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Endoplasmic reticulum-associated amino-peptidase 1 and rheumatic disease: genetics

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Abstract

Purpose of review—This article will review the genetic evidence implicating *ERAP1*, which encodes the endoplasmic reticulum-associated amino-peptidase 1, in susceptibility to rheumatic disease.

Recent findings—Genetic variants and haplotypes of *ERAP1* are associated with ankylosing spondylitis, psoriasis, and Behçet's disease in people of varying ancestries. In each of these diseases, disease-associated variants of *ERAP1* have been shown to interact with disease-associated class I Human Leukocyte Antigen (HLA) alleles to influence disease risk. Functionally, disease-associated missense variants of *ERAP1* concertedly alter ERAP1 enzymatic function, both quantitatively and qualitatively, while other disease-associated variants influence *ERAP1* expression. Therefore, *ERAP1* haplotypes (or allotypes) should be examined as functional units. Biologically, this amounts to an examination of the gene regulation and function of the protein encoded by each allotype. Genetically, the relationship between disease risk and *ERAP1* allotypes should be examined to determine whether allotypes or individual variants produce the most parsimonious risk models.

Summary—Future investigations of *ERAP1* should focus on comprehensively characterizing naturally-occurring *ERAP1* allotypes, examining the enzymatic function and gene expression of each allotype, and identifying specific allotypes that influence disease susceptibility.

Keywords

major histocompatibility complex; antigen processing; epistasis

Introduction

The gene encoding the endoplasmic reticulum-associated amino-peptidase 1 (ERAP1) protein is highly polymorphic with several common polymorphisms encoding variant amino

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Conflicts of interest

None

acids (1). This peptidase trims peptides that have been transported from the intracellular space into the endoplasmic reticulum (ER). Trimming is required for efficient peptide loading onto class I major histocompatibility complex (MHC) molecules, which are displayed on the surface of nearly all cell types. MHC class I-peptide complexes play important roles in immune surveillance and in innate and adaptive immune functions through their interactions with T-cell receptors (TCRs) and several cell activating and inhibitory receptors, including the killer cell immunoglobulin-like receptors (KIRs), the killer cell lectin-like receptors (KLRs), and the leukocyte immunoglobulin-like receptors (LILRs). Similar to TCR-peptide specificity, the inhibitory receptors also exhibit selectivity for peptides bound to MHC class I (2). Several *ERAP1* coding variants are associated at genome-wide significance with three rheumatic diseases, ankylosing spondylitis (AS) (3–5), psoriasis (6, 7), and Behçet's disease (BD) (8), which all have strong associations with MHC class I molecules. Strong interactions of coding *ERAP1* variants with the appropriate disease-specific Human Leukocyte Antigen (HLA) class I proteins suggest that ERAP1 trimming of peptides plays a role in susceptibility to these class I HLA-associated diseases (4, 6, 8). Changes to the structure of the ERAP1 protein are likely to influence the nature of peptides bound in the active site and their ability to be trimmed, and therefore could influence the peptidome that is available for class I HLA binding and presentation. Although coding and non-coding *ERAP1* SNPs and three or four marker SNP haplotypes have been associated with AS, psoriasis, and BD, the data reported are often insufficient to enable direct comparisons of haplotypes and their disease associations between studies. Recently, coding variation in *ERAP1* and alterations in ERAP1 activity have been explored with the idea that ERAP1 amino acid variants may concertedly influence its function (4, 9, 10), and therefore more complete ERAP1 amino acid sequence or allotype information, and even allotype combinations, may be needed to understand ERAP1 function and its role in disease pathogenesis.

In this review, we encapsulate the existing genetic literature implicating *ERAP1* variation in rheumatic diseases. The functional consequences of *ERAP1* variation are discussed in detail by Tran and colleagues later in this issue [Tran T and Colbert RA, this issue].

Example of ERAP1 allotype assembly from HapMap reference populations

In order to discuss and study *ERAP1* haplotypes/allotypes and their role in genetically-complex diseases, it is critical to accurately identify and classify the haplotypes in a standardized way. For disease association analyses, the allotypes should be based on common missense variants in *ERAP1*, as observed in large, ancestrally-defined reference populations of healthy individuals. As an example, we have examined the 1000 Genomes dataset and identified 10 missense SNPs in *ERAP1* that were present at greater than 5% minor allele frequency in at least one super-population (Table 1). Haplotype analysis including the 9 missense variants that were genotyped in the HapMap CEU or ASN (HCB + JPT) individuals reveals 10 haplotypes with a frequency of greater than 1% in one or more of the populations (Table 2). These haplotypes are derived from an ancestral haplotype (Hap1), which bears the alleles found in chimpanzees, orangutans, and macaques (Table 2). An examination of the linkage disequilibrium structure of the common, missense variants in the CEU and ASN populations are shown in Figure 1. In the ensuing discussion of the

associations between *ERAP1* and rheumatic diseases, we will attempt to unify the discussion using the *ERAP1* allotypes defined in the HapMap populations (Table 2).

Genetic variation of *ERAP1* and susceptibility to ankylosing spondylitis

Genetic variants of *ERAP1* have clearly been shown to contribute to AS susceptibility, first in U.S. and U.K. cohorts (3), and subsequently in many other populations (4, 11–17). The relationship between AS and *ERAP1* (called *ARTS1* at the time) was originally identified by the Wellcome Trust Case Control Consortium (WTCCC) and Australo-Anglo-American Spondylitis Consortium genome-wide association study (GWAS) of AS (3). In this study of 1471 AS patients from the U.K. and U.S., 5 non-synonymous SNPs of *ERAP1* were found to significantly influence AS risk, with the minor alleles of rs27044 (Q730) and rs30187 (K528) conferring disease risk and of rs10050860 (N575), rs2287987 (V349), and rs17482078 (Q725) protecting against its development (Table 3). The variant most strongly associated with AS in the meta-analysis was K528, however the variant most strongly associated with AS in the U.K. population, Q730, was not examined in the U.S. population or in the meta-analysis. This study did not include haplotypic association testing or conditional analysis of *ERAP1* SNPs, and it did not address whether the disease-associated variants represented independent association signals. In a follow-up, fine-mapping study that included 1604 AS cases of European ancestry, Harvey *et al*. identified six AS-associated *ERAP1* missense variants (rs26653 [R127], M349, K528, D575, R725, and Q730; Table 3) (1). Among these, Q730 was the most significantly associated, but regional LD precluded nomination of any single variant as the source of disease risk on the basis of genetics alone. Interestingly, with the exception of R127, all of the AS risk alleles are the ancestral alleles and the derived alleles are associated with disease protection (Table 2). Among the HapMap *ERAP1* allotypes (Table 2), the AS-protective V349 and Q725 variants are found exclusively on Hap10, along with the majority of the N575 variants. The K528 risk variant is present in Haps 1–3 and the Q730 risk variant is found in Haps 1 and 2 (Table 2).

The studies that have evaluated *ERAP1* haplotypes for association with AS have been limited, both by the markers genotyped and by their sample size. Maksymowich *et al.* examined 6 *ERAP1* variants in three case-control collections that included a total 992 AS patients from Canada (18). They identified 3 *ERAP1* variants, P127R, R528K, and D575N, that each significantly influenced AS risk (Table 3). By examining contiguous 3-marker haplotypes of the 6 *ERAP1* variants, the authors identified several specific haplotypes that affected AS risk (Table 3). The haplotypes most strongly associated with AS were the haplotype of K528-D575-E730 (KDE), which conferred risk of AS, and the haplotype of P127-I276-R528 (PIR), which protected against AS. Within the HapMap *ERAP1* allotypes, the risk KDE haplotype is only found within Hap3, while the PIR protective haplotype is found in Haps 6, 7, and 10. However, if the PIR haplotype tags the same effect as the adjacent, protective 3-marker haplotype (I276-R528-N575 or IRN), then the combined PIRN haplotype is specific to Hap10 (Table 3).

A GWAS by Evans *et al.* that included over 5000 AS patients refined our understanding of the association of *ERAP1* variants with AS (4). The authors examined AS-associated loci for gene-gene interactions and discovered epistasis between *HLA-B*27* and *ERAP1*. In one of

the first reports of genetic epistasis in a human disease, they showed that the K528 variant conferred risk of AS specifically in *HLA-B*27*-positive individuals. Additionally, they used conditional analysis to reveal the presence of two independent effects on AS risk at the *ERAP1* locus. These included a primary risk effect, tagged by K528, and a secondary protective effect, tagged by N575. They went on to report that individuals homozygous for R528 and N575 (RN) had a 3- to 4-fold reduction in AS risk. In agreement with previous studies, the RN haplotype predominantly tags Hap10 in the HapMap CEU and ASN populations (Table 2).

Kadi *et al.* examined the 5 AS-associated *ERAP1* variants from the WTCCC AS study in case-control cohorts from France and Belgium that included 436 AS patients (19), but only 3 of these variants were genotyped in both cohorts. The authors replicated the reported associations of AS with the K528 (risk), N575 (protective), and Q725 (protective) variants, with the strongest association between AS and K528. Haplotypic analysis of these 3 variants revealed a significant omnibus association between AS and the 528-575-725 haplotypes (Table 3). An examination of specific haplotypes formed by these residues identified R528-N575-Q725 (RNQ) as an AS protective haplotype and K528-D575-R725 (KDR) as an AS risk haplotype. The protective RNQ haplotype specifically tags Hap10 of the HapMap allotypes, while the risk KDR haplotype is found in Haps 1–3 (Tables 2 and 3).

Similarly, Bettencourt *et al.* examined the 5 AS-associated variants from the WTCCC study in a collection of 200 HLA-B*27 positive AS patients and 200 HLA-B*27 positive healthy subjects (20). This study replicated the associations of each of these 5 SNPs with AS, identifying the strongest association with the AS risk variant, K528. Haplotype analysis of 4 of these 5 SNPs identified two haplotypes of variants encoding residues 349-528-575-725 that significantly affected AS risk: V349-R528-N575-Q725 (VRNQ) was an AS-protective haplotype and M349-K528-D575-R725 (MKDR) was an AS risk haplotype. Similar to the study from Kadi *et al.*, the MKDR risk haplotype is found within the HapMap Haps 1–3, while the protective VRNQ haplotype is specific to Hap 10.

Taken together, these data indicate that at least two *ERAP1* allotypes independently influence susceptibility to AS, one conferring disease risk and the other affording protection against disease. Based on comparisons of the reported AS-associated *ERAP1* haplotypes with the *ERAP1* allotypes in HapMap individuals (Tables 2 and 3), Hap10 is an AS protective haplotype while one or more of Haps1–3 appear to be AS risk haplotypes. Furthermore, the association of the K528 allele with AS risk was replicated in two studies of East Asians (5, 21). Although K528 is present on Haps1–3 in the CEU population, it is found predominantly on Hap2 in the ASN population, suggesting that Hap2 is the major *ERAP1* risk allotype among East Asians.

In a series of two papers, Reeves *et al.* further investigated combinatorial effects of *ERAP1* variants by examining naturally-occurring *ERAP1* haplotypes and allotypes from human subjects and cell lines (11, 12). This work suggests that Hap2 (*002 in their study) encodes an ERAP1 molecule that efficiently trims peptides and yields relatively high production of MHC-peptide complexes, while a haplotype that was identical to Hap10 on the basis of its common alleles (*001 in their study) encoded an ERAP1 molecule that trimmed peptides

poorly, leading to relatively low production of MHC-peptide complexes (11, 12). These observations are supported by an *in vitro* study of human ERAP1 that identified enhanced peptide trimming by forms of ERAP1 containing AS-risk variants and reduced peptide trimming by those bearing AS-protective variants (4). This is also consistent with two studies of naturally-occurring *ERAP1* polymorphisms and their effects on ERAP1 enzyme activity and the resultant peptidome (22, 23). The authors went on to demonstrate perfect segregation of *ERAP1* allotype combinations between cases and controls, leading them to conclude that the effect of the *ERAP1* locus on AS risk is due to the net enzymatic effect produced by combinations of *ERAP1* allotypes (12).

Although the functional studies of the protein products of *ERAP1* allotypes by Reeves *et al.* were consistent with previous studies, the distribution of *ERAP1* variants and allotypes within their collection of 17 AS cases and 19 healthy subjects was surprisingly inconsistent with the existing AS literature. Specifically, the AS risk allele (K528) and risk allotype (Hap2 or *002) were more common among controls than cases, while the AS protective allele (E730) and protective allotype (Hap10 or *001) were more common among cases than controls. The source of this discrepancy is unclear, and this issue is unlikely to be resolved without an analogous, sequencing-based study of the ERAP1 locus in a substantially larger AS case-control collection.

It has also been hypothesized that AS-associated variants or allotypes may influence disease risk by affecting *ERAP1* expression. Constantino *et al.* recently reported that the K528-D575-R725 AS risk haplotype (equivalent to Hap10) was strongly correlated with reduced *ERAP1* mRNA levels, more so than was any individual AS-associated variant (24). This raises the possibility that AS-associated *ERAP1* allotypes may contain both coding variants that influence AS risk through changes in enzymatic function and noncoding variants that influence AS risk through alterations in gene expression.

Genetic variation of *ERAP1* and susceptibility to psoriasis

Genetic variants of *ERAP1* have been shown to influence psoriasis susceptibility, originally in populations of European ancestry (6, 25), and subsequently in Han Chinese (7, 26, 27). The original report by Strange *et al.*, a GWAS that included 2178 psoriasis cases, revealed that two *ERAP1* variants, rs27524 (noncoding) and rs30187 (K528), were genome-wide significant risk factors for psoriasis (6). Conditional analysis was unable to discriminate between the effects of the two psoriasis-associated variants, suggesting that these variants represent the same association signal. The authors also identified dominant epistasis between *HLA-Cw*0602* and the K528 variant of ERAP1. The second study, including 10,588 cases of European ancestry, identified rs27432, an intronic SNP in strong LD with Q730, as the variant most strongly associated with psoriasis (25). Although the associations of K528 and Q730 may implicate one or more of the Haps1–3 as psoriasis risk factors (Table 2), it is unclear whether the effect of ERAP1 on psoriasis will be explained by single variant or allotypic associations.

Several studies have also examined the association of *ERAP1* variants with psoriasis in the Han Chinese population. A multi-phase GWAS that included 8312 cases of psoriasis from

China identified rs151823, a noncoding SNP ~16 kb upstream of *ERAP1*, as a psoriasis-protective allele (26). Another association study of psoriasis, which included a combination of exome sequencing and *ERAP1* targeted resequencing data from 10,727 cases, identified genome-wide significant protective associations between psoriasis and both the P127 and E730 variants of ERAP1, but surprisingly it failed to replicate the association between psoriasis and K528 (7). Importantly, P127 is in strong LD with E730 in East Asian HapMap samples, but not in those of European ancestry (Figure 1). Finally, Sheng *et al.* performed a sequencing-based association study of psoriasis that included 15,207 cases from China (27). This revealed an association between psoriasis and rs27043, which was located in intron 16 of *ERAP1*, but did not establish whether this SNP association was independent from the noncoding SNP, rs151823, or the P127 or E730 variants. The psoriasis risk association with Q730, which specifically tags Hap2 among HapMap ASN haplotypes, but not with the R528 variant that is associated with psoriasis protection in individuals of European ancestry, emphasizes the disease risk associated with Hap2, which is found at high frequency in East Asians, and implies disease protection afforded by Hap10, which is found at high frequency in the HapMap CEU population but at low frequency in East Asians (Table 2).

Genetic variation of *ERAP1* and susceptibility to Behçet's disease

The association between *ERAP1* and BD was first identified by Kirino *et al.* in a large case-control collection of Turkish ancestry that included 1209 cases (8). The authors demonstrated that the N575 and Q725 variants of ERAP1 recessively conferred risk of BD, and similar to AS and psoriasis, the authors also identified genetic epistasis between an ERAP1 variant (Q725) and the BD-associated MHC class I allele, *HLA-B*51*. If we extrapolate *ERAP1* allotypes from these risk variants, Hap10 is the BD risk haplotype. Importantly, the effect of Q725/N575/Hap10 on BD susceptibility is in the opposite direction from their effect on AS and psoriasis risk, conferring risk of BD while protecting against AS and psoriasis. The genetic model under which *ERAP1* variants interact with disease-associated MHC class I alleles also differed between these diseases, with a dominant effect in AS and psoriasis and a recessive effect in BD.

A study by Conde-Jaldon *et al.* examined ERAP1 variants in a collection of 362 cases 460 controls from Spain (28). The study failed to replicate the association between individual variants of *ERAP1* and BD. However given its recessive nature, this study was not adequately powered to identify the association.

Conclusion

Genetic variation of *ERAP1* influences susceptibility to several class I HLA-associated rheumatic diseases, and in each case, genetic epistasis exists between *ERAP1* variants and the disease-associated HLA alleles. In AS, data have consistently demonstrated that the *ERAP1* locus has at least two independent effects on disease susceptibility, one affording protection and a second conferring risk. Allotypic extrapolation with HapMap data suggests that these effects may be attributable to allotypes rather than individual genetic variants. In psoriasis, both protective and risk variants have been identified, however no study has established whether these variants represent one or more signals. In BD, a recessive

interaction between the *ERAP1* locus and *HLA-B*51* confers strong disease risk, and interestingly, the same variant/allotype that confers BD risk is protective against AS and likely psoriasis. Going forward, genetic investigations of *ERAP1* and its role in the class I HLA-associated rheumatic diseases should focus on identifying naturally-occurring *ERAP1* allotypes based on both protein coding and noncoding variants. These naturally-occurring allotypes should be tested for disease association in large case-control collections, and their effect on *ERAP1* expression and ERAP1 enzymatic function should be interrogated.

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subsequent studies seeking to explore naturally-occuring ERAP1 haplotypes/allotypes. [PubMed: 23733883]

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Key Points

- Genetic variants and haplotypes of *ERAP1* influence susceptibility to AS, psoriasis and BD, and epistasis between *ERAP1* variants and disease-associated class I HLA alleles have been identified in each of these diseases.
- Based on comparisons of the existing literature with *ERAP1* allotypes assembled from European and East Asian HapMap populations, the most common European allotype (Hap10) affords protection against both AS and likely psoriasis, but it confers risk of BD.
- Additionally, Haps1–3 confer risk of AS and psoriasis in European populations, while Hap 2, the most common Asian allotype, is a strong risk factor in East Asians.
- Future investigations of *ERAP1* in rheumatic diseases should be directed at identifying the naturally-occurring allotypes, testing these allotypes for disease associations, and examining *ERAP1* expression levels and the enzymatic function of the ERAP1 protein produced by each allotype.

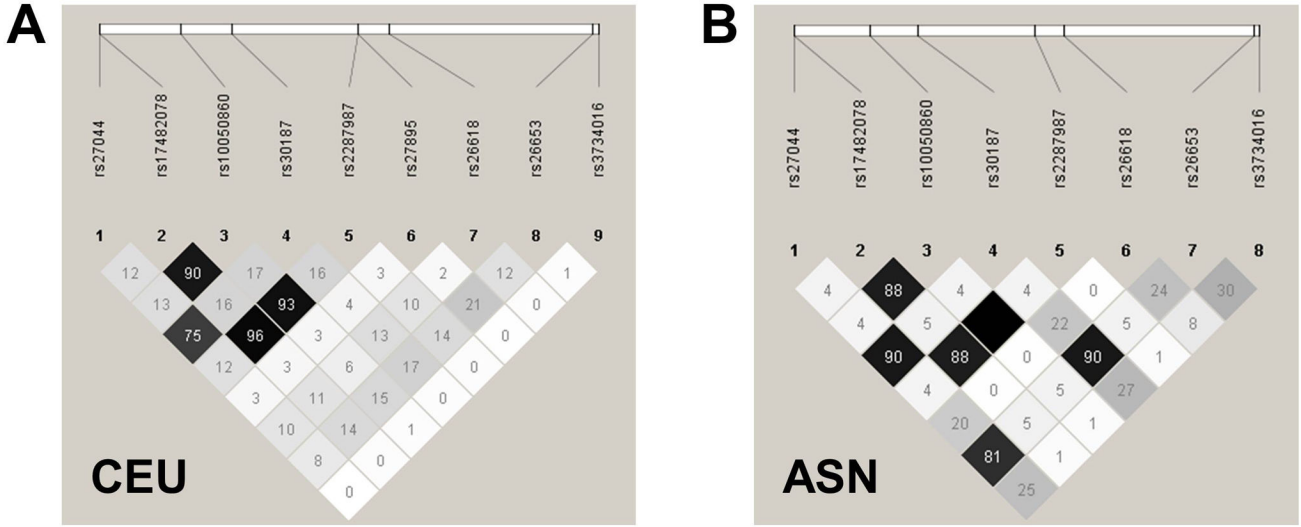

Figure 1. Linkage disequilibrium (LD) among common missense variants of *ERAP1* in CEU and ASN HapMap populations

The LD plots demonstrate pairwise r^2 values from the sets of common, missense variants of *ERAP1* derived from 80 unrelated members of the CEU population **(A)** and 80 unrelated members of the ASN population **(B)**. The minor allele of rs27895 had a frequency of 0.001 in the ASN population, and therefore it was excluded from LD analysis in that population. ASN, east Asian, the combined Japanese in Tokyo (JPT) and Han Chinese in Beijing (CHB) CEU, CEPH, Utah residents with ancestry from northern and western Europe.

Table 1

ERAP1 missense SNPs from the 1000 Genomes Project super-populations*

SNP ID	Amino acid change (ancestral/non-ancestral)	cDNA change (ancestral/non-ancestral)	EUR Freq. (% ancestral/ % non-ancestral)	AFR Freq. (% ancestral/% non-ancestral)	ASN Freq. (% ancestral/% non-ancestral)
rs72773968	T12I	C/T	86.2/13.8	99.5/0.5	99.6/0.4
rs3734016	E56K	G/A	95.9/4.1	91.9/8.1	82.8/17.2
rs26653	P127R	C/G	71.8/28.2	48.2/51.8	52.1/47.9
rs26618	I276M	A/G	77.3/22.7	80.4/19.6	71.4/28.6
rs27895	G346D	G/A	93.6/6.4	76.2/23.8	99.9/0.1
rs2287987	M349V	A/G	77.5/22.5	93.4/6.6	94.2/5.8
rs30187	K528R	A/G	35.0/65.0	40.2/59.8	45.3/54.7
rs10050860	D575N	G/A	77.1/22.9	93.5/6.5	94.2/5.8
rs17482078	R725Q	G/A	77.6/22.4	94.6/5.4	94.2/5.8
rs27044	Q730E	C/G	28.5/71.5	28.9/71.1	42.9/57.1

*Table includes *ERAP1* missense SNPs that were present at minor allele frequency > 0.05 in at least 1 of the 3 super-populations of the 1000 Genomes Project data. EUR, European superpopulation; AFR, African superpopulation; ASN, Asian superpopulation.

Table 2

Haplotypes of common *ERAP1* missense variants in HapMap populations*

										Freq. (%)	
AA position	**56**	**127**	**276**	**346**	**349**	**528**	**575**	**725**	**730**	**CEU**	**ASN**
Ancestral AA	E	P	I	G	M	K	D	R	Q		
Non-ancestral AA	K	R	M	D	V	R	N	Q	E		
Hap1 (*013) ancestral	E	P	I	G	M	K	D	R	Q	12.0	-
Hap2 (*002)	E	R	I	G	M	K	D	R	Q	13.7	43.7
Hap3	E	R	I	G	M	K	D	R	E	5.6	2.5
Hap4 (*008)	E	R	I	G	M	R	D	R	E	1.3	2.5
Hap5	E	R	I	D	M	R	D	R	E	7.5	-
Hap6	E	P	I	G	M	R	D	R	E	7.4	1.2
Hap7	K	P	I	G	M	R	D	R	E	2.5	24.4
Hap8	E	P	M	G	M	R	D	R	E	21.9	20.0
Hap9	E	P	M	G	M	R	N	R	E	1.2	-
Hap10 (*001)	E	P	I	G	V	R	N	Q	E	26.2	5.0
Freq. total										99.3	99.3

*Haplotypes were determined in 80 unrelated members of CEU population and 80 unrelated members of the ASN population. Haplotypes with frequencies > 1% in either CEU or ASN population are displayed. Genotypes for rs72773968 (T12I) were not present in the HapMap data. Non-ancestral AAs are shown as grey shaded boxes. AA, amino acid (single letter code); CEU, CEPH, Utah residents with ancestry from northern and western Europe; ASN, east Asian, the combined Japanese in Tokyo (JPT) and Han Chinese in Beijing (CHB).

Table 3

Summary of *ERAP1* haplotype associations in ankylosing spondylitis and comparison to *ERAP1* allotypes from HapMap CEU and ASN populations

Study	HapMap *ERAP1* allotypes	SNP identifiers and amino acid substitutions (ancestral allele/ non-ancestral allele)										p value
		rs72773968 T12I	rs3734016 E56K	rs26653 P127R	rs26618 I276M	rs27895 G346D	rs2287987 M349V	rs30187 K528R	rs10050860 D575N	rs17482078 R725Q	rs27044 Q730E	
WTCCC (3)							X	X	X	X	X	
Harvey *et al.* (1)				X			X	X	X	X	X	
Maksymowych *et al.* (18)			X	X	X			X	X		X	
	Hap10							G [R]	A [N]		G [E]	8.0×10^{-4}
	Hap10				A [I]			G [R]	A [N]			9.0×10^{-4}
	Haps6, 7, 10			C [P]	A [I]			G [R]				9.0×10^{-5}
	Haps1, 6, 10		C [E]	C [P]	A [I]							5.0×10^{-3}
	Hap3							A [K]	G [D]		G [E]	7.0×10^{-8}
	Haps1 – 3				A [I]			A [K]	G [D]			1.0×10^{-2}
	Haps2 - 3			G [R]	A [I]			A [K]				5.0×10^{-3}
	Haps2 - 5		C [E]	G [R]	A [I]							2.0×10^{-3}
Kadi *et al.* (19)							X	X	X	X	X	
								Omnibus association test				7.8×10^{-7}
	Haps1-3							A [K]	G [D]	G [R]		6.2×10^{-4}
	Hap10							G [R]	A [N]	A [Q]		5.7×10^{-6}
	Haps4 - 8							G [R]	G [D]	G [R]		0.15
Bettencourt *et al.* (20)							X	X	X	X	X	
	Haps4 - 8						A [M]	G [R]	G [D]	G [R]		0.5
	Haps1 – 3						A [M]	A [K]	G [D]	G [R]		6.8×10^{-3}
	Hap10						G [V]	G [R]	A [N]	A [Q]		3.1×10^{-2}

Individual markers that were tested for association with AS in each study are indicated by an X, where red indicates risk associated with minor allele, green indicates protection associated with minor allele, and black indicates a non-significant association. Haplotypic associations with AS in each study are shown in closed boxes, where red boxes indicate a risk haplotype and green boxes indicate a protective haplotype. Individual markers reported within haplotypes are noted as “cDNA nucleotide [amino acid]”. P values of haplotypic associations are extracted from the respective studies.