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Influence of ERAP1 and ERAP2 gene polymorphisms on disease susceptibility in different populations

Yufeng Yao[a,b], Nannan Liu[a], Ziyun Zhou[a], Li Shi[a,b,*]

[a] Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming 650118, China
[b] Yunnan Key Laboratory of Vaccine Research & Development on Severe Infectious Disease, Kunming 650118, China

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ABSTRACT

The endoplasmic reticulum aminopeptidases (ERAPs), ERAP1 and ERAP2, makes a role in shaping the HLA class I peptidome by trimming peptides to the optimal size in MHC-class I-mediated antigen presentation and educating the immune system to differentiate between self-derived and foreign antigens. Association studies have shown that genetic variations in *ERAP1* and *ERAP2* genes increase susceptibility to autoimmune diseases, infectious diseases, and cancers. Both *ERAP1* and *ERAP2* genes exhibit diverse polymorphisms in different populations, which may influence their susceptibly to the aforementioned diseases. In this article, we review the distribution of *ERAP1* and *ERAP2* gene polymorphisms in various populations; discuss the risk or protective influence of these gene polymorphisms in autoimmune diseases, infectious diseases, and cancers; and highlight how *ERAP* genetic variations can influence disease associations.

1. ERAP gene introduction

1.1. ERAPs play an important role in the antigen presentation process

An important part of the human immune system is the presentation of endogenous peptides by major histocompatibility complex (MHC) class I molecules to $CD8^+$ T cells. This educates the immune system to differentiate between self-derived and foreign antigens, resulting in the clearance of infected or tumor cells. This presentation process is the result of a series of reactions: 1) antigens are degraded in the cytosol into peptide precursors by the proteasome; 2) these precursors translocate, via transporter associated with antigen presentation (TAP) proteins, into the endoplasmic reticulum (ER) lumen; 3) within the ER, the precursors are trimmed by endoplasmic reticulum aminopeptidases (ERAPs) into final peptides and loaded onto MHC class I molecules; and 4) peptide-MHC class I complexes are released from the ER and transported via the Golgi to the plasma membrane for antigen presentation to $CD8^+$ T cells [1,2]. ERAPs have been found to trim peptides to the optimal size for MHC-I binding [3,4] but can also over-trim and destroy MHC-I ligands. During the process of MHC class I antigen presentation, they play a role to ensure the correct assembly of the peptide-loading complex (PLC) [5,6].

ERAPs, including ERAP1 and ERAP2, were initially identified as homologues of human placental leucine aminopeptidase or insulin-regulated aminopeptidase, and they belong to the oxytocinase subfamily of the M1 zinc metallopeptidases family [7]. They are expressed in various human tissues, such as the heart, placenta, and spleen, and are regulated by interferon-γ (IFN-γ) [3,8]. ERAP1 and ERAP2 share approximately 50% amino acid identity to common zinc-binding motifs for the enzymatic activity [9,10]. These enzymes trim the N-terminal of MHC I-bound precursor peptides into the correct and final lengths of 8–10 amino acids, which stabilizes the conformation of the MHC class I PLC. This is an essential step in exporting the MHC class I with bound peptide to the cell surface [6,9,11,12].

Abbreviations: AAU, Acute anterior uveitis; AFR, African; AMR, Admixed American; AS, ankylosing spondylitis; BD, Behcet's disease; BSCR, Birdshot chorioretinopathy; BU, Birdshot Uveitis; CC, Cervical carcinoma; CD, Crohn's disease; CT, Congenital Toxoplasmosis; EAS, East Asian; ER, endoplasmic reticulum; ERA, enthesitis-related arthriti; ERAPs, endoplasmic reticulum aminopeptidases; EUR, European; GWAS, genome-wide association study; HCV, Hepatitis C virus chronic infection; HLA, human leucocyte antigen; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; JIA, Juvenile Idiopathic Arthritis; KD, Kawasaki disease; LMP, molecular weight peptide; MHC, major histocompatibility complex; MS, multiple sclerosis; NSCLC, non-small cell lung carcinoma; PE, Preeclampsia; PLC, peptide-loading complex; PS, psoriasis; PsA, psoriatic arthritis; PsC, psoriatic without arthritis; PV, psoriasis vulgaris; RA, rheumatoid arthritis; SAS, South Asian; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphisms; SpA, spondyloarthritis; T1D, Type 1 Diabetes; TAP, transporter associated with antigen presentation

* Corresponding author at: Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming 650118, China.
E-mail address: shili.imb@gmail.com (L. Shi).

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1.2. The gene construction and molecular structure of ERAPs

The human *ERAP* genes are located on chromosome 5q15 in opposite orientation. The *ERAP1* gene is 47,379 bp in length and comprises 20 exons. Exon 6 and 7 encode the GAMEN consensus sequence and zinc-binding motif, respectively. Exon 19 encodes the splicing donor sequences. ERAP1 has two isoforms, isoform 1 and isoform 2. Isoform 1 contains 948 amino acids, and isoform 2 contains 941 amino acids with its termination codon in exon 19. The *ERAP2* gene is 41,438 bp in length and comprises of 19 exons, in which consensus motifs are encoded by exon 6 and 7. In exon 10, an alternative splice may cause an insertion of a stop codon, producing a non-catalytic, truncated form of *ERAP2* [9,13].

The crystal structure of ERAP1 revealed typical HEXXH(X18)E zinc-binding and GAMEN motifs, consisting of four domains-Domain I (residues 46–254), Domain II (residues 255–529), Domain III (residues 530–614), and Domain IV (residues 615–940) [11,14]. Domain I consists of eight stranded β-sheets and docks on top of domain II. Domain II contains the active site with the GAMEN and zinc-binding/gluzincin motifs. Among the conserved catalytic residues of M1 aminopeptidases, Glu320, His353, Glu354, His357, and Glu376, but not Tyr438, are structurally accommodated at an essentially identical position in Domain II. Domain III is similar to domain I, while domain IV is composed solely of α-helices [9].

The ERAP1 molecule can crystalize in two conformations, either a closed conformation or an open conformation. The closed conformation produces an active catalytic pocket within a large cavity formed by the domains I, II, and IV, while the open conformation is rather catalytically inactive due to a lack of an active catalytic pocket. Two major differences between the closed and open conformations may critically affect ERAP1 activity. The extensive domain transition between both conformations is essential for the bind-cleave-release catalytic activity of the enzyme during the peptide trimming process [11,15]. Recent study found some key *ERAP1* variants may lead to allele-dependent alternate expression of two distinct isoforms and significant differentiates in the types of ERAP-1 protein produced [16]. The structure and domain of ERAP2 are similar to that of ERAP1 [17]. The X-ray crystal structures of ERAP1 and ERAP2 indicate that their enzyme conformations are suited for trimming precursor peptides. Peptide trimming by ERAP1 has been confirmed by several studies, and ERAP2 has been shown to cooperate with ERAP1 to trim a large variety of precursor peptides in order to generate mature epitopes for binding to MHC class I molecules. Function as “molecular rulers”, ERAP1 can catch both N and C terminal residues of the precursor peptide [6]. ERAP1 prefers hydrophobic C-terminal residues and exhibits poor cleavage of N-terminal acidic and basic residues, while ERAP2 prefers to cleave N-terminal basic residues, especially arginine [4,18,19]. ERAP1 can cleave all peptide bonds except those involving Pro, and preferentially cleaves 9–16 longer peptides, and is virtually inactive with 8-mers and shorter peptides to fit the optimal length of MHC-I ligands [18]. On contrary, ERAP2 can cleave very few residues, being most efficient to Arg, and preferentially cleaves best 9-mers and shorter peptides, becoming progressively less efficient with longer ones [4,16,19,20]. Moreover, the binding substrates for both ERAP1 and ERAP2 are affected by their sequences downstream of their N-terminal sequences, but in different ways [4,21].

1.3. Polymorphisms and evolution of the ERAP genes

Although ERAP is an important component of the antigen presentation pathway, it exhibits a considerable amount of gene polymorphisms. There are 40,517 single nucleotide polymorphisms (SNPs) in the introns and exons of human *ERAP1* gene. However, *ERAP2* is not as polymorphic as *ERAP1*, with only 11,097 SNPs (https://www.ncbi.nlm.nih.gov/snp). Several studies have demonstrated that the polymorphic variations in ERAP1 and ERAP2 may affect the enzymatic activity and selectivity of these proteins [17,20,22–25]. Furthermore, these SNPs are located at essential structural positions that may change the conformation of ERAP1 and ERAP2 [9,14,24].

Population studies, disease association studies, and evolutionary analyses have suggested that the high level of polymorphisms in the human immune system is a result of host-pathogen balance selection and evolutionary pressures. Since ERAPs is involved in the antigen presentation process, it may be a target for the natural selection by several pathogens [26–28]. Sequence alignment analyses have revealed that both *ERAP1* and *ERAP2* genes have evolved under purifying selection. This balance selection has driven the recurrent appearance of destabilizing variants in ERAP2, and using 3-D-structure protein analysis, three positively selected sites 416Y, 420V, and 857A have been identified, but appear to not be involved in the proteolytic activity of the protein [29]. Furthermore, one of the positively selected sites (R528K, rs30187) in ERAP1 has been identified as a target of balancing selection [26,29]

Although ERAP1 and ERAP2 share 51% sequence homology and can form heterodimers, the evolution of these two genes is different [4]. Unlike *ERAP1*, which widely exists in mammals, *ERAP2* does not exist in rodents, including mice, rats, and guinea pigs. Evolutionary studies suggest that *ERAP2* originated from a relatively recent duplication of the *ERAP1* gene [28]. Frequency distribution analyses in different populations found that ERAP2 showed a strong and consistent signature under balancing selection, maintaining intermediate-frequency alleles. The estimated coalescent time of ERAP2 is about 1.44 Mya, while the common ancestor of ERAP1 variants is about 2.84 Mya [28].

2. ERAP1 and ERAP2 gene polymorphisms in populations

2.1. Polymorphisms of the ERAP1 gene in different populations

Since the genetic diversity of different ethnicities may contaminate the disease association results, we collected all the SNPs that were reported to be associated with autoimmune disease, infectious disease, and cancer, and compared their distributions across several ethnicities: African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS) (https://www.ncbi.nlm.nih.gov/snp/?term = ERAP1). Some polymorphic variation distal from the active site of ERAP1 can translate to changes in function, which affect enzymatic activity and substrate binding. The variation of rs30187 (K528R), which has been confirmed to directly reduce the activity of ERAP1 or indirectly alter the expression levels of ERAP1, showed similar frequencies of 35–45% in different populations worldwide. Rs10050860 (N575D) and rs17482078 (Q725R), located in high linkage disequilibrium (LD), conferred protection against several diseases through reduced peptide trimming and antigen presentation by MHC class I molecules[30–32]. The frequencies of rs10050860 were 0.065, 0.131, 0.058, 0.229, and 0.069 in AFR, AMR, EAS, EUR and SAS ethnicities, respectively, and the frequencies of rs17482078 were similar to rs10050860, with frequencies of 0.054, 0.124, 0.058, 0.224, and 0.065, respectively. Rs27044 (Q730E), which can influence ERAP1 length preferences, showed the highest frequencies in EAS (0.429) and AMR (0.349), but exhibited lower frequencies in AFR (0.289), EUR (0.285), and SAS (0.269).

2.2. Polymorphisms of the ERAP2 gene in different populations

The polymorphisms in *ERAP2* were not as high as those in *ERAP1*. The allelic substitution of Asn to Lys, rs2549782 (K392N), which is located adjacent to the catalytic center, may cause a marked change in the substrate specificity of ERAP2 [24]. Rs2549782 is in high LD with rs2548538 (P435P), rs2287988 (Q563Q), rs1056893 (S775S), and rs2248374 (located in splice /intron region) in most of the populations around the world. The frequencies of these five SNPs were similar, and the minor allele frequencies in AFR, AMR, EAS, EUR, and SAS

ethnicities were 0.399, 0.421, 0.472, 0.480 and 0.472, respectively (https://www.ncbi.nlm.nih.gov/snp/?term = ERAP2). The data from association studies were mostly comparable with NCBI with only a small difference and the mean value of the minor allele of rs2549782, rs2548538, rs2287988, rs1056893, and rs2248374 was 0.375, 0.383, 0.383, 0.380 and 0.418, respectively [26,33–42]. However, in Chileans (mixed white and Amerindian), rs2549782 was not in LD with rs2548538. These Chilean ERAP2 haplotype structure may allow the expression of the major T allele in rs2549782 encoding Asn, which could impact peptide trimming and antigen presentation, indicating the unrecognized complexity of the ERAP2 locus in different populations [33]. Compared to the above SNP coding changes, rs17408150 (Q669L) and rs17486915 (H689H) showed frequencies almost lower than 5%. Other SNPs in introns exhibited higher frequencies, but limited diversity in different populations.

2.3. ERAP gene haplotype distribution in different populations

The haplotypes were constructed using different SNPs at *ERAP* genes based on the LD between these SNPs. However, the distribution of LD differed in various populations. We previously constructed haplotypes using four SNPs of *ERAP1* in both the Han Chinese and Polish populations and found that the Chinese exhibited LD between rs26653 and rs30187, rs26653 and rs27044, and rs30187 and rs27044, whereas only two SNPs, rs30187 and rs27044, were in comparable LD in the Poles[43]. Vanhille et al. constructed haplotypes using five SNPs (rs2549782/rs2548538/rs2248374/rs2287988/rs1056893) of *ERAP2* [33], and found haplotypes of these five SNPs were in strong LD in African-Americans; however, SNP rs2549782 was not found to be in LD with the other four SNPs in the Chilean population. Though rs2549782 and rs2248374 were reported to either affect the substrate specificity of ERAP2 or associate with ERAP2 protein expression, the LD between these two SNPs were identified in African-American populations, but not in Chilean populations [33].

According to the LD analysis, the haplotypes were constructed and their frequencies also exhibited diversity in different populations (Table 1). Ombrello et al. examined the 1000 Genomes Dataset and reported 10 haplotypes with a frequency > 1% in one or more populations. These haplotypes are derived from the ancient haplotype 1, rs3734016/rs26653/rs26618/rs27895/rs2287987/rs30187/rshttps://doi.org//10050860/rs17482078/rs27044-GCTCTTCCG. Haplotype 10 (GCTCCCTTC) and haplotype 8 (GCCCTCTTC) are predominant in CEU (CEU, CEPH, Utah residents with ancestry from northern and western Europe) populations with frequency of 26.2% and 21.9%, respectively, while haplotype 2 (GGTCTTCCG) and haplotype 7 (ACTCTTCCG) are predominant in ASN (East Asian, the combined Japanese in Tokyo and Han Chinese in Beijing) populations with frequencies of 43.7% and 24.4% [44]. In our previous study, the haplotype rs26653/rs26618/rs30187/rs27044-CTTG is most predominant in the Chinese population, with a frequency of 47.6%. However, it is the third common haplotype in the Poles, with frequencies of 14%. The most predominant haplotype, rs26653/rs26618/rs30187/rs27044-GTCC, in the Poles is the third common haplotype in the Chinese, with frequencies of 31.7% and 20.2%, respectively [43]. The predominant haplotype in the Dutch was rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653-CCCGCG (21.7%), and the predominant haplotype in the Indonesian-Balinese was GCCGTC (39.5%). Neither of these two haplotypes were identified in the Indonesian-Javanese population. Haplotype rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653-GTCGTC was the predominant haplotype in the Indonesian-Javanese population, with frequencies as high as 42.0%. However, it was only 18.1% in the Dutch. In addition, Haplotype rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653-CCCGTC and CCCATG exist in the Dutch and Indonesia-Javanese populations, with frequencies of 8.1% and 1.0%, and 4.7% and 6.2%, respectively [45,46].

3. ERAP1 and ERAP2 confer susceptibility to diseases

3.1. ERAP1 and ERAP2 confer susceptibility to autoimmune diseases

3.1.1. Association of ERAP1 alleles and genotypes with autoimmune diseases

In 2007, a genome-wide association study (GWAS) of autoimmune diseases conducted by the Wellcome Trust Case Control Consortium and the Australo-Anglo-American Spondylitis Consortium reported the association of ERAP1 with ankylosing spondylitis (AS) [30]. Then, Australo-Anglo-American Spondyloarthritis C et al. confirmed this result [31]. Studies have indicated that *ERAP1* SNPs may influence the creation of antigen-derived peptides for presentation to the immune system, shedding light on the development of autoimmune diseases [4,6].

In 2016, Ellinghaus et al. analyzed Immunochip genotype data of AS, Crohn's disease (CD), psoriasis (PS), primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) and identified the common shared risk loci, which indicated that these autoimmune diseases may share common etiologies [47]. For *ERAP1*, SNPs are associated with AS [30,31,36,48–66], PS [67–72], spondyloarthritis (SpA) [65,73], rheumatoid arthritis (RA) [74], psoriatic arthritis [75], psoriasis vulgaris (PV) [37], systemic lupus erythematosus (SLE) [76], Kawasaki disease [77], multiple sclerosis (MS) [78], CD [78], birdshot uveitis (BU) [42], type 1 diabetes (T1D) [79], Behcet's disease (BD) [80], and inflammatory bowel disease (IBD) [41]. About 60 SNPs were involved in these studies, including rs27037, rs7711564, rs27044, rs17482078, rs10050860, rs30187, rs27434, rs2287987, rs27895, rs3734016, rs7277396, rs151823, rs26618, and rs26653, all of which have been reported in more than one population (Supplementary Table 1).

The polymorphism variation of rs30187(R528) has been reported as a major risk factor for autoimmune diseases, which has been found to be associated with AS in the Han Chinese, Iranian, Romanian, and Spanish populations and MS in the Italian populations [53,59,61,65]. Moreover, the minor allele T has been identified to increase susceptibility to several diseases in various populations, including AS in British, Canadian, Portuguese, Han Chinese, and Korean populations; AS and acute anterior uveitis in British, Australian, and New Zealand populations; BU in Dutch populations; CD and MS in Italian populations; PS in Caucasian and Indian populations; PV in Polish populations; SpA in Belgian, French and Romanian populations; and T1D in British populations [30,50,51,53,55,58,59,61,63,65]. However, the risk has not been identified with AS in Hungarian, Russian and Turkish populations, BU in Spanish ancestry, enthesitis-related arthritis in Indian populations, or IBD in Caucasians, or SLE in Caucasians [41,49,54,64,66,76]. One of the reasons of rs30187 associated with the autoimmune diseases may due to its influence on the kinetics of the conformational transition between the active and inactive states of the enzyme [81,82]. The other reason is that these polymorphisms could affect the expression level, as well as the relative levels of the two isoforms. Differences in ERAP1 expression have an obvious effect on peptide cleavage and the differences in the posttranscriptional dynamics between the two isoforms may affecting isoform proportions on the overall expression of the ERAP1 protein [16,81].

Rs27044 (Q730E) has been reported to correlate with the production of different lengths of antigen peptides, which results in a change in the susceptibility to some autoimmune diseases [15,22]. The G allele have been identified as a risk factor for AS in British, Hungarian, Portuguese, Romania, Korean, and Han Chinese populations, the genotype is associated with AS in Han Chinese, Hungarian, and Romanian populations. However, the association of G allele with AS have not been found in Canadian, Russian, Spanish, or Turkish populations [30,48,51,54,58,59,61–65]. A meta-analysis in a total of 19,902 AS patients and 39,750 controls from 22 studies revealed a significant association between AS and the G allele of rs27044 [83]. The G allele risk has also been investigated in several diseases studies: for BU in the Dutch but not in the Spanish [42], for PS in both Han Chinese and

Table 1
Association studies between ERAP haplotypes and diseases in different populations.

Disease	Ethnicity	Case	Control	Haplotypes	Fre. (%)		P value	OR (95%CI)	S/P	References
					Case	Control				
AS	Canadian	992	1437	rshttps://doi.org//10050860/rs30187/rs26618 T/C/T			9×10^{-4}		P	[60]
AS	Canadian	992	1437	rshttps://doi.org//10050860/rs30187/rs26618 C/T/T			0.010		S	[60]
AS	Iranian	381	312	rs13167972/rs469876/rs30187/rs27434 A/A/C/G	8.9	9.8	0.672			[53]
AS	Iranian	387	316	rs13167972/rs469876/rs30187/rs27434 A/A/T/A	22.6	16.0	0.009		S	[53]
AS	Iranian	387	316	rs13167972/rs469876/rs30187/rs27434 A/A/T/G	11.2	8.8	0.185			[53]
AS	Iranian	381	316	rs13167972/rs469876/rs30187/rs27434 A/G/C/G	18.1	21.1	0.182			[53]
AS	Iranian	387	316	rs13167972/rs469876/rs30187/rs27434 A/G/T/G		0.3	–			[53]
AS	Iranian	351	297	rs13167972/rs469876/rs30187/rs27434 G/A/C/A		0.2	–			[53]
AS	Iranian	278	279	rs13167972/rs469876/rs30187/rs27434 G/A/C/G	20.2	26.9	0.011		P	[53]
AS	Iranian	387	316	rs13167972/rs469876/rs30187/rs27434 G/A/T/A	16.5	15.0	0.519			[53]
AS	Iranian	387	316	rs13167972/rs469876/rs30187/rs27434 G/A/T/G	1.7	0.3	0.076			[53]
AS	Iranian	387	316	rs13167972/rs469876/rs30187/rs27434 G/G/C/G	0.7	1.6	0.321			[53]
AS	Russian	84	77	rs17482078/rshttps://doi.org//10050860/rs2287987 C/C/T	86.0	75.0	0.026	1.960(1.120–3.460)	S	[54]
AS	Russian	84	77	rs17482078/rshttps://doi.org//10050860/rs2287987 T/T/C	8.0	20.0	0.003	0.330(0.170–0.670)	P	[54]
AS	Portuguese	200	559	rs17482078/rshttps://doi.org//10050860/rs30187/rs2287987 C/C/C/T	38.0	41.0	0.480			[63]
AS	Portuguese	200	559	rs17482078/rshttps://doi.org//10050860/rs30187/rs2287987 C/C/T/T	46.0	37.0	0.007		S	[63]
AS	Portuguese	200	559	rs17482078/rshttps://doi.org//10050860/rs30187/rs2287987 T/T/C/T	15.0	21.0	0.031		P	[63]
AS	Canadian	992	1437	rs26618/rs3734016/rs26653 T/G/C			0.002		S	[60]
AS	Canadian	992	1437	rs26618/rs3734016/rs26653 T/G/G			0.005		P	[60]
AS	Chinese	796	1150	rs27037/rs27980/rs27044 G/C/C	8.5	11.9	0.002	0.690(0.550–0.870)	P	[61]
AS	Chinese	797	1150	rs27037/rs27980/rs27044 T/A/G	0.8	1.2	0.004	0.210(0.070–0.610)	P	[61]
AS	Chinese	796	1149	rs27037/rs27980/rs27044 T/C/G	47.5	39.3	$< 1 \times 10^{-5}$	1.380(1.120–1.580)	S	[61]
AS	Romania	137	139	rs27044/rs30187 T/C	9.9	9.3	0.800			[65]
AS	Romania	137	139	rs27044/rs30187 C/C	60.1	67.8	0.050			[65]
AS	Romania	137	139	rs27044/rs30187 T/G	29.8	22.7	0.050			[65]
AS	Canadian	992	1437	rs27044/rshttps://doi.org//10050860/rs30187 C/C/T			7×10^{-8}	1.810(1.460–2.440)	S	[60]
AS	Canadian	992	1437	rs27044/rshttps://doi.org//10050860/rs30187 C/T/C			8×10^{-4}		P	[60]
AS	Chinese	100	100	rs27434/rs7711564 A/C	32.0	19.0	0.005	2.082(1.253–3.459)	S	[56]
AS	Canadian	992	1437	rs30187/rs26618/rs26653 C/T/G			9×10^{-5}	0.770(0.670–0.880)	P	[60]
AS	Canadian	992	1437	rs30187/rs26618/rs26653 T/T/C			0.005		S	[60]
AS	Chinese	100	100	rs7711564/rs27434 G/C	15.0	13.5	1.000	0.961(0.502–1.841)		[56]
AS	Chinese	100	100	rs7711564/rs27434 A/G	21.5	23.0	0.599	1.155(0.688–1.942)		[56]
AS	Chinese	100	100	rs7711564/rs27434 G/G	36.0	44.5	–	–		[56]
AS*	Romania	150	108	rs27044/rs30187 C/C	59.3	70.5	0.010		P	[65]
AS*	Romania	105	108	rs27044/rs30187 C/T	10.0	5.6	0.090			[65]
AS*	Romania	105	108	rs27044/rs30187 G/T	30.6	23.8	0.100			[65]
BU	Dutch	84	890	rs2287987/rs10044354 C/C	14.0	8.0	0.330	1.340(0.750–2.400)		[42]
BU	Spanish	46	2103	rs2287987/rs10044354 C/C	10.0	8.0	0.630	1.200(0.570–2.530)		[42]
BU	Dutch	84	890	rs2287987/rs10044354 T/C	23.0	49.0	3.5×10^{-8}	0.300(0.200–0.460)	P	[42]
BU	Spanish	46	2103	rs2287987/rs10044354 T/C	37.0	51.0	0.006	0.530(0.340–0.840)	P	[42]
BU	Dutch	84	890	rs2287987/rs10044354 T/T	39.0	31.0	0.050	1.440(0.990–2.080)		[42]
BU	Spanish	46	2103	rs2287987/rs10044354 T/T	34.0	30.0	0.360	1.230(0.790–1.920)		[42]
BU	Dutch	84	890	rs2287987/rs10044354 C/T	24.0	12.0	1.4×10^{-6}	3.100(1.960–4.900)	S	[42]
BU	Spanish	46	2103	rs2287987/rs10044354 C/T	19.0	11.0	0.004	2.290(1.310–4.020)	S	[42]
CC	Dutch	127	124	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/T/G/T/C	6.5	4.7	0.399	0.719(0.333–1.553)		[46]
CC	Dutch	127	124	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/C/G/C/G	24.2	21.7	0.498	0.866(0.571–1.314)		[46]
CC	Dutch	127	124	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/C/G/T/C	5.6	8.7	0.190	0.585(0.792–3.173)		[46]
CC	Dutch	127	124	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/C/G/T/G	1.5	8.7	0.488	0.810(0.446–1.471)		[46]
CC	Indonesian-Bali	103	68	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/T/A/T/G	11.8	9.2	0.697	1.310(0.360–4.830)		[45]
CC	Indonesian-Java	98	105	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/T/G/T/C	1.3	2.6	0.409	0.490(0.090–2.530)		[45]
CC	Indonesian-Bali	103	68	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 G/C/C/G/T/C	32.4	39.5	0.481	0.730(0.310–1.720)		[45]
CC	Indonesian-Java	98	105	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 G/C/T/A/T/C	7.5	5.4	0.420	1.430(0.610–3.370)		[45]
CC	Dutch	127	124	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 G/C/T/G/T/C	8.8	18.1	0.002	2.282(1.327–3.923)	P	[46]
CC	Indonesian-Java	98	105	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/C/A/C/G	5.6	3.7	0.402	1.540(0.570–4.170)		[45]
CC	Indonesian-Java	98	105	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/C/A/T/G	11.3	6.2	0.090	1.930(0.900–4.130)		[45]

(*continued on next page*)

Table 1 (*continued*)

Disease	Ethnicity	Case	Control	Haplotypes	Fre. (%)		P value	OR (95%CI)	S/P	References
					Case	Control				
CC	Dutch	127	124	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/C/A/T/G	4.8	4.7	0.952	0.975(0.430–2.214)		[46]
CC	Indonesian-Java	98	105	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/C/G/C/G	35.6	35.5	0.968	1.010(0.650–1.550)		[45]
CC	Indonesian-Java	98	105	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/C/G/T/C	1.3	1.0	0.865	1.200(0.170–8.500)		[45]
CC	Indonesian-Bali	103	68	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/T/A/C/G	8.8	3.9	0.316	2.350(0.450–12.320)		[45]
CC	Indonesian-Bali	103	68	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/C/T/G/C/G	32.4	35.5	0.763	0.870(0.370–2.050)		[45]
CC	Indonesian-Java	98	105	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/T/C/G/T/G	5.0	1.5	0.075	3.390(0.880–13.010)		[45]
CC	Dutch	127	124	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/T/C/G/T/G	24.2	18.4	0.114	0.708(0.461–1.088)		[46]
CC	Indonesian-Bali	103	68	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 C/T/T/G/T/G	5.9	6.6	0.902	0.890(0.160–4.820)		[45]
CC	Indonesian-Bali	103	68	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 G/C/C/A/T/C	2.9	2.6	0.933	1.120(0.100–12.800)		[45]
CC	Indonesian-Java	98	105	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 G/C/T/G/T/C	31.9	42.0	0.051	0.650(0.420–1.000)		[45]
CC	Dutch	127	124	rs27044/rshttps://doi.org//10010860/rs30187/rs3734016/rs26618/rs26653 G/C/T/G/T/G	13.7	13.0	0.813	0.940(0.562–1.572)		[46]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 G/C/C/C	0	0.0	–	–		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 G/T/T/G	0.0	1.0	–	–		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 C/C/C/G	28.2	22.8	0.029	1.311(1.028–1.671)		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 C/C/T/C	2.7	4.3	0.083	0.600(0.334–1.076)		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 C/C/T/G	19.0	20.0	0.548	0.922 (0.707–1.202)		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 C/T/T/C	3.5	3.3	0.870	1.050(0.586–1.881)		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 G/C/C/G	0.4	0.5	–	–		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 G/C/T/C	0.0	0.0	–	–		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 G/C/T/G	0.1	0.2	–	–		[91]
HCV	YNH	376	324	rs27044/rs30187/rs26618/rs26653 G/T/T/C	46.3	47.9	0.387	0.911(0.737–1.125)		[91]
NSCLC	YNH	420	385	rs27044/rs30187/rs26618/rs26653 C/C/C/G	23.2	28.7	0.003	1.406(1.122–1.762)		[43]
NSCLC	Polish	317	506	rs27044/rs30187/rs26618/rs26653 C/C/C/G	25.5	26.0	0.853	1.022(0.814–1.282)		[43]
NSCLC	YNH	420	385	rs27044/rs30187/rs26618/rs26653 C/T/T/C	3.1	3.7	0.430	1.240(0.722–2.129)		[43]
NSCLC	Polish	317	506	rs27044/rs30187/rs26618/rs26653 C/T/T/C	7.2	7.3	0.962	1.009(0.688–1.481)		[43]
NSCLC	Polish	317	506	rs27044/rs30187/rs26618/rs26653 G/T/T/C	34.7	31.7	0.178	0.865(0.700–1.069)		[43]
NSCLC	YNH	420	385	rs27044/rs30187/rs26618/rs26653 G/T/T/C	47.6	35.3	< 0.00001	0.632(0.517–0.774)	S	[43]
NSCLC	YNH	420	385	rs27044/rs30187/rs26618/rs26653 C/C/G/T	20.2	21.5	0.305	1.135(0.891–1.446)		[43]
NSCLC	Polish	317	506	rs27044/rs30187/rs26618/rs26653 C/C/G/T	14.0	12.3	0.303	0.856(0.636–1.151)		[43]
NSCLC	Polish	317	506	rs27044/rs30187/rs26618/rs26653 C/C/T/C	11.8	15.3	0.041	1.351(1.012–1.803)	P	[43]
NSCLC	YNH	420	385	rs27044/rs30187/rs26618/rs26653 C/C/T/C	4.3	2.5	0.057	0.585(0.334–1.024)		[43]
NSCLC	YNH	420	385	rs27044/rs30187/rs26618/rs26653 G/C/T/C	0.1	3.3	< 0.00001	58.560(7.630–449.230)	P	[43]
NSCLC	Polish	317	506	rs27044/rs30187/rs26618/rs26653 G/C/T/C	6.2	7.3	0.418	1.176(0.793–1.744)		[43]
psoriasis	Indian	911	1020	rs27044/rs30187/rs26653 C/C/C	10.8	12.4	0.300	0.870(0.680–1.130)		[69]
psoriasis	Indian	911	1020	rs27044/rs30187/rs26653 C/C/G	33.9	41.8	0.000	0.730(0.620–0.870)	P	[69]
psoriasis	Indian	911	1020	rs27044/rs30187/rs26653 C/T/C	15.7	14.5	0.320	1.120(0.890–1.420)		[69]
psoriasis	Indian	911	1020	rs27044/rs30187/rs26653 C/T/G	5.2	3.7	0.061	1.470(0.980–2.220)		[69]
psoriasis	Indian	911	1020	rs27044/rs30187/rs26653 G/C/C	2.9	1.3	–	–		[69]
psoriasis	Indian	911	1020	rs27044/rs30187/rs26653 G/C/C	2.1	1.9	–	–		[69]
psoriasis	Indian	911	1020	rs27044/rs30187/rs26653 G/T/C	19.4	15.3	0.005	1.370(1.100–1.700)	S	[69]
psoriasis	Indian	911	1020	rs27044/rs30187/rs26653 G/T/G	9.9	9.1	0.400	1.130(0.850–1.490)		[69]
SpA	Belgian	320	248	rs17482078/rshttps://doi.org//10050860/rs30187 C/C/C	43.0	43.0	0.357			[73]
SpA	French	414	384	rs17482078/rshttps://doi.org//10050860/rs30187 C/C/C	37.0	40.0	0.181			[73]
SpA	Belgian	320	248	rs17482078/rshttps://doi.org//10050860/rs30187 T/T/C	12.0	19.0	0.001		P	[73]
SpA	French	414	384	rs17482078/rshttps://doi.org//10050860/rs30187 T/T/C	14.0	22.0	7.2×10^{-5}		P	[73]
SpA	Belgian	320	248	rs17482078/rshttps://doi.org//10050860/rs30187 C/C/T	39.0	30.0	0.001		S	[73]
SpA	French	414	384	rs17482078/rshttps://doi.org//10050860/rs30187 C/C/T	41.0	36.0	0.039		S	[73]
SpA*	Romania	150	108	rs27044/rs30187 C/T	9.3	5.6	0.100			[65]
SpA*	Romania	150	108	rs27044/rs30187 C/C	57.0	70.5	0.002		P	[65]
SpA*	Romania	150	108	rs27044/rs30187 G/T	33.5	23.8	0.010		S	[65]

P: Protective, S: Susceptible, AS: ankylosing spondylitis, AS*: AS with HLA-B27 +, BU: birdshot Uveitis, CC: cervical carcinoma, HCV: hepatitis C chronic infection, NSCLC: non-small cell lung carcinoma, SpA: spondyloarthritis, SpA*: SpA with HLA-B27 +, YNH: YNH.

Indian populations [68,69], for SpA in the French, but not in the Belgians [73]. The polymorphism of rs27044 is located within the extended internal cavity of ERAP1, where it may interact with the C-terminal moiety of a long peptide substrate, affecting the length selection of the antigen presentation process and increasing the preference of ERAP1 for shorter substrates which is likely related to the involvement of this residue in substrate binding [12,22].

The rs17482078 SNP was shown to be associated with AS in British, Caucasian, Han Chinese, Hungarian, Portuguese, Russian and Spanish populations, as well as with BU in Dutch populations, and SpA in French populations [30,36,54,63,66]. The rs10050860 SNP was reported to be associated with AS in British, Canadian, Caucasian, Hungarian, Portuguese, Russian, Spanish and Han Chinese populations; BU in Spanish and Dutch populations; SpA in Belgian population; and BD in Han Chinese population [30,42,51,54,66,73,80]. Similar to the rs27434 (A356A) SNP, both rs2287987 (V349M) and rs26653 (P127R) exhibited risk to certain autoimmune diseases in specific populations [31,36,51,56]. On the contrary, some SNPs, including rs26618 (M276I), rs72773968 (I12T), rs3734016 (K56E), rs27895 (D346G), rs2287987, did not show an association, even though they were located in the functional domain of ERAP1 [42,59,73].

Aside from SNPs located within the exon, SNPs located within introns have also been studied in different autoimmune diseases and have been shown to be more diverse in different population. For example, rs27037 has been studied in British, Han Chinese, and Turkish AS patients and healthy controls. Both the T allele or TG genotype showed an increased risk for AS in British and Han Chinese populations in the Zhejiang, Beijing, Taiwan provinces, and Shanghai + Nanjing city; however, it was not found in Turkish and another Han Chinese population in Jiangsu province [31,36,48,52,58,61,64]. The SNP rs7711564 showed an association with AS in the Han Chinese in the Shanghai + Nanjing cites, but not in the Zhejiang and Shanxi provinces or in Turkish populations [36,56–58,64]. Similarly, rs27980 showed an association with AS in the Han Chinese in Zhejiang, and Taiwan provinces, and Shanghai + Nanjing cities, but not in Beijing and Jiangsu provinces or in Turkish populations [36,48,52,57,58,61,64]. For rs27434, the A allele or AG genotype had an increased risk for AS in British, Iranian and Han Chinese populations in the Zhejiang, Beijing, Shanxi provinces, but not in Shanghai + Nanjing cities [31,36,51–53,56,57]. The discrepancy in these results indicates that, even for the same disease in Han Chinese population, the risk of specific diseases from certain SNPs is ambiguous. Though the Han Chinese originate from the Huaxia group, the genetic distinct between northern and southern Han has been identified using short tandem repeats (STRs), SNP, and HLA genes [84–86]. Moreover, the integration with other ethnic populations during the past 5000 years and habitation in vast landscapes with an enormous population makes the Han Chinese more complex. These results have also been investigated in Canadians with AS. The minor allele T of rs30187 showed an increased risk for AS in Alberta, but not in Newfoundland and Toronto Canadians [60].

3.1.2. Association of ERAP2 genes and genotypes with autoimmune diseases and immune-relevant diseases

Studies that have investigated the associations between ERAP2 and autoimmune diseases have focused on AS juvenile idiopathic arthritis (JIA), PV, IBD, birdshot chorioretinopathy (BSR), and BU (Supplementary Table 2). The minor allele G of rs2549782 causes a non-conservative amino acid substitution, which may alter the enzymatic activity and substrate specificity of ERAP2 [24]. In 2009, Johnson et al. investigated the association of ERAP2 genes with pre-eclampsia (PE) in an Australian/New Zealand familial cohort and in a Norwegian case/control cohort [87]. They revealed that rs2549782 was a novel PE risk in both populations. Then, Hill et al. confirmed that the minor allele G of rs2549782 was associated with an increased risk for PE in the African American population, but it is not a risk factor in the Chilean population [34]. The increased PE susceptibility risk of the G allele of rs2549782 has not been found in the Chinese Han [40]. Furthermore, no risk has been identified concerning the association of rs2549782 with IBD in Spanish populations [41]. Rs2549782 was in LD with rs2248374, which is associated with a splice-site variant caused by the major allele G of rs224837 that results in nonsense-mediated RNA decay, precluding protein expression [88]. The variation of rs2248374 has been reported be a risk for PV in Polish populations and BU in Dutch populations [42]. On the contrary, the association of rs2248374 variation has not been identified with BU or IBD Spanish populations, or PE in African-American and Chilean populations [33,41,42]. For AS be considered, the result is discrepancy. In 2011, Harvey et al. did not found the association between rs2248374 and AS in UK origin population [35]. However, in 2012, Robinson, et al. studied European Immunochip HLA-B27-positive patients, HLA-B*27-positive controls and unselected European controls, and found this SNP was significant association with AS, which indicating that the loss-of-expression of ERAP2 induced by G allele of rs2248374 is protective in both HLA-B*27-negative and HLA-B*27-positive disease [28,89].

Similar to *ERAP1*, several SNPs in the intron region of *ERAP2* also showed an association with autoimmune diseases. Interestingly, rs7705093 increased susceptibility to BSR in Dutch, Spanish and British populations. This was confirmed by functional analyses that revealed that the polymorphism risk allele near *ERAP2* was strongly associated with high mRNA and protein expression of *ERAP2* in B cells [39]. The G allele of another SNP, the rs75862629 in the ERAP2 promoter, strongly down-modulates ERAP2 expression and couples with a significant higher expression of ERAP1 [82]. In an association study with BU, the minor allele T of rs10044354 showed increased risk in both Dutch and Spanish populations [42]. In addition, the minor G allele of rs27290 showed increased risk for JIA in Australian populations [90].

3.1.3. Association of ERAP haplotypes with autoimmune diseases

The ERAP haplotypes were constructed based on the coding SNPs and analyzed for increased susceptibility or protectively for AS, BU, PS and SpA (Table 1) [42,53,54,56,61,63,65].

For AS, specific haplotypes of the minor T allele of rs30187 showed increased susceptibility in certain populations: rshttps://doi.org//10050860/rs30187/rs26618-CTT, rs27044/rshttps://doi.org//10050860/rs30187-CCT, and rs27044/rshttps://doi.org//10050860/rs30187-CCT in Canadian; rs13167972/rs469876/rs30187/rs27434-AATA in Iranian; and rs17482078/rshttps://doi.org//10050860/rs30187/rs2287987-CCTT in Portuguese. On the contrary, specific haplotypes of the minor C allele of rs30187 were protective for AS in certain populations: rshttps://doi.org//10050860/rs30187/rs26618-TCT, rs27044/rshttps://doi.org//10050860/rs30187-CTC, and rs17482078/rshttps://doi.org//10050860/rs30187/rs2287987-TTCC in Canadian; rs13167972/rs469876/rs30187/rs27434-GACG in Iranian; and rs17482078/rshttps://doi.org//10050860/rs30187/rs2287987-TTCC in Portuguese [53,54]. These haplotypes contain some strong risk alleles as rs27044, rs10050860, and rs26653. However, this association was not comparable in all populations. For example, the rs27044/rs30187-TC, CC, and TG haplotypes were not associated with AS in Romanians, and the rs7711564/rs27434-GC, AG, and GG haplotypes were not associated with AS in the Chinese Han [56,65].

For BU, Kuiper et al. found that the combined rs2287987/rs10044354 haplotype was associated with BU more strongly than either SNP alone [42]. Moreover, rs2287987/rs10044354-CT was a risk factor in both Dutch and Spanish populations, which resulted in significantly altered expression of ERAP1 isoforms in transcriptomic data, decreased protein expression, and distinct enzymatic activity [42].

For SpA, the rs17482078/rshttps://doi.org//10050860/rs30187-CCT haplotype was significantly associated with an increased risk of SpA in the Dutch and Belgian, whereas the TTC haplotype was associated with a reduced risk of SpA [73]. In the PS study in Indian populations, the most frequent haplotype, rs26653/rs30187/rs27044-GCC, which was comprised of the major alleles of the three SNPs, showed significantly reduced risk to the disease, while the rs26653/

rs30187/rs27044-CTG haplotype, which contained the minor alleles, showed significantly increased risk to the disease [69].

3.2. ERAP1 and ERAP2 confer susceptibility to infectious disease

Since the antigen presentation system plays a major role in the interaction between pathogens and host resistance, ERAPs may be potential targets and modulators of infectious diseases. In 2010, Cagliani *et al.* studied the association of ERAPs and human immunodeficiency virus 1 (HIV-1) infection and found that the polymorphisms of the *ERAP1* and *ERAP2* genes may be maintained through long-standing balancing selection, and that ERAP2 conferred resistance to HIV infection likely via the presentation of a distinctive peptide repertoire to $CD8^+$ T cells [26]. The rs2549782 of *ERAP2* gene is associated with HIV in Italians which the TT genotype is over-represented in this HIV-1-exposed seronegative group [26]. The risk of rs2549782 has also been identified in Spanish populations exposed to HIV-1 infection by intravenous drug users [38]. In our previous study, we did not find the association of rs2549782 with HCV chronic infection in the Chinese Han [91]. However, we found that the A allele of rs2248374 (located in splice /intron region) showed increased risk for chronic HCV compared with the G allele [91]. In 2010, Tan *et al.* genotyped seven SNPs in *ERAP2* in congenital toxoplasmosis patients and healthy controls in North America, but did not identify an association between *ERAP2* and *Toxoplasma gondii* infection [92].

Polymorphisms in rs149173 (intron region) have been associated with susceptibility to *T. gondii* infection in American population, but not with HIV infection in Italian population [26,92]. Polymorphisms in rs17481856 (L848L) show an association with congenital toxoplasmosis, rs26618 with chronic hepatitis C, and rs27439 with AIDs, while other SNPs do not show susceptibility associations with infectious diseases [26,91,92]. Not only polymorphisms in the *ERAP1* coding region, such as rs27044 and rs30187, which may affect the enzymatic activity of ERAP1, have been shown to be a risk factor for HIV, HCV or toxoplasmosis infection, but also those in *ERAP1* introns were associated with infectious diseases (Supplementary Tables 1 and 2).

3.3. ERAP1 and ERAP2 confers susceptibility to cancer

The efficient and correct presentation of tumor peptides by MHC class I complexes is an important role in the anti-tumor response. *ERAP* genes and proteins have been investigated in human tumors and found to be correlated with tumors, in addition to carcinoma recurrence and survival. Several studies on ERAP1 and ERAP2 expression in tumors have revealed that genetic, transcriptional, and post-transcriptional control mechanisms may be involved in the regulation of ERAP expression [93–95]. Furthermore, defects in ERAP expression may be involved in the immune evasion mechanisms of tumors [96,97]. The ERAP genes and haplotypes associated with cancers were summarized in Table 1 and Supplementary Tables 1 and 2.

Recent studies have revealed that polymorphisms impacting the enzymatic activity of ERAP1 alter the repertoire of peptides presented by HLA class I molecules, resulting in tumor immune evasion [98]. Mehta et al. genotyped 13 coding SNPs in low molecular weight peptide 2(*LMP2)*, *LMP7*, *TAP1*, *TAP2*, and *ERAP1* genes in cervical carcinoma (CC) and explored the association of *ERAP1* gene variation with cancer in Dutch populations [46]. They found the rs26653 and rs27044 was significantly associated with altered CC risk, and the presence of minor alleles C and G, respectively, exhibited increased CC risk [46]. Moreover, the haplotype rs3734016/rs26653/rs26618/rs30187/rshttps://doi.org//10010860/rs27044-GCTTCG was identified to be a risk for CC [46]. Then, Mehta et al. [99] continued to investigate the variation of ERAP1 in the clinical outcome of CC and revealed that ERAP1 is an important contributing factor for cervical carcinogenesis, progressive tumor growth, and survival. They found genotype distributions of rs26653, rs26618, and rs30187 were significantly associated with the presence of lymph node metastases, while the genotype distributions of rs3734016 and rs26653 were significantly associated with overall survival [99]. The haplotype of the combination of the major C allele of rs3734016 and the minor G allele of rs26653 was significantly associated with CC survival [99]. In 2015, Mehta *et al.* analyzed polymorphisms in components of the antigen processing machinery, including ERAP genes in two Indonesian populations, the Balinese and the Javanese [45]. They found that the G allele of rs26653, C allele of rs27044, and C allele of rs30187 were significantly associated with altered CC risk in the Javanese population, but not in the Balinese population [45]. And the genotypes of rs26653, rs27044, rs30187, and rs10050860 were associated with CC occurrence in the Javanese, but not in the Balinese populations [45].

We previously genotyped four SNPs, rs26653, rs27044, rs30187, and rs26618 in non-small cell lung carcinoma (NSCLC) patients and healthy controls from both Han Chinese and Polish populations [43]. All four SNPs showed an association with NSCLC in the Han Chinese population; however, none of the SNPs showed an association with NSCLC in the Polish population. Haplotype analysis showed the same results as allele analysis. The haplotype rs26653/rs26618/rs30187/rs27044-CTTG, which consisted of NSCLC-protective alleles in all four positions, was strongly protective against NSCLC. However, the haplotype GCCC, which possessed three SNPs that predispose to NSCLC, was associated with NSCLC in the Han Chinese population. In contrast, there were no haplotypes that were associated with NSCLC in the Polish population. One of the reasons for the variations in ERAP1-NSCLC association in the different populations might be because of the significant differences in the SNP genotype frequencies between the Chinese and Polish (except for rs26618). Another may be related to the difference in HLA allelic distribution between the Chinese and Polish [100]. *HLA* genes showed huge diversity in different populations and these polymorphisms can dramatically alter the size, shape, and polarity of side chain binding pocket of HLA residue. Some peptides presented by HLA class I molecules depend on ERAP1 trimming for optimal antigen generation and may not be presented when lacking of a proper *ERAP1* allele [101].

Though the actual influence of ERAP1 polymorphism in shaping the constitutive peptidomes of MHC-I molecules remained much less explored, studies on epistasis interaction between ERAPs and HLA alleles in autoimmune disease shed a light on the potential mechanism[102]. Several studies have confirmed that the *ERAP1* polymorphisms were strongly associated with HLA-B*27 and HLA-B*40 in AS [32,65,103,104], HLA-C*06 in psoriasis and PV [37,105], and HLA-A*29 and HLA-B*51 in BD [106]; while ERAP2 polymorphisms were associated with HLA-B*27 in AS [89] and HLA-A*29 in BD [42]. In 2018, *Lopez de Castro JA* summarized the consequences of the alteration in the peptidome and indicated that genetics background of *ERAPs* may influence the generation or destruction of specific epitopes and the following antigen presenting capacity [102]. *ERAP1* and *ERAP2* polymorphisms may alter the peptidome quantitation and change the tolerogenic or autoimmune features of MHC-I molecules [107,108], which resulting in the total affinity of the peptidome and affect NK recognition [109,110]. Thus, different HLA alleles in different populations may require different peptides for an immune response to specific antigens. Moreover, peptides presented in one population may be insensitive to ERAP1, whereas those in another may not. However, all these epistasis studies were performed in UK, Australian, Canada and European populations, the future studies in other populations are required.

4. Conclusion

ERAP is a critical component of the MHC class I antigen presentation and processing complex. ERAPs makes a role in shaping the HLA class I peptidome by trimming peptides to the optimal size for the generation of a proper adaptive immune response. The following are the major conclusions from our review: ① The population differences in

genetic structure may influence the disease process at both the SNP and haplotype level. ② The SNP risk alleles that encode the enzymatic activity of *ERAP* and their haplotypes have a strong LD with other SNPs, which places these SNPs in a critical role in autoimmune diseases. ③ Association studies between infectious diseases and cancers and *ERAP1* and *ERAP2* indicate that ERAP1 and ERAP2 may play a key role in antigen presentation, thereby influencing infection with specific pathogens or tumor antigens presentation. ④ Further studies using competent comparative analysis and functional validation assays, as well as epistasis interaction between *ERAPs* and *HLA* genes are needed in different populations, so that the mechanism of how ERAP1 and ERAP2 influences infectious diseases and cancers, and the process of antigen presentation can be properly explored.

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Conflicts of interest

The authors declare that there are no conflicting interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2019.02.011.

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