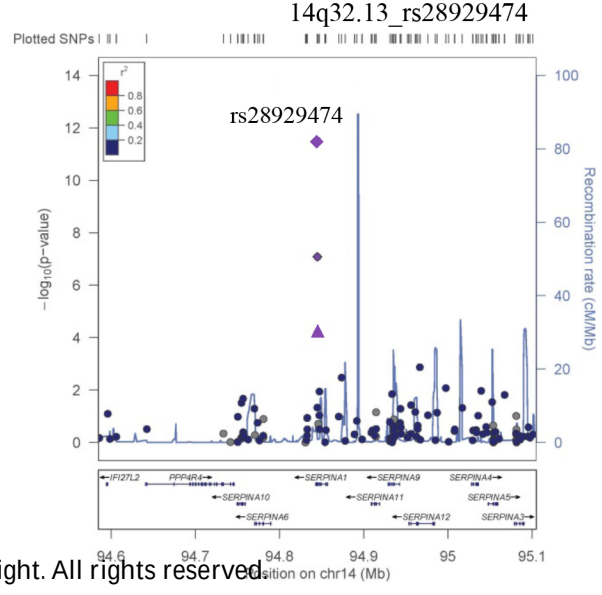
PTPN22

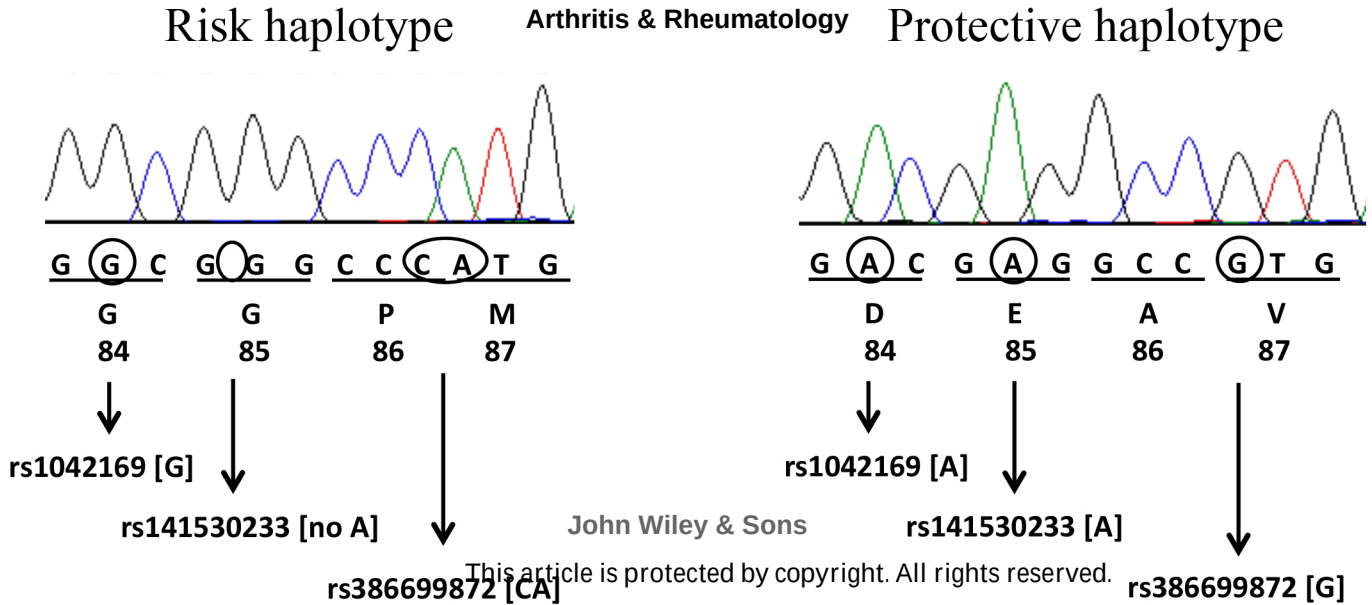


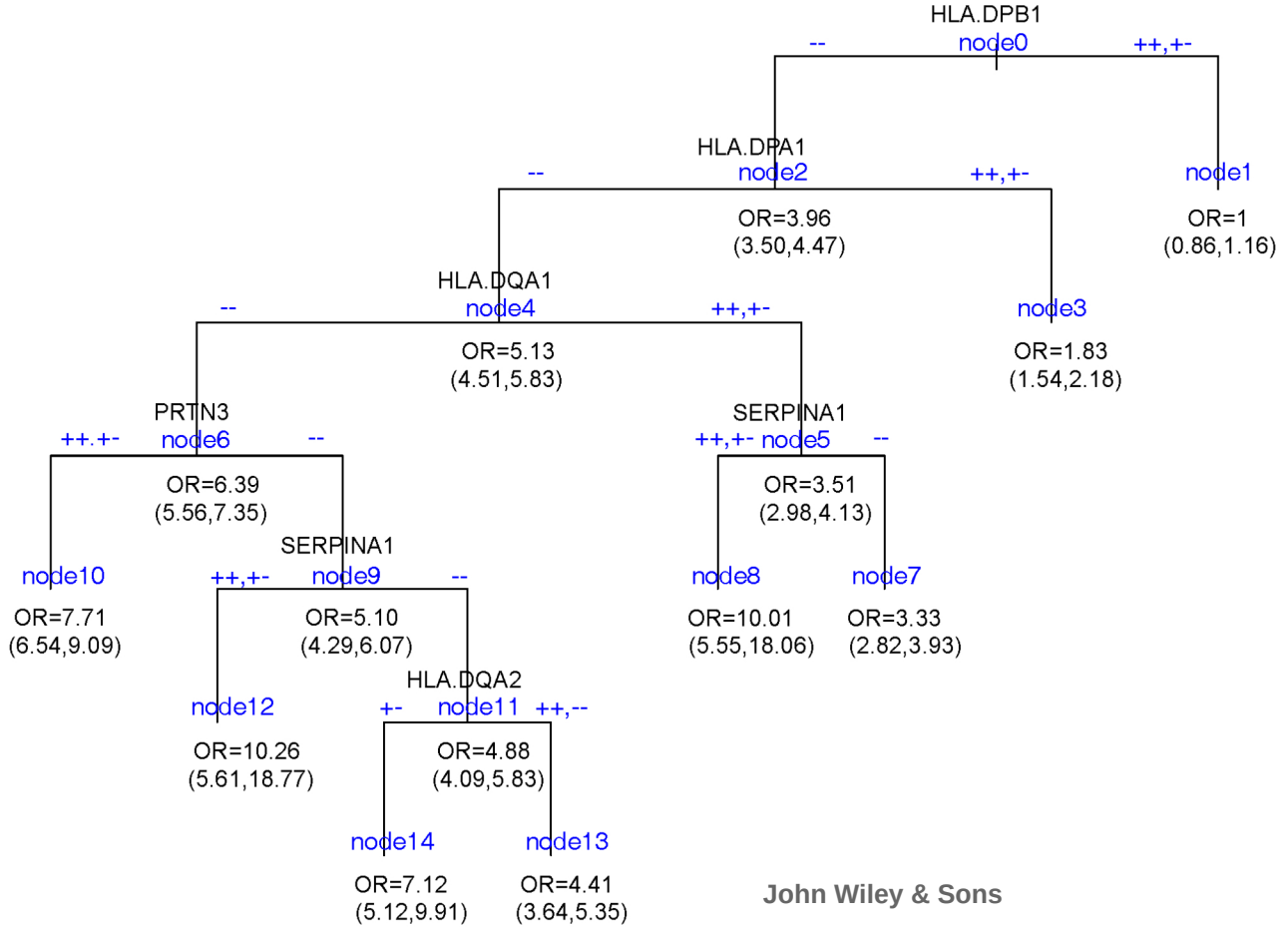
PRTN3



SERPINA1







Node	N. Cases	N. Controls
0	Parent Node	
1	416	2418
2	1570	2305
3	257	818
4	1313	1487
5	392	649
6	921	838
7	361	631
8	31	18
9	372	424
10	549	414
11	342	407
12	30	17
13	255	336
14	87	71