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The genetics of Takayasu arteritis

Paul Renauer¹ and Amr H. Sawalha^{1,2}

¹University of Michigan, department of internal medicine, division of rheumatology, Ann Arbor, MI, USA

²University of Michigan, center for computational medicine and bioinformatics, Ann Arbor, MI, USA

Summary

Takayasu arteritis (TAK) is a rare systemic vasculitis that is characterized by granulomatous inflammation of the aorta and its major branches. The cellular and biochemical processes involved in the pathogenesis of TAK are beginning to be elucidated, and implicate both cell and antibody-mediated autoimmune mechanisms. In addition, the underlying etiology to TAK may be explained, at least in part, by a complex genetic contribution. The most well-recognized genetic susceptibility locus for the disease is the classical HLA allele, *HLA-B*52*, which has been confirmed in several ethnicities. The genetic susceptibility with *HLA-B*52*, as well as additional classical alleles and loci, implicate both HLA class I and class II involvement in TAK. Furthermore, genetic associations with genes encoding immune response regulators, pro-inflammatory cytokines and mediators of humoral immunity may directly relate to disease mechanisms. Non-HLA susceptibility loci that have been recently established for TAK with a genome-wide level of significance include *FCGR2A/FCGR3A*, *IL12B*, *IL6*, *RPS9/LILRB3*, and a locus on chromosome 21 near *PSMG1*. In this review, we present the complex genetic predisposition to TAK and discuss how recent findings identified potential targets in the pathogenesis and treatment of the disease.

Introduction

Takayasu arteritis (TAK) is a rare chronic vasculitis characterized by granulomatous inflammation that predominantly affects the aorta and its major branches [1]. The disease may present with a broad range of non-specific symptoms such as fatigue, fever, weight loss, arthralgia, and myalgia [2]. The arterial inflammation in TAK can lead to blood vessel wall thickening that may result in severe complications, including aortic regurgitation, arterial stenosis, ischemia, and progressive occlusion. All arterial layers can be affected by inflammation, and vascular damage is thought to arise through cell-mediated autoimmune processes [2]. Indeed, TAK aortic tissues are known to have cellular infiltration by monocytes, neutrophils, natural killer (NK) cells, gamma-delta ($\gamma\delta$) T cells, as well as both CD4⁺ and CD8⁺ T cells [3]. In particular, the cytotoxic activity of infiltrating NK cells, $\gamma\delta$ T cells, and CD8⁺ T cells may induce vascular injury through the release of perforin to

Correspondence: Amr H. Sawalha, 5520 MSRB-1, SPC 5680, 1150W Medical Center Drive, Ann Arbor, MI 48109, USA. asawalha@umich.edu.

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arterial vascular cell surfaces. The recognition, adhesion, and pro-apoptotic activity of the immune cell infiltrates are thought to result from increased aortic expression of intracellular adhesion molecule 1 (ICAM1), HLA class I and class II molecules, as well as 4-1BBL, Fas, and MICA cell-stress markers [3,4].

In addition to cell-mediated autoimmunity, accumulating evidences suggest that TAK pathogenesis may also involve antibody-mediated autoimmunity. In a subset of patients, TAK has been associated with increased serum and Fc receptor-loaded immune complexes [5]. In addition, TAK peripheral blood B cells were reported to have increased production of auto-antibodies, including anti-endothelial cell, anti-cardiolipin, anti- β 2 glycoprotein-I, and anti-annexin V antibodies (AECA, ACA, A β 2GPI, and AAV, respectively) [6]. TAK has also been associated with increased immune reactivity to mycobacterium 65-kD heat shock protein (mHSP65) [7]. This reactivity is likely non-specific as there is a highly significant correlation between the targeting of mHSP65 and homologous human HSP60 (mHSP60) both by antibodies and T cells [8]. *Mycobacterium tuberculosis* has also been suggested to participate in TAK pathogenesis due to reports of previous infections in patients and similarities in disease manifestations; however, many patients lack any evidence of infection [9].

Although the mechanisms underlying TAK pathogenesis are incompletely understood, genetic predisposition to the disease may provide important insight into its etiology and potential treatment. A genetic basis for TAK was first suggested in case reports of familial aggregation of the disease in the 1960's [10]. Since then, genetic susceptibility loci to the disease have been identified throughout the genome, implicating a potential role in the disease for the genes encoding human leukocyte antigen (HLA) specificities, immune response regulators, pro-inflammatory cytokines, and a key receptor in complement-binding. Herein, we will provide an in-depth review of the genetic contribution to TAK.

HLA genes

The HLA class I (HLA-A, HLA-B, and HLA-C) and class II (HLA-DR, HLA-DQ, and HLA-DP) molecules are typically involved in peptide presentation for the recognition of self and foreign antigens [11]. The HLA region that encodes these molecules is considered to be the most polymorphic region in the genome, and has been associated with > 100 diseases, which are predominantly autoimmune [12]. The classical HLA alleles have also been an important focus in TAK, for which Naito et al. reported the HLA-B5 serotype as the first genetic association with the disease in 1977 (table I) [13]. Since then, high-resolution genomic approaches have identified the association as the *HLA-B*52:01* allele, which is the only *HLA-B* allele associated with the disease at a genome-wide significance level ($P < 5 \times 10^{-8}$) [14,15]. This association has become the most well-recognized and reported genetic susceptibility for TAK and has been confirmed in Japanese, Chinese, Korean, Thai, Indian, Turkish, Greek, Mexican Mestizo, and European-American populations [14–21]. In addition, the serotype/allele has been significantly associated with several TAK clinical features, including aortic regurgitation, left ventricular dysfunction, congestive heart failure, early age of onset (< 40 years of age), and non-type I vessel involvement based on the

angiographic classification of the International Conference on Takayasu's Arteritis in Tokyo [16,22–25].

The *HLA-B*39* allele has also been identified with a modest association with TAK in a Japanese population. Although this susceptibility was not found in other populations, it was proposed that the *HLA-B*39* association is related to *HLA-B*52* by a shared epitope of the peptide binding groove, which included glutamic acid and serine residues at the 63 (63E) and 67 (67S) positions, respectively [26,27]. In support, this 63E and 67S residue combination was associated with TAK in Japanese and Mexican Mestizo populations [26,28]. A recent analysis of HLA-B residues also identified an independent association of TAK with a histidine at position 171, which is also located within the peptide-binding groove [15]. Strong associations ($P < 5 \times 10^{-5}$) have been identified in other *HLA-B* alleles, including *HLA-B*67:01* as a risk allele in Japanese [15,29] and *HLA-B*13:02* as a risk allele in a meta-analysis of Turkish and European-American populations [14]. The HLA-B51 serotype was also strongly associated with the risk for TAK in an Indian cohort but not in other populations [18,24].

The *HLA-A* and *HLA-C* alleles have been extensively studied in TAK, yet the only genome-wide significant association identified thus far is *HLA-Cw*12:02*, which was shown to be increased in patients of Japanese, Turkish, and European-American descent [14,29]. However, the *HLA-Cw*12:02* association is thought to be dependent on *HLA-B*52*, with which it is in high linkage disequilibrium (LD). TAK has also been strongly associated with *HLA-Cw*07:01* as a protective allele in Turkish and European-American populations, as well as the HLA-A10 serotype in a Japanese population [14,30]. Due to conflicting reports of HLA-A10 as a protective and risk serotype for TAK, it is likely that this association represents differences within the study populations rather than a true association with the disease [30,31].

In the HLA class II region, TAK was associated at a genome-wide significance with *HLA-DRB1*07* in Chinese patients, and the presence of this allele correlated with an earlier age of onset [32,33]. Strong associations have been described between TAK and the *HLA-DPB1*09:01* and *HLA-DRB1*15:02* alleles in Japanese patients [27,29,34,35]; however, the *HLA-B*52* susceptibility is thought to explain these associations due to its high LD with both *HLA-DPB1*09:01* and *HLA-DRB1*15:02* [27,35].

In addition to classical HLA alleles, genetic associations in TAK have been reported in other variants within the HLA region. In Japanese patients, a genome-wide significant association was identified within the coiled-coil alpha-helical rod protein 1 (*CCHCR1*; rs9263739; table II), which was suggested to be dependent on *HLA-B*52:01* based on its high LD [36]. Similarly, an *HLA-B/MICA* association (rs12524487) with genome-wide significance in Turkish and European-American populations may also be explained by its high LD with *HLA-B*52:01* in the Turkish cohort [14]; however, the rs12524487 association was shown to be independent of the classical HLA allele in the European-American cohort. A microsatellite (*C1-2-A*238*) in the *HLA-B/MICA* locus was also identified with a strong association to TAK, but the association did not reach genome-wide significance [37]. It is unclear whether the *HLA-B/MICA* locus effects ultimately depend on the *HLA-B*52* allele,

but *MICA* or regulatory intergenic variants within the *HLA-B/MICA* locus should not be ruled out as a potential target of the genetic effects. Aberrant genetic regulation of *MICA* may explain its strong expression in TAK aortic tissues, which is suspected to initiate perforin-mediated vascular lesions in the disease through the activation of its counterpart NKG2D receptors expressed on the infiltrating NK cells, CD8⁺ T cells, and $\gamma\delta$ T cells [3,4,38]. A genome-wide significant effect was also found in the *HLA-DRB1/HLA-DQB1* locus, which was marked by two associations (rs189754752 and rs113452171) with a genome-wide significance in a meta-analysis of Turkish and European-American populations [14].

Taken together, extensive research of the HLA genomic region in TAK has identified associations with *HLA-B*52*, *HLA-Cw*12:02* and *HLA-DRB1*07* classical alleles and effects in the *CCHCR1*, *HLA-B/MICA*, and *HLA-DRB1/HLA-DQB1* loci at a genome-wide significance level. The genetic association with *HLA-B*52* has been confirmed and validated in several populations, and may explain the *HLA-Cw*12:02*, *CCHCR1*, and *HLA-B/MICA* associations due to high LD. Additional studies will also be useful to replicate and further investigate the *HLA-DRB1*07* and *HLA-DRB1/HLA-DQB1* effects.

Of interest, giant cell arteritis (GCA), which is another large vessel vasculitis that shares several clinical, histopathological, and angiographic features with TAK, is characterized by a predominantly class II association within the HLA and a weaker genetic effect in the class I region. This is in contrast to the HLA association in TAK, though both genetic effects in HLA classes I and II seems to be in the same loci in both diseases [14,39]. This argues for a gradient phenotype-specific genetic effect within the HLA that might play a role in determining the phenotypic presentation of large vessel vasculitis. Patients with an HLA susceptibility predominantly in the class I region present as TAK, while those with a predominant genetic susceptibility within class II develop clinical features more consistent with GCA. Of course, this hypothesis assumes the presence of other genetic susceptibility loci throughout the genome that predisposes to large vessel vasculitis in general, upon which the specifics of the HLA genetic variants, and perhaps other additional loci, will then play a role to refine the large vessel vasculitis phenotype clinically to either defined diseases.

Immune response regulatory genes

Outside of the HLA, TAK has been associated with several susceptibility loci in and around genes involved in regulating the immune response. We recently identified a genome-wide significant association in the *RPS9/LILRB3* locus (rs11666543) [40]. The associated SNP co-localized with a putative active enhancer marked by H3K27ac histone modifications in multiple cell types. In addition, this SNP was a multi-gene expression quantitative trait locus (eQTL), whose risk allele strongly correlated with the down-regulation of leukocyte immunoglobulinlike receptor B3 (*LILRB3*). As *LILRB3* binds to HLA class I molecules to inhibit immune cell stimulation, decreased expression was suggested to contribute to an unregulated immune response. The study also reported a strong association in an intronic locus of the leukocyte immunoglobulin-like receptor A3 (*LILRA3*; rs410852), which encodes an LILR molecule that stimulates pro-inflammatory cytokine production and induces proliferation of cytotoxic CD8⁺ T cells and NK cells [41]. In another study, TAK

was strongly associated with a locus of the gene for interleukin 38 (*IL38*), formerly known as *IL-1F10* (rs3811058) [42]. IL-38 has an anti-inflammatory role through the potent suppression of the production of pro-inflammatory mediators (IL-6, IL-8, IL-17, IL-22, CCL2, and APRIL) in both TLR-stimulated and un-stimulated peripheral blood mononuclear cells [43,44]. Thus, these genetic susceptibilities in *RPS9/LILRB3*, *LILRA3*, and *IL38* suggest that improper regulation of the immune response may be involved in the disease pathogenesis.

Pro-inflammatory genes

Non-HLA genetic susceptibilities for TAK have also been found with pro-inflammatory cytokine genes. A genetic effect in an intron of the *IL6* pro-inflammatory gene was recently associated with TAK susceptibility at a genome-wide significance level [40]. This effect co-localized with a putative enhancer element that was marked by H3K27ac histone modification in multiple cell types. In patients with TAK, IL-6 levels have been shown to be elevated in the serum, and this cytokine has been proposed to be involved in the disease pathogenesis [45,46]. IL-6 involvement is further evidenced by the effective treatment of refractory TAK by anti-IL-6 receptor monoclonal antibody (tocilizumab) in multiple case reports [47].

An *IL12B* locus effect was also associated with TAK susceptibility at a genome-wide significance level, both in a meta-analysis of our Turkish and European-American cohorts, and an independent study in Japanese patients and controls [14,36]. Although the effect was not detected in a Chinese population study, this discrepancy may relate to the low sample size [21]. In Japanese patients, the *IL12B* effect was shown to have a synergistic relationship with the *CCHCR1/HLA-B*52* effect. Furthermore, a recessive model of the effect (rs6871626) displayed a significant correlation with the development and severity of aortic regurgitation and disease severity, as measured by time-averaged CRP levels. A recent study extended these findings reporting the association of rs6871626 allelic dosage with TAK severity as defined by age of onset < 20 years, steroid resistance, and/or disease relapse [48]. *IL12B* encodes the p40 subunit of IL-12 and IL-23 cytokines and has been previously associated to inflammatory conditions such as ankylosing spondylitis and ulcerative colitis [49,50]. In a pilot clinical study, IL-12B monoclonal antibody (ustekinumab) was also shown to be a potential treatment option for patients with TAK [51]. Therefore, the genetic effects in *IL6* and *IL12B* may contribute to the pro-inflammatory phenotype of TAK, and suggest the potential for incorporating genetic susceptibility information in the development of new and repurposed therapy options.

Complement-binding genes

The genetic susceptibility for TAK may implicate humoral immunity in the disease pathogenesis. Our previous work demonstrated a genome-wide significant disease association with an eQTL (rs10919543) that tagged an Fc fragment of IgG receptor IIa/IIIa (*FCGR2A/3A*) locus [14]. In addition, the eQTL risk allele was correlated with upregulation of *FCGR2A* in lymphoblastoid cells. This genetic locus has previously been associated with a genome-wide significance in Kawasaki disease [52], and modest significance in giant cell

arteritis [53] and ANCA-associated vasculitis [54]. *FCGR2A* has an important role in humoral immunity, and it is expressed on most leukocytes and can bind immune complexes to initiate antibody-dependent cellular cytotoxicity and the release of pro-inflammatory mediators [55].

Conclusion

Although incompletely understood, the etiology of TAK is known to involve a complex genetic contribution. This contribution is marked by genes encoding HLA class I and class II specificities, immune response regulators, pro-inflammatory cytokines, and a complement-binding receptor, which relate to known processes involved in TAK pathogenesis. Further exploration of these genetic susceptibilities and their functional consequences may reveal the underlying mechanisms of TAK, as well as identify targets for new and repurposed therapy options.

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Table 1

Associations between Takayasu arteritis and classical HLA alleles/serological specificities. Associations are shown for case-control comparative studies that included at least 30 patients. *P*-values are presented for the most significant associations with a given allele or serotype within each ethnic population. Highly significant and genome-wide significant associations ($P < 5 \times 10^{-5}$ and $P < 5 \times 10^{-8}$, respectively) with non-specific *P*-values reported in the original articles, are shown with specific *P*-values (*P**) that were calculated using reported chi-squared values or by chi-squared test using allele/serotype frequencies and the statistical model of the respective study

HLA allele/ serotype	Study population	<i>P</i> -value (<i>P</i> *)	Odds ratio	References
HLA-A				
A10	Japanese	$< 1 \times 10^{-4}$ (4.86×10^{-5})	4.41	Numano-1979 [30]
A*30:01	Korean	4.8×10^{-2}	NA	Lee-2007 [16]
HLA-B				
B*13:02	Turkish, EA	3.25×10^{-7}	3.184	Saruhan-Direskeneli-2013 [14]
B*39:01	Japanese	$< 3 \times 10^{-2}$	2.90	Kitamura-1998 [35]
B*39:02	Japanese	$< 5 \times 10^{-3}$	20.9	Yoshida-1993, Kimura-1996, Kitamura-1998, Kimura-2000 [26,27,35,37]
B5	Japanese	$< 1 \times 10^{-4}$ (1.97×10^{-5})	3.63	Naito-1977, Naito-1978, Numano-1979 [13,30,31]
	Indian	$< 3 \times 10^{-8}$ (6.13×10^{-9})	4.3	Mehra-1996 [56]
B51	Indian	$< 5.0 \times 10^{-6}$ (3.12×10^{-6})	NA	Mehra-1998 [18]
B52	Japanese	$< 1 \times 10^{-4}$ (1.17×10^{-7})	7.8	Isohisa-1978, Sasazuki-1979, Isohisa-1982, Moriuchi-1982, Dong-1992, Yajima-1992, Kimura-1996 [22,27,34,57-60]
	Korean	< 0.02	3.59	Park-1992 [61]
	Indian	$< 1.7 \times 10^{-5}$ (8.91×10^{-6})	NA	Mehra-1998 [18]
B*52	Japanese	$< 1 \times 10^{-3}$ (5.98×10^{-9})	3.73	Yoshida-1993, Kimura-1996, Kitamura-1998, Kimura-2000 [26,27,35,37]
	Turkish	0.00 (4.03×10^{-6})	3.7	Sahin-2012 [24]
	Chinese	$< 1 \times 10^{-3}$ (1.41×10^{-10})	NA	Yang-2016 [21]
B*52:01	Japanese	1.6×10^{-16}	2.82	Takamura-2012, Terao-2013 [15,29]
	Turkish, EA	8.98×10^{-10}	4.806	Saruhan-Direskeneli-2013 [14]
	Korean	2.5×10^{-2}	NA	Lee-2007 [16]
B*67:01	Japanese	1.8×10^{-7}	3.62	Takamura-2012, Terao-2013 [15,29]
HLA-C				

HLA allele/ serotype	Study population	P-value (P*)	Odds ratio	References
Cw6	Korean	$< 5 \times 10^{-2}$	2.42	Park-1992
Cw*07:01	Turkish, EA	3.74×10^{-6}	0.466	Saruhan-Direskeneli-2013
Cw*12:02	Turkish, EA	4.01×10^{-10}	4.476	Saruhan-Direskeneli-2013
	Japanese	$< 1 \times 10^{-4}$ (9.46×10^{-11})	3.42	Takamura-2012
HLA-D				
Dw12	Japanese	$< 2 \times 10^{-3}$	2.50	Sasazuki-1979, Isohisa-1982, Takeuchi-1990
HLA-DP				
DPB1*09	Chinese	3×10^{-3}	9.15	Lv-2011
DPB1*09:01	Japanese	$< 2 \times 10^{-2}$ (8.50×10^{-6})	3.0	Dong-1992, Kimura-1996
DPB1*17:01	Chinese	3×10^{-3}	3.1	Lv-2011
HLA-DQ				
DQw1	Japanese	$< 2 \times 10^{-2}$	12.6	Moriuchi-1982
DQw2	Korean	$< 1 \times 10^{-2}$	3.07	Park-1992
DQB1*06:01:01	Japanese	2×10^{-4}	1.98	Takamura-2012
HLA-DR				
DR2	Japanese	$< 1 \times 10^{-3}$	6.0	Moriuchi-1982
DR7	Korean	$< 4 \times 10^{-2}$	2.28	Park-1992
DR8	Indian	$< 5 \times 10^{-2}$	4.7	Mehra-1996
DRB1*04	Chinese	$< 1 \times 10^{-3}$	2.43	Dang-2002
DRB1*07	Chinese	$< 1 \times 10^{-3}$ (6.16×10^{-9})	4.42	Dang-2002, Lv-2015
DRB1*15:02	Japanese	$< 1 \times 10^{-3}$ (1.81×10^{-5})	2.65	Dong-1992, Kimura-1996, Kitamura-1998
	Korean	4.6×10^{-2}	NA	Lee-2007
DRB1*15:02:01	Japanese	$< 1 \times 10^{-4}$ (9.25×10^{-8})	2.92	Takamura-2012
DRB5*01:02	Japanese	$< 3 \times 10^{-4}$	2.80	Dong-1992

EA: European-American.

Table II

Genetic associations between Takayasu arteritis and HLA variants (excluding classical HLA alleles) and non-HLA loci. Associations are shown for case-control comparative studies that included at least 30 patients. *P*-values are presented for the most significant associations with a given variant within each ethnic population

Gene/locus	Variant	Allele	Population	<i>P</i> -value	Odds ratio	Reference
<i>CCHCR1</i>	rs9263739	T	Japanese	2.8×10^{-21}	2.44	Terao-2013 [36]
<i>HLA-B/MICA</i>	rs12524487	T	Turkish, EA	5.57×10^{-16}	3.29	Saruhan-Direskeneli-2013 [14]
	C1-4-1	C1-4-1*221	Japanese	$< 7 \times 10^{-5}$	0.30	Kimura-2000 [37]
	MIB	MIB*332	Japanese	$< 2 \times 10^{-5}$	4.32	Kimura-2000 [37]
<i>IL12B</i>	rs6871626	A	Japanese	1.7×10^{-13}	1.75	Terao-2013 [36]
		A	Turkish, EA	7.31×10^{-6}	1.48	Saruhan-Direskeneli-2013 [14]
	rs56167332	A	Turkish, EA	2.18×10^{-8}	1.54	Saruhan-Direskeneli-2013 [14]
	rs3213113	CC	Turkish	7×10^{-3}	3.7	Saruhan-Direskeneli-2006 [64]
<i>FCGR2A/FCGR3A</i>	rs10919543	G	Turkish, EA	5.89×10^{-12}	1.81	Saruhan-Direskeneli-2013 [14]
	rs10919543	GG	Chinese	$< 1 \times 10^{-3}$	6.53	Qin-2016 [65]
<i>Chr21q22</i>	rs2836878	G	Turkish, EA	3.62×10^{-10}	1.79	Renauer-2015 [40]
	rs35475565	A	Turkish, EA	4.39×10^{-7}	1.62	Saruhan-Direskeneli-2013 [14]
<i>HLA-DQB1/HLA-DRB1</i>	rs113452171	T	Turkish, EA	3.74×10^{-9}	2.34	Saruhan-Direskeneli-2013 [14]
	rs189754752	G	Turkish, EA	4.22×10^{-9}	2.47	Saruhan-Direskeneli-2013 [14]
<i>IL6</i>	rs2069837	A	Turkish, EA	6.70×10^{-9}	2.08	Renauer-2015 [40]
	rs1800795	CG	Turkish	1×10^{-3}	0.4	Saruhan-Direskeneli-2006 [64]
	rs1800797	AG	Turkish	1×10^{-2}	0.4	Saruhan-Direskeneli-2006 [64]
<i>RPS9/LILRB3</i>	rs11666543	G	Turkish, EA	2.34×10^{-8}	1.64	Renauer-2015 [40]
<i>MICA/MICB</i>	C1-2-A	C1-2-A*238	Japanese	$< 3 \times 10^{-7}$	3.59	Kimura-2000 [37]
<i>MLX</i>	rs665268	G	Japanese	5.2×10^{-7}	1.50	Terao-2013 [36]
<i>IL1F10</i>	rs3811058	TT	Mexican	6×10^{-7}	0.20	Soto-lopez-2013 [42]
<i>PCSK5</i>	rs6560480	C	Turkish, EA	9.34×10^{-7}	1.49	Renauer-2015 [40]
<i>ZFPM2</i>	rs1113601	A	Turkish, EA	1.69×10^{-6}	1.79	Renauer-2015 [40]

Gene/locus	Variant	Allele	Population	P-value	Odds ratio	Reference
<i>TNFA</i>	<i>TNFA</i> Haplotype (rs361525, rs1800629, rs1799724, rs1800630, rs1799964)	GGCAT	Chinese Han	2×10^{-6}	NA	Ly-2011 [66]
<i>LOC100289420/FAM19A5</i>	rs9615754	C	Turkish, EA	3.70×10^{-6}	1.72	Renauer-2015 [40]
<i>LILRA3</i>	rs410852	G	Turkish, EA	3.74×10^{-6}	1.47	Renauer-2015 [40]
<i>SLC16A7/LOC100289417</i>	rs7956657	A	Turkish, EA	6.13×10^{-6}	1.67	Renauer-2015 [40]
<i>PPM1G/NRBP1</i>	rs11675428	A	Turkish, EA	8.06×10^{-6}	1.85	Renauer-2015 [40]
<i>PTK2B</i>	rs13260543	A	Turkish, EA	8.97×10^{-6}	1.43	Renauer-2015 [40]
	rs7005183	A	Turkish, EA	9.01×10^{-6}	1.43	Renauer-2015 [40]
<i>EEFSEC</i>	rs10934853	C	Japanese	2.6×10^{-5}	1.40	Terao-2013 [36]
<i>HLA-C/RPL3</i>	C1-2-5	C1-2-5*208	Japanese	$< 7 \times 10^{-5}$	2.75	Kimura-2000 [37]
<i>PONI</i>	rs854560	A	Mexican	1×10^{-4}	3.80	Huesca-Gomez-2013 [67]
	rs705379	A	Mexican	1.1×10^{-2}	1.79	Huesca-Gomez-2013 [67]
	rs662	G	Mexican	4.3×10^{-2}	1.60	Huesca-Gomez-2013 [67]
<i>IL1RN</i>	rs2234663	4cnv	Mexican	2.24×10^{-4}	2.74	Soto-lopez-2013 [42]
	rs2234663-rs315952	4cnv-C	Mexican	1×10^{-3}	2.20	Soto-lopez-2013 [42]
	rs315952	TC	Mexican	4×10^{-4}	3.18	Soto-lopez-2013 [42]
	rs315951	G	Mexican	3.3×10^{-2}	1.77	Soto-lopez-2013 [42]
	rs419598	TT	Mexican	3.7×10^{-2}	2.10	Soto-lopez-2013 [42]
<i>RIPPLY2</i>	rs1570843	T	Japanese	3.1×10^{-4}	1.34	Terao-2013 [36]
<i>NOB4</i>	C1-3-1	C1-3-1*291	Japanese	$< 4 \times 10^{-3}$	2.07	Kimura-2000 [37]
<i>MICA</i>	rs138201170	Deletion	Japanese	4×10^{-3}	0.39	Kimura-2000 [37]
	rs41293539	CT	Japanese	$< 1 \times 10^{-3}$	5.0	Kimura-1998, Kimura-2000 [37,68]
<i>NFKB1I</i>	<i>IKBLP</i> *0.3 haplotype (rs3219186, rs3219185, rs3219184, rs2071592)	(T)8-C-G-T	Japanese	6.5×10^{-4}	2.47	Shibata-2006 [69]
<i>IL2</i>	rs2069762	GT	Turkish	5×10^{-3}	0.4	Saruhan-Direskeneli-2006 [64]
<i>DMXL2</i>	rs12102203	A	Japanese	8.1×10^{-3}	1.24	Terao-2013 [36]
<i>IL1B</i>	rs16944	TC	Mexican	2.0×10^{-2}	0.41	Soto-lopez-2013 [42]

EA: European-American.