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Genome-wide association study identifies susceptibility loci in *IL6*, *RPS9/LILRB3*, and an intergenic locus on chromosome 21q22 in Takayasu's arteritis

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Abstract

Objective—Takayasu's arteritis is a rare large vessel vasculitis with incompletely understood etiology. We performed the first unbiased genome-wide association study (GWAS) in Takayasu's arteritis.

Methods—Two independent Takayasu's arteritis cohorts from Turkey and North America were included in our study. The Turkish cohort consisted of 559 patients and 489 controls, and the North American cohort consisted of 134 European-derived patients and 1,047 controls. Genotyping was performed using the Omni1-Quad and Omni2.5 genotyping arrays. Genotyping data were subjected to rigorous quality control measures and subsequently analyzed to discover genetic susceptibility loci for Takayasu's arteritis.

Results—We identified genetic susceptibility loci for Takayasu's arteritis with a genome-wide level of significance in *IL6* (rs2069837, OR= 2.07, $P= 6.70\times10^{-9}$), *RPS9/LILRB3* (rs11666543, OR= 1.65, $P= 2.34\times10^{-8}$), and an intergenic locus on chromosome 21q22 (rs2836878, OR= 1.79, $P= 3.62\times10^{-10}$). The genetic susceptibility locus in *RPS9/LILRB3* is located within the leukocyte receptor complex (LRC) gene cluster on chromosome 19q13.4, and the disease risk variant in this locus correlates with reduced expression of multiple genes including the inhibitory leukocyte immunoglobulin-like receptor gene *LILRB3* ($P= 2.29\times10^{-8}$). In addition, we identified candidate susceptibility genes with suggestive levels of association ($P <1\times10^{-5}$) including *PCSK5, LILRA3, PPM1G/NRBP1, and PTK2B* in Takayasu's arteritis.

Conclusion—This study identified novel genetic susceptibility loci for Takayasu's arteritis and uncovered potentially important aspects in the pathophysiology of this form of vasculitis.

INTRODUCTION

Takayasu's arteritis is a rare inflammatory disease that typically involves the aorta and its major branches (1-3). The disease causes arterial stenosis, blood-vessel wall thickening, dilation, and progressive occlusion, leading to potentially life-threatening ischemia, aortic regurgitation, and absent or reduced pulses (1-3). Takayasu's arteritis can manifest with a broad range of non-specific symptoms including fever, fatigue, arthralgia, myalgia, and weight-loss, and has a typical age of onset between 20 and 40 years of age (4, 5). The

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disease occurs worldwide and in all ethnicities, but the highest prevalence has been reported in East Asia, India, and Mexico. It is much more common in women, although the extent of this sex bias seems to be ethnicity-dependent (4, 6).

The etiology of Takayasu's arteritis remains elusive. However, there is strong evidence for genetic contribution to the disease pathogenesis supported by the repeatedly confirmed genetic association with *HLA-B*52* across multiple ethnicities (7-10). Recently, the genetic association between Takayasu's arteritis and the HLA extended region was investigated using dense genotyping and imputation analysis (11). These data, derived by examining two sets of patients and controls from two different ethnicities, established the presence of two independent genetic associations within the HLA region in Takayasu's arteritis (11). The strongest such association is in the *HLA-B*/*MICA* region and the second genetic association is in the *HLA-DQB1/HLA-DRB1* locus in HLA class II. Outside the HLA, we have previously established the genetic association between Takayasu's arteritis and genetic variants in *IL12B* (encoding the P40 regulatory subunit of IL-12 and IL-23 cytokines), and in the genetic region encoding Fc-γ receptors IIA and IIIA with a genome-wide level of significance (11). The genetic association with the same genetic variants in *IL12B* was simultaneously described and confirmed in a Japanese cohort of Takayasu's arteritis (12).

In this study, we performed the first unbiased genome-wide association study in Takayasu's arteritis in two ethnically divergent cohorts of patients and controls.

METHODS

Patients and controls

We studied two ethnically divergent cohorts of patients with Takayasu's arteritis and controls from Turkey and North America. The Turkish cohort included 559 patients enrolled by the Turkish Takayasu's Study Group and 489 healthy controls, and the North American cohort included 134 European-American (EA) patients enrolled in the Vasculitis Clinical Research Consortium Longitudinal Study of Takayasu's Arteritis and 1,047 EA controls. All patients fulfilled the 1990 American College of Rheumatology classification criteria for Takayasu's arteritis (13). Our sample size has ~90% power to detect a genetic effect with an odds ratio of 1.55 and with a genome-wide significant *P* value of 5×10^{-8}, for variants with a minor allele frequency (MAF) of 0.35, with an estimated disease prevalence of 2 per million for Takayasu's arteritis, and using an additive genetic model. Genotyping data from the 1,047 EA controls were derived from the database of Genotypes and Phenotypes (dbGaP, study accession: phs000187.v1.p1). The study was approved by the Institutional Review Boards and the Ethics Committees at all participating institutions, and all study participants signed an informed written consent.

Genotyping and data analysis

Genotyping of patients and controls was performed using the Omni1-Quad and Omni2.5 genotyping platforms (Illumina). Genotyping data from SNPs included on both platforms were available for evaluation in both cohorts. Following genotyping, we followed rigorous quality control measures as previously described (11, 14). In brief, samples were excluded

from the analysis based on population stratification by principal components analysis (>4 standard deviations), identity by descent (IBD>0.4), and autosomal heterozygosity (>2 standard deviation around the mean). A 10-component principal components analysis was performed using Eigenstrat version 4.2 (**Supplementary Figure 1**) (15), and IBD and heterozygosity analysis were performed with PLINK (16). Genotyped markers were filtered for minor allele frequency (MAF>0.01), genotype success rate (GSR>0.9), and Hardy-Weinberg equilibrium *P* value ($HWP_{Controls}$>0.01, HWP_{Cases}>0.0001). Markers with differential missingness between patients and controls (*P*<0.05) were also excluded from the analysis. After applying the quality control measures detailed above, a total of 474,442 variants were evaluated in the Turkish cohort and 547,389 in the EA cohort. A total of 516 patients and 462 controls in the Turkish cohort, and 119 patients and 993 controls in the EA cohort were included in the final analysis. Genomic control (GC) was performed using filtered non-HLA variants with minor allele frequencies > 0.02, and showed no to minimum evidence of population stratification in our cohorts ($\lambda GC_{Turkish}$= 1.05, λGC_{EA}= 1.00). Genetic association analyses were performed using a basic allelic chi-square test with 1 degree of freedom, and the results were given as asymptotic *P* values. Meta-analysis was then performed using a fixed-effects model, and the results were filtered to exclude SNPs with a Cochrane's Q-statistic *P* value <0.05. Meta-analysis was performed using PLINK and haplotype structure analysis was performed using Haploview 4.2 (17).

Additional genetic variants up to the 1000 Genomes Project density were imputed in the three non-HLA genetic loci that were detected with a GWAS level of association with Takayasu's arteritis. Imputation was performed using Impute 2 (18) and a combined reference panel consisting of 1,092 individuals (19). We applied a posterior probability imputation threshold of 0.9, and filtered imputed variants based on MAF (>1%), imputation success rate (> 90% of individuals), and HWP (> 0.0001) in controls prior to analysis, as previously described (11). Adjusted associations between SNPs were performed using conditional logistic regression in PLINK. Regional linkage disequilibrium (LD) plots were generated using the programing language R version 3.1.1.

Expression quantitative trait loci (eQTL) analysis

Expression quantitative trait loci analysis was performed to detect correlation between the presence or absence of the risk alleles in the identified Takayasu's arteritis susceptibility loci and transcript expression levels in whole blood and lymphoblastoid cell lines. This was performed using the Genotype-Tissue Expression (GTEx) Project (20) and GENe Expression VARiation (Genevar) expression quantitative trait loci databases (21).

RESULTS

We identified four association peaks that passed the level of genome-wide significance. In addition to the association with the HLA regions (rs12524487, $P= 8.17\times10^{-20}$), three genetic associations in non-HLA loci were identified (**Figure 1**). We identified the genetic association between Takayasu's arteritis and *IL6* (rs2069837, $P= 6.70\times10^{-9}$), *RPS9/LILRB3* (rs11666543, $P= 2.34\times10^{-8}$), and an intergenic locus on chromosome 21q22 that is closest to *PSMG1* (rs2836878, $P=3.62\times10^{-10}$) (**Table 1**).

Using the imputation approach described above, we identified additional genetic variants within these loci that are associated with the risk for Takayasu's arteritis (Figure 2, Supplementary Figures 2, 3, and 4, and Supplementary Tables 1 and 2). There are a total of 10 and 11 genotyped or imputed SNPs with evidence for at least modest genetic association ($P<0.05$) that are in LD ($r^2>0.7$) with the index SNP rs2836878 in the chromosome 21q22 genetic region, in the Turkish and European-American cohorts, respectively. The high LD in this locus precluded localization of this genetic effect to a single genetic variant using conditional regression analysis. However, the LD structure in this locus, informed by a trans-ancestral data from the Turkish and the European-American cohorts, indicates that this association in chromosome 21q22 is explained by a relatively small genetic region extending from 40,463,283-40,466,744 (HG19) located in the intergenic region between *PSMG1* and *LOC101928435* (**Supplementary Figure 2**).

A similar approach was attempted to further localize the novel genetic association we identified in Takayasu's arteritis in the *RPS9*/*LILRB3* locus located on chromosome 19q13.4. This gene-rich locus includes multiple genes in the leukocyte immunoglobulin-like receptor family that are known to be expressed on antigen presenting and other immunocompetent cells and interact with HLA class I. The LD structure and genetic association results, using genotyped and densely imputed genetic variants in this region, localized the genetic effect tagged by the index SNP in this locus (rs11666543) to a region that includes *RPS9* and *LILRB3* (**Supplementary Figure 3**). Similar to the genetic effect in chromosome 21q22, very high to complete LD precluded further localization to a single genetic variant. As this genetic effect is in a gene rich region, it is possible that the functional effect of the identified genetic variants might extend to other genes on this same locus. Therefore, we performed eQTL analysis to determine if the index SNP in this locus (rs11666543) affects expression levels of any of the genes or transcripts located within 1 million base pairs upstream and downstream from this SNP. We detected significant reduction in the expression of *LILRB3* in lymphoblastoid cell lines in the presence of the risk allele (G) in rs11666543 ($P=2.29\times10^{-8}$) (**Figure 3**). The genetic variant rs11666543 is also associated with significant down regulation of *RPS9*, and upregulation of a long non-coding (lnc) RNA (CTB-83J4.1), and the pseudogene *LILRP1* in a whole blood expression eQTL database (**Figure 4**). CTB-83J4.1 and *LILRP1* are located ~16kb and 500kb from rs11666543, respectively. Together, these data suggest that the genetic risk variant tagged by the SNP rs11666543 is a putative functional variant that alters the expression of multiple transcripts within this gene-rich region on chromosome 19q13.

We also identified a novel genetic association between *IL6* and Takayasu's arteritis (rs2069837, $P_{\text{Turkish}}= 1.92\times10^{-7}$, $P_{\text{EA}}= 2.32\times10^{-3}$, $P_{\text{meta}}= 6.70\times10^{-9}$). This genetic variant located within the second intron of *IL6* is not in LD with any other variant that we genotyped or imputed in this locus. This is also consistent with the LD data in HapMap, and explains why only a single variant in this genetic locus was identified as a risk variant for Takayasu's arteritis. We used ENCODE data to determine if this genetic variants in *IL6* localizes to a regulatory genetic region. We found that rs2069837 in *IL6* overlaps with an H3K27 acetylated region indicating that this genetic variant is located within an active enhancer.

In addition to identifying genetic associations in *IL6*, *RPS9*/*LILRB3*, and chromosome 21q22 with a genome level of significance ($P < 5\times10^{-8}$), we identified several novel genetic susceptibility loci for Takayasu's arteritis with a suggestive evidence of association with the disease ($P < 1\times10^{-5}$). These include PCSK5, ZFPM2, LOC100289420/FAM19A5, LILRA3, SLC16A7/LOC100289417, PPM1G/NRBP1, and PTK2B (**Table 2**).

Genetic association results ($P < 1\times10^{-5}$) in the two independent cohorts are presented in **Supplementary Tables 3 and 4**.

DISCUSSION

We performed the first unbiased genome-wide association study in Takayasu's arteritis and discovered and characterized novel genetic susceptibility loci that predispose to Takayasu's arteritis in independent cohorts from Turkey and North America. We established three risk loci for the disease, outside of the HLA region, with a genome-wide level of significance ($P < 5\times10^{-8}$). Two of these loci, *IL6* and *RPS9*/*LILRB3*, point to important immuno-regulatory pathways that could further explain the underlying immunopathology of this large-vessel vasculitis. The third genetic locus we established with a GWAS level of significance in Takayasu's arteritis is located in a region on chromosome 21q22. This same genetic susceptibility locus confers risk for ulcerative colitis and ankylosing spondylitis (22, 23), and the risk variant in this locus has been recently shown increase the expression of two novel lncRNA transcripts in this intergenic region (24).

A role for interleukin (IL)-6 in the pathogenesis of Takayasu's arteritis has been suspected from previous studies reporting increased serum IL-6 levels in patients compared to healthy controls (25, 26). IL-6 plays an important role in regulating multiple aspects of the immune response, including the differentiation of T cells into T helper 17 cells and regulatory T cells (27). Previous candidate gene association studies have suggested a modest effect for genetic variants within the promoter region of *IL6* in Takayasu's arteritis (28). While our data do not show evidence for associations with these two promoter region variants ($P > 0.05$), we report a novel genetic association in Takayasu's arteritis with a genetic variant located in a regulatory region within the second intron of *IL6*. This genetic variant is located within an experimentally-identified active enhancer region, as suggested by the presence of a histone H3K27 acetylation mark within this locus and across multiple cell types. Multiple case reports have suggested successful treatment of refractory Takayasu's arteritis with monoclonal anti-IL-6 receptor antibody (tocilizumab) (29).

Our discovery of a genetic risk locus for Takayasu's arteritis on the leukocyte receptor complex (LRC) immune-regulatory gene rich region of chromosome 19q13.4 uncovers a potentially novel aspect of this disease. This genomic region includes genes encoding for killer immunoglobulin-like receptors (KIR), leucocyte immunoglobulin-like receptors (LILR), and leucocyte-associated immunoglobulin-like receptors (LAIR) (30). Using dense imputation and trans-ancestral mapping, we localized the genetic susceptibility locus for Takayasu's arteritis in this region to *RPS9*/*LILRB3*. The LILR gene family encodes inhibitory receptor proteins consisting of two or four extracellular immunoglobulin domains, a transmembrane domain, and one to four cytoplasmic immunoreceptor tyrosine-based

inhibitory motifs (ITIMs) (30). LILRB3 binds to HLA class I antigens and generally provide a negative inhibitory signal to limit an immune response and prevent autoreactivity. Our data indicate that the index SNP in the *RPS9*/*LILRB3* locus tags a functional genetic variant that regulates multiple genes within this extended region. Specifically, the Takayasu's risk allele in rs11666543 correlates with reduced mRNA expression of *RPS9, LILRB3,* and increased expression of the pseudogene *LILRP1* located over 500kb from this SNP. In addition, the risk allele in this locus correlates with increased expression of a lncRNA (CTB-83J4.1) that is over 16kb away. These data suggest a long-range interaction within this genomic region, and a possible chromatin looping configuration that brings multiple genes spread across this complex region into close proximity to this functional regulatory locus that includes rs11666543 and that confers risk to Takayasu's arteritis.

Our expression quantitative trait loci analysis in the chromosome 19q13.4 locus that indicates significant reduction in *LILRB3* expression with the Takayasu's risk allele suggests loss of inhibitory signaling that could result in enhanced uncontrolled immune activation upon MHC class I antigen presentation. It is intriguing that HLA class I is strongly associated with the risk for Takayasu's arteritis. Our study was underpowered to establish epistatic interaction between the HLA class I risk locus in Takayasu's (tagged by rs12524487 in *HLA-B*/*MICA*) and *RPS9*/*LILRB3* (data not shown). The variant tagging the *RPS9*/*LILRB3* genetic effect in Takayasu's arteritis also alters the mRNA expression of *RPS9* which encodes for ribosomal protein S9 and is a component of the 40S ribosomal subunit.

We have previously used the Immunochip custom-designed genotyping platform and reported significant genetic associations with *IL12B* and *FCGR2A*/*FCGR3A* in Takayasu's arteritis (14). The Immunochip platform included 196,524 genetic variants and allowed for very dense coverage and genotyping in ~200 genetic loci with a previous reported association in immune-mediated diseases. These same variants in *IL12B* and *FCGR2A*/*FCGR3A* were not included in the GWAS platform used in this study, and could not be imputed and analyzed. The genetic association results with the genotyped variants in these two loci in this study are presented in **Supplementary Figure 5**. Indeed, only one genetic variant analyzed in this study was in LD with the previously reported risk variant in *IL12B,* and no variant was in in LD with the previously reported risk variant in *FCGR2A*/*FCGR3A* (**Supplementary Tables 5 and 6**). Therefore, we predict that additional genetic susceptibility loci for Takayasu's arteritis would be discovered in future studies when more comprehensive genotyping platforms or sequencing experiments are performed.

In summary, this multi-ethnic first GWAS study in Takayasu's arteritis established three additional genetic susceptibility loci with a genome-wide level of significance for this disease. Out study revealed important novel aspects in the pathogenesis of Takayasu's arteritis, and brings the total number of established genetic risk loci with a genome-wide level of significance in this disease to seven. These are the two independent MHC loci in HLA class I and class II, *FCGR2A*/*FCGR3A*, *IL12B*, *IL6*, *RPS9*/*LILRB3*, and the intergenic locus on chromosome 21q22 near *PSMG1*. Uncovering the genetic basis for Takayasu's arteritis has the great potential to lead to a better understanding of the disease pathogenesis and the discovery of novel therapeutic targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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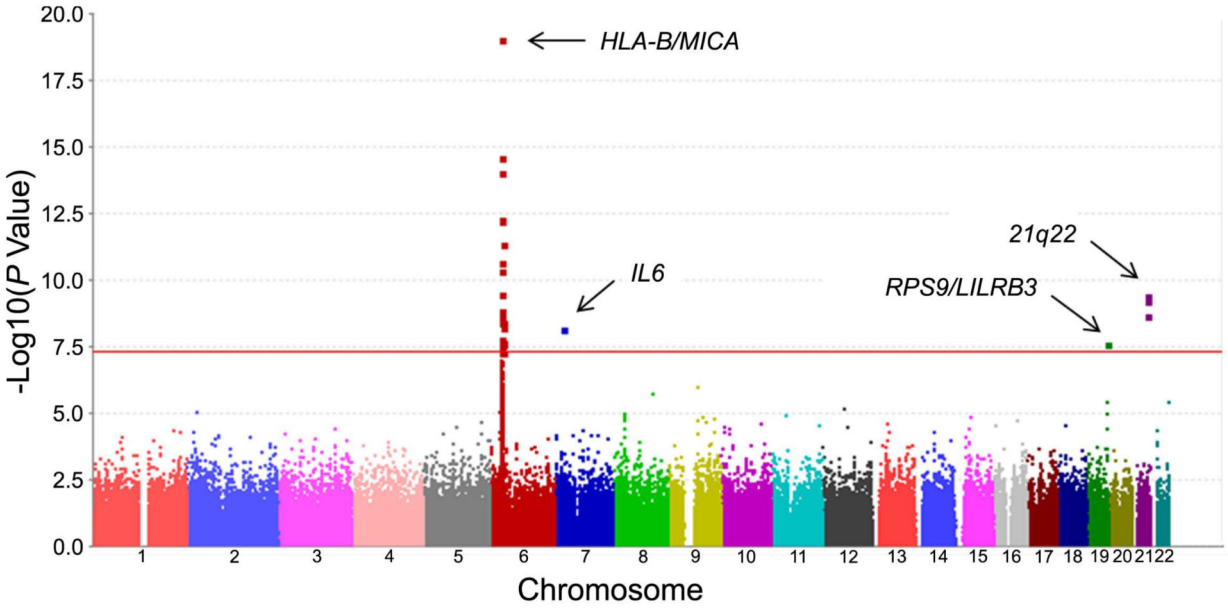

Figure 1.

Manhattan plot showing the meta-analysis results for genotyped variants in the Turkish and European-American cohorts. The red line represents the threshold for genome-wide level of significance ($P = 5\times10^{-8}$).

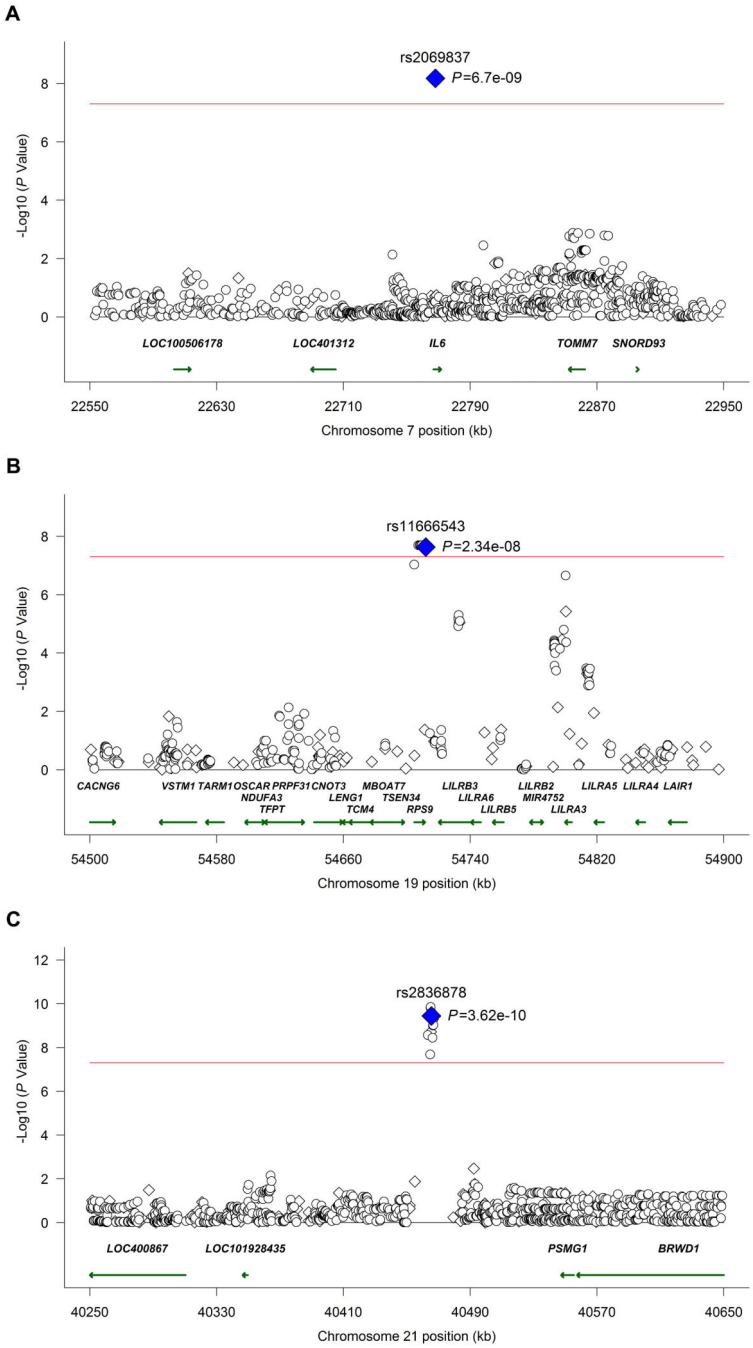

Figure 2.

Regional meta-analysis results for genotyped and imputed variants in both the Turkish and European-American cohorts. Association results are shown in the *IL6*, *RPS9/LILRB3*, and chromosome 21q22 loci, in panels A, B, and C, respectively. Genotyped variants are represented as diamonds and imputed variants as circles. The red line shows the threshold for a genome-wide level of significance ($P = 5\times10^{-8}$).

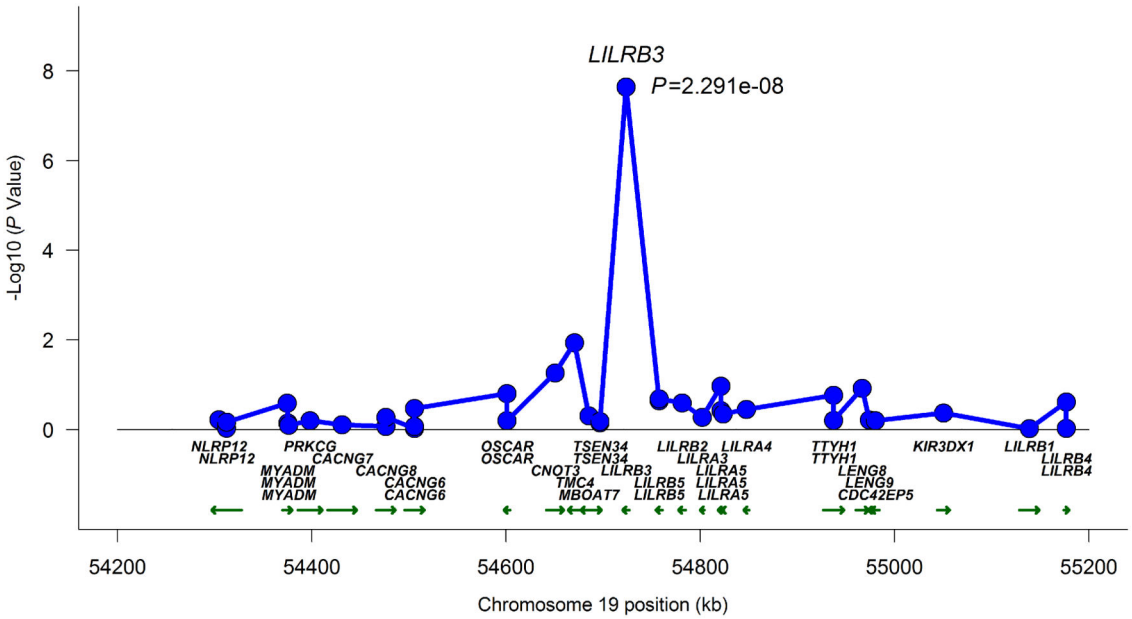

Figure 3.

Expression quantitative trait loci (eQTL) association between rs11666543 and chromosome 19q13.4 genes in lymphoblastoid cell lines. The risk allele (G) was associated with significant reduction in mRNA expression of leukocyte immunoglobulin-like receptor gene *LILRB3* (P= 2.29×10^{-8}).

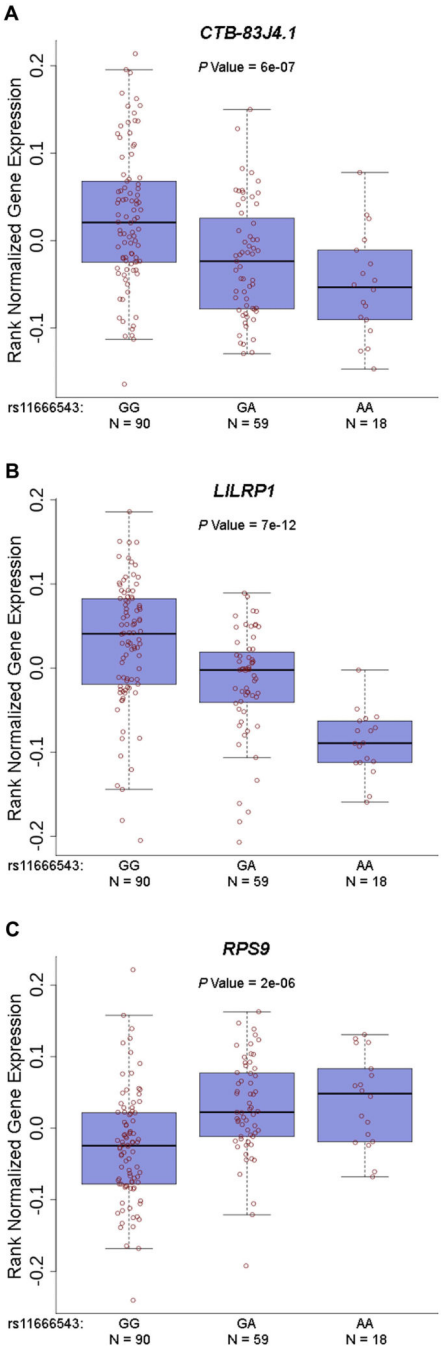

Figure 4.

Expression quantitative trait loci (eQTL) associations between rs11666543 and several transcripts in 19q13.4 in whole blood. The risk allele (G) in rs11666543 correlates with increased expression of the lncRNA CTB-83J4.1 and *LILRP1*, and decreased expression of *RPS9* in whole blood (A, B, and C, respectively).

Table 1

Genome-wide association analysis results showing genetic variants outside of the HLA region that are significantly associated ($P < 5\times10^{-8}$) with Takayasu's arteritis in the Turkish and European-American cohorts.

		Turkish Cohort					European-American Cohort					Meta-Analysis		
Locus/ Variant	**Minor Alleles**	**Case MAF**	**Control MAF**	**OR**	**95% CI**	***P* Value**	**Case MAF**	**Control MAF**	**OR**	**95% CI**	***P* Value**	**OR**	***P* Value**	***Q*-statistic *P* Value**
IL6														
rs2069837	G	0.10	0.19	0.51	0.39-0.66	1.92E-07	0.03	0.09	0.32	0.15-0.69	2.32E-03	0.48	6.70E-09	0.274
RPS9/LILRB3														
rs11666543	A	0.19	0.30	0.56	0.45-0.69	3.55E-08	0.24	0.29	0.74	0.54-1.02	6.27E-02	0.61	2.34E-08	0.134
21q22														
rs2242944	A	0.30	0.40	0.65	0.54-0.78	4.98E-06	0.22	0.36	0.51	0.37-0.70	3.07E-05	0.61	1.93E-09	0.211
rs2836878	A	0.19	0.29	0.56	0.46-0.70	9.24E-08	0.17	0.27	0.55	0.39-0.78	7.23E-04	0.56	3.62E-10	0.912
rs2836881	T	0.19	0.29	0.57	0.46-0.70	1.40E-07	0.17	0.27	0.55	0.39-0.78	6.85E-04	0.56	5.16E-10	0.879

MAF=minor allele frequency, OR=odds ratio, CI=confidence interval

Table 2

Genetic variants with a suggestive evidence for association in Takayasu's arteritis (meta-analysis *P* value $<1\times10^{-5}$).

SNP	Minor Allele	Position	Gene Symbol	Gene Location	OR	*P* Value	*Q*-statistic *P* Value
rs6560480	C	Chr9: 78599133	*PCSK5*	INTRON	1.49	9.34E-07	0.676
rs1113601	G	Chr8: 106338217	*ZFPM2*	INTRON	0.56	1.69E-06	0.834
rs9615754	T	Chr22: 48479166	*LOC100289420/FAM19A5*	INTERGENIC	0.58	3.70E-06	0.195
rs410852	G	Chr19: 54800371	*LILRA3*	INTRON	1.47	3.74E-06	0.966
rs7956657	A	Chr12: 60228857	*SLC16A7/LOC100289417*	INTERGENIC	1.67	6.13E-06	0.188
rs11675428	C	Chr2: 27642734	*PPM1G/NRBP1*	INTERGENIC	0.54	8.06E-06	0.316
rs13260543	G	Chr8: 27251325	*PTK2B*	INTRON	0.70	8.97E-06	0.156
rs7005183	G	Chr8: 27260484	*PTK2B*	INTRON	0.70	9.01E-06	0.141

MAF=minor allele frequency, OR=odds ratio, CI=confidence interval.