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ORIGINAL ARTICLE

HLA-DR genotypes in patients with systemic lupus erythematosus in Taiwan

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Abstract

Background: Different human leukocyte antigen (HLA)-DR genotypes have been known to be associated with the risk of development of systemic lupus erythematosus (SLE) in different populations, although Lu et al. have reported previously that no correlation exists between the HLA-DR genotype and disease manifestation in SLE patients in Taiwan. We investigated the effects different HLA-DR genotypes had on SLE incidence in Taiwanese patients as to whether risk alleles were associated with different clinical manifestations, and the effects risk alleles had on the age of disease onset.

Methods: Two hundred thirty-four SLE patients and 346 healthy controls were enrolled. HLA-DR genotyping was performed with the HLA FluoGene DRDQ kit for each subject. Chi-square tests and *t* tests were performed for statistical analysis.

Results: HLA-DR2 was significantly more frequently found in SLE patients than in controls (odds ratio [OR] = 2.05, 95% CI, 1.44-2.92, $p < 0.001$). Notably, HLA-DR6 appeared to trend toward negative correlation with SLE, whereas HLA-DR8 appeared to trend toward positive correlation. HLA-DR2 patients had an earlier onset of disease as well as a higher prevalence of oral ulcer, avascular necrosis of bone, and renal involvement (lupus nephritis).

Conclusion: HLA-DR2 was associated with SLE susceptibility in this Taiwanese population as well as lower age of disease onset and more severe clinical manifestations.

Keywords: Alleles; Genotypes; Human leukocyte antigen; Lupus nephritis; Systemic lupus erythematosus

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, multifaceted autoimmune disease that can present as fever, skin rashes, fatigue, and pain or swelling of the joints; it is associated with the production of autoantibodies, and is known to be associated with both environmental and genetic factors. Some of these environmental factors include infection as well as exposure to cigarette smoke, ultraviolet light, and certain chemicals and medications,[1–4] whereas genetic factors include a family history of SLE.[5,6]

Over the past several decades, numerous loci across the human genome have been identified as being associated with SLE. Genetic loci located on chromosome 1 play important roles in immune surveillance, immune clearance, and involved in the pathogenesis of SLE. Tsao et al[7] presented evidence for linkage of a chromosome 1 region to SLE, whereas Moser et al[8] reported evidence for linkage of chromosome 1q to SLE in African-American pedigrees. In a meta-analysis, Karassa et al[9] showed the polymorphism of Fcγ receptor IIa, which is encoded on chromosome 1, to be associated with SLE risk in multiple ethnic groups. In addition to genes located on chromosome 1, the human leukocyte antigen (HLA) system, a complex of several hundred genes that encodes a variety of cell surface proteins, is located on the short arm of chromosome 6 and also plays a crucial role in the adaptive immune response and the pathogenesis of SLE.

The HLA system was first reported in the 1970s by Grumet et al[10] to be associated with autoimmune disorders. Since the mid-1980s, different HLA genotypes have been demonstrated to be related to the pathogenesis of different autoimmune diseases, including SLE.[11] Previous studies have shown the possession of different HLA-DR genotypes to be associated with SLE in different populations; for example, possession of HLA-DR3 is associated with SLE in Caucasians,[12–14] whereas HLA-DR15 is associated with SLE in southern Chinese[15] and Japanese[16] populations. Several linkage analysis studies have showed that 6p11-21, the location of HLA, was the risk locus of SLE.[5,6,17–19] A study using transmission disequilibrium testing demonstrated the association of HLA-DRB1*1501, and not DRB1*0301, with SLE in Americans[20]; however, a similar study showed HLA-DRB1*0301

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to be a risk factor in Caucasian SLE patients in the United Kingdom.[21] Multiple genome-wide association studies also revealed an association between the HLA region on chromosome 6p21 and the development of SLE,[22,23] although a study reported by Lu et al[24] concluded that, in Taiwanese patients, no HLA-DRB1 allele was significantly associated with SLE. This study aims to investigate whether HLA-DR genotypes are associated with SLE in Taiwanese patients, as well as whether any HLA-DR genotypes that are associated with an increased risk of SLE (hereafter referred to as risk alleles) are also associated with specific clinical manifestations of SLE.

2. METHODS

We performed a review of 234 SLE patients (208 females, 26 males) and 346 healthy controls (301 females, 45 males) who underwent follow-up at the Rheumatology clinic at Kaohsiung Medical University Hospital. The collection of patient data for the purpose of this study was performed in accordance with the WMA Declaration of Helsinki, and was approved by the Institutional Review Board at Kaohsiung Medical University Hospital. All patients meet the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) Classification Criteria for SLE.[25] The symptoms and signs of SLE for each patient were reviewed, as well as patient age at disease onset and laboratory findings.

HLA-DR genotyping was done with the commercially available HLA FluoGene DRDQ kit (Inno-Train Diagnostik GmbH, Kronberg, Germany), which uses a sequence-specific primer for amplification with polymerase chain reaction.

Anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, anti-ENA, anticardiolipin, and anti–β2-glycoprotein 1 antibodies were measured with commercial kits by using fluoro-enzyme-immunoassay (EliA kit; Phadia AB, Uppsala, Sweden). Lupus anticoagulant was detected using a commercial kit (simplified dilute Russell's viper venom test; Siemens Healthineers, Erlangen, Germany). We further investigated the association of risk alleles (defined as HLA-DR genotypes that significantly increase SLE incidence) with the age of disease onset and the individual clinical manifestations of SLE. We defined renal involvement (lupus nephritis) in accordance with the 2019 EULAR/ACR classification criteria for SLE.[25]

Statistical analyses were performed with SPSS Statistics software (IBM, Armonk, NY) and G*Power software (Heinrich Heine University Düsseldorf, Düsseldorf, Germany). Chi-square tests were performed to evaluate the differences in HLA-DR genotype frequencies between SLE patients and healthy controls. Alpha level was set at 0.05; *p*-values were corrected for multiple comparisons, whereas a *t* test was performed to compare the mean age of disease onset between patients with and without risk alleles, and chi-square tests were performed to compare the strength of association between different disease manifestations and the presence of risk alleles.

3. RESULTS

The demographics and clinical characteristics of the SLE patients are described (Table 1). The average age of disease onset was found to be 28.9 ± 12.2 years.

Clinically, fever was noted in 39.3% of the patients, whereas mucocutaneous lesions and arthritis were noted in 72.2% and 64.1% of the patients, respectively. Renal involvement (lupus nephritis) was found in 55.1% of the patients. Serologically, SLE-specific antibodies were found in 74.8% of the patients, whereas antiphospholipid antibodies were found in 32.5%.

The genotype frequency of HLA-DR2 was found to be significantly higher (OR = 2.05, 95% CI, 1.44-2.92) in SLE patients than in controls ($p < 0.001$) (Table 2). We plotted the data (HLA-DR vs uncorrected odds ratio) as a forest plot to better illustrate the higher genotype frequency of HLA-DR2 (Fig. 1). This increased frequency was still significant after *p*-value correction ($p_{corr} < 0.010$). Notably, the HLA-DR6 genotype appeared to trend toward negative correlation with SLE incidence (OR = 0.57, 95% CI, 0.36-0.90, $p = 0.015$, p_{corr} = non-significant), whereas the HLA-DR8 genotype appeared to trend toward positive correlation (OR = 1.63, 95% CI, 1.10-2.42, $p = 0.014$, p_{corr} = non-significant) (Table 2).

Further exploratory analysis was performed after identifying HLA-DR2 as a risk allele. In SLE patients, HLA-DR2 was associated with a lower age of disease onset, as well as a higher prevalence of oral ulcer (OR = 2.092, 95% CI, 1.19-3.67), avascular necrosis of bone (OR = 3.74, 95% CI, 1.76-7.93), and renal involvement (lupus nephritis) (OR = 2.05, 95% CI, 1.19-3.51) (Table 3). We then plotted these clinical manifestations against the odds ratios that would be conferred by possession of HLA-DR2 (Fig. 2).

Table 1

Demographics and clinical characteristics of SLE

Sex	**F**	**208**
	M	**26**
Onset age (mean ± SD)	**28.9 ± 12.2 y**	
Clinical manifestations	n = 234 (%)	
Fever	92 (39.3)	
Mucocutaneous	169 (72.2)	
Alopecia	83 (35.5)	
Oral ulcer	73 (31.2)	
Malar rash	126 (53.8)	
Discoid	27 (11.5)	
SCLE	8 (3.4)	
Photosensitivity	64 (27.4)	
Raynaud's	42 (17.9)	
Arthritis	150 (64.1)	
Cutaneous vasculitis	51 (21.8)	
Lymphadenopathy	46 (19.7)	
Deep vein thrombosis	8 (3.4)	
Neuropsychiatric	7 (3.0)	
Avascular necrosis of bone	36 (15.4)	
Serositis	60 (25.6)	
Pleurisy	58 (24.8)	
Pericarditis	28 (12.0)	
Peritonitis	3 (1.3)	
Renal involvement	129 (55.1)	
Laboratory data	n = 234 (%)	
Hematological involvement	153 (65.4)	
Leukopenia	128 (54.7)	
Thrombocytopenia	72 (30.8)	
Hemolytic anemia	29 (12.4)	
SLE-specific antibodies	175 (74.8)	
Anti-dsDNA	169 (72.2)	
Anti-Sm	42 (17.9)	
Anti-RNP	77 (32.9)	
Anti-Ro	142 (60.6)	
Anti-La	47 (20.1)	
Anti-ENA	182 (77.8)	
Antiphospholipid antibodies	76 (32.5)	
Anticardiolipin	51 (21.8)	
β2-glycoprotein 1	12 (5.1)	
Lupus anticoagulant	40 (17.1)	

SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus.

Table 2

Frequencies of HLA-DR alleles in patients with SLE and healthy controls

DR	SLE, n = 234 (%)	Control, n = 346 (%)	OR (95% CI)	*p*	p_{corr}
1	1 (0.4)	2 (0.6)	0.74 (0.07-8.19)	0.804	NS
2	98 (41.9)	90 (26.0)	2.05 (1.44-2.92)	<0.001	<0.010
3	37 (15.8)	56 (16.2)	0.97 (0.62-1.53)	0.904	NS
4	49 (20.9)	81 (23.4)	0.87 (0.58-1.29)	0.484	NS
5	76 (32.5)	130 (37.6)	0.80 (0.56-1.13)	0.209	NS
6	32 (13.7)	75 (21.7)	0.57 (0.36-0.90)	0.015	NS
7	14 (6.0)	14 (4.0)	1.51 (0.71-3.23)	0.286	NS
8	65 (27.8)	66 (19.1)	1.63 (1.10-2.42)	0.014	NS
9	55 (23.5)	91 (26.3)	0.861 (0.59-1.27)	0.447	NS
10	4 (1.7)	5 (1.4)	1.186 (0.32-4.47)	0.801	NS

HLA = human leukocyte antigen; NS = not significant; OR = odds ratio; p_{corr} = *p*-values corrected by Bonferroni method; SLE = systemic lupus erythematosus.

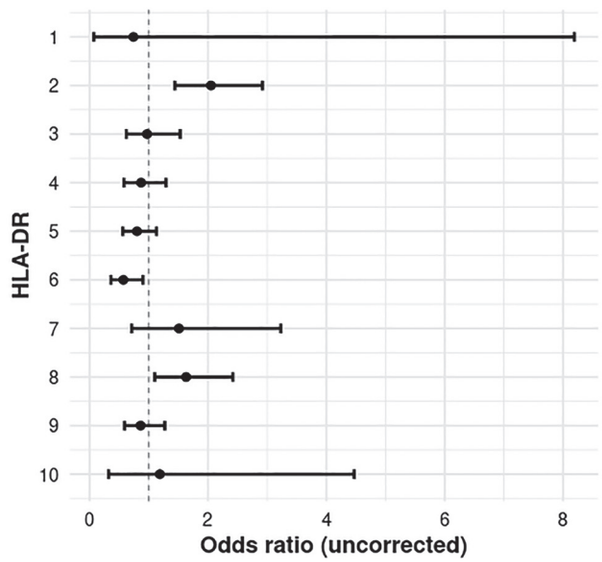

Fig. 1 Forest plot of uncorrected odds ratios of HLA-DR alleles in SLE patients vs healthy controls. HLA = human leukocyte antigen; SLE = systemic lupus erythematosus.

4. DISCUSSION

In this study, HLA-DR2 was found to be positively correlated with susceptibility to SLE in Taiwanese patients. In addition, we found that the presence of HLA-DR2 in SLE patients was associated with a higher prevalence of oral ulcer, avascular necrosis of bone, and renal involvement.

Many genes and immune pathways are involved in the pathogenesis of SLE. As a classical autoimmune disease, endogenous autoantigens bound to HLA class I trigger an immune response in SLE. HLA-DR, an HLA class II receptor that binds with exogenous antigens, is also known to be associated with various autoimmune diseases. A discrepancy seemingly arises between these mechanisms, but can be explained by the involvement of autophagy and cross-presentation in antigen presentation. During antigen presentation in general, endogenous antigens are presented by HLA class I molecules, while exogenous antigens are presented by HLA class II molecules; however, autophagosomes containing damaged organelles and autoantigens also serve as a source of endogenous peptides that also bind to HLA class II molecules.[26] SLE is linked to large amounts of apoptotic cells in various tissues,[27] and autoantigens are known to be translocated into apoptotic bodies during the process of apoptosis.[28] Autoantigens derived from phagocytosed apoptotic cells are efficiently expressed on HLA class II molecules on dendritic cells,[29] which phagocytose apoptotic cells more efficiently than macrophages.[27,30] It has been proposed that a defect in the

Table 3

Comparison of clinical manifestations between HLA-DR2(+) and HLA-DR2(–) SLE patients

Clinical manifestations	DR2(+), n = 93 (%)	DR2(–), n = 141 (%)	*p*	OR (95% CI)
Onset age (mean ± SD)	26.0 ± 9.9 y	30.8 ± 13.2 y	0.002	NA
Malar rash	52 (55.9)	74 (52.5)	NS	
Oral ulcer	38 (40.9)	35 (24.8)	0.01	2.092 (1.19-3.67)
Photosensitivity	28 (30.1)	36 (25.5)	NS	
Arthritis	63 (67.7)	87 (61.7)	NS	
Cutaneous vasculitis	22 (23.7)	29 (20.6)	NS	
Serositis	23 (24.7)	37 (26.2)	NS	
Avascular necrosis of bone	24 (25.8)	12 (8.5)	<0.001	3.74 (1.76-7.93)
Hematologic	59 (63.4)	94 (66.7)	NS	
Neuropsychiatric	3 (3.2)	4 (2.8)	NS	
Renal involvement	61 (65.6)	68 (48.2)	0.009	2.05 (1.19-3.51)
SLE-specific antibodies	71 (76.3)	104 (73.8)	NS	
Antiphospholipid antibodies	28 (30.1)	43 (30.5)	NS	

t test used for comparison of onset age; chi-square test used for comparison of other clinical manifestations.
NA = not applicable; NS = not significant; OR = odds ratio; SLE = systemic lupus erythematosus.

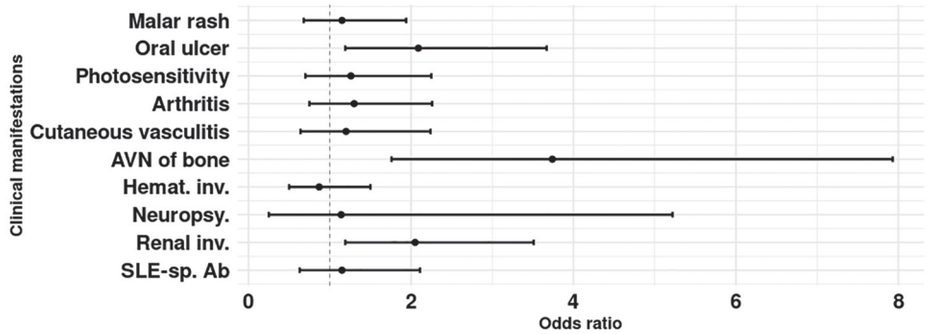

Fig. 2 Odds ratios of clinical manifestations in DR2-positive vs DR2-negative SLE. SLE = systemic lupus erythematosus.

clearance of apoptotic cells leads to an overload of apoptotic cells and a breakdown of self-tolerance in SLE.[31]

Various studies conducted in different populations have shown that susceptibility to SLE is influenced by different HLA-DR genotypes in different populations. Our findings are compatible with previous studies performed in East Asian populations that include Chinese, Japanese, and Korean patients.[15,16,32] Furukawa et al[33] suggested that, in Japanese SLE patients, increased DR15, decreased DR13, and decreased DR14 were associated with SLE. Lee[32] suggested in 2003 that, in Koreans, HLA-DRB1*15 polymorphism is an independent risk factor for SLE.

In our study, we found that HLA-DR2 (ie, HLA-DR15 and HLA-DR16 taken together) is positively correlated with susceptibility to SLE. Conversely, we also noted that possession of HLA-DR6 appeared to trend toward negative correlation with SLE, and although this result was not statistically significant, it was consistent with findings from previous studies, such as the protective effects conferred by HLA-DR6 alleles including DRB1*13 and *14 as reported by Furukawa et al,[33] and HLA-DR6 allele HLA-DRB1*13 as reported by Bettencourt et al.[34]

SLE affects the kidneys in about 50% of patients, with lupus nephritis being the most common cause of SLE-related kidney injury, of which 10% of patients will progress to end-stage renal disease.[35] HLA-DR2, specifically the variant HLA-DR15, has been associated with lupus nephritis in many discrete populations[36–42]; additionally, the subvariant HLA-DRB1*1503 has been found by Bastian et al[43] to be associated with new or worsening proteinuria. Chung et al[44] previously reported association of HLA-DR2 and HLA-DR3 with lupus nephritis in a meta-analysis of three genome-wide association studies of 2000 unrelated European women with SLE, whereas Niu et al[45] noted in a review that HLA-DR4 and HLA-DR11 (a component of HLA-DR5) conferred a protective effect against lupus nephritis, and that HLA-DR3 and HLA-DR15 (a component of HLA-DR2) conferred an increased risk. Our study revealed that possession of HLA-DR2 was associated with development of lupus nephritis in Taiwanese SLE patients, which is compatible with previous studies.

Our study revealed an association between possession of HLA-DR2 and avascular necrosis. We performed a literature review for avascular necrosis and its association with different HLA genotypes. Morimoto et al[46] reported that HLA-DQA1*0601 is negatively associated with aseptic bone necrosis, but little other literature is available. Our findings may be novel or might be confounded by the fact that patients possessing HLA-DR2 generally have a more severe clinical course, and the incidence of avascular necrosis in these patients could be related to more aggressive treatment with high doses of glucocorticoids.[47] Prasad et al had investigated whether any clinical, laboratory, or therapeutic differences other than use of glucocorticoids existed between SLE patients who did and did not develop osteonecrosis, but could not identify any other factors which conferred risk or protection.[48,49] Several previous studies attempted to examine whether the presence of antibodies related to antiphospholipid syndrome (APS antibodies, ie, lupus anticoagulant, anticardiolipin antibodies, and anti–β2-glycoprotein 1 antibodies) was related to the incidence of osteonecrosis, but results were controversial. Jones et al[50] investigated whether abnormal levels of coagulation factors were associated with osteonecrosis, and reported that osteonecrosis patients were more likely to have high levels of anticardiolipin antibody IgG. Conversely, Mok et al[48] investigated whether the presence of APS antibodies was associated with avascular necrosis in SLE patients, but no link could be established. We examined whether the presence of APS antibodies was associated with the incidence of avascular necrosis in our study group, but found no correlation (APS antibody positive vs negative, OR = 0.731, 95% CI, 0.325-1.647, *p*-value not significant).

We found possession of HLA-DR2 to be positively associated with the formation of oral ulcers. Smikle et al[51] previously reported a positive association between DRB1*15/16 and oral ulcers in Jamaican SLE patients, and Selvaraja et al[52] reported that HLA-DRB1*15 was significantly associated with oral ulcer in Malay SLE patients. Similarly, Bang et al[53] reported that HLA-DRB1*15:01 is associated with oral ulcers and renal disorders. Our findings are consistent with the results from these studies.

HLA genotypes have long been known to be correlated with age at disease onset of SLE, as well as its presentation.[54,55] In addition, several studies have observed a correlation between a lower age at disease onset and more serious manifestations of disease.[56,57] We found that in SLE patients, possession of HLA-DR2 was associated with an earlier onset of disease and a more severe disease course.

Recent studies have also outlined the role of type I interferon as a possible genetic signature for SLE,[58] and therapeutics targeting the type I interferon pathway have been approved.[59] Stickler et al[60] previously reported that a proliferative response of $CD4^+$ T cells to interferon-beta (IFN-β)-1b was associated with the presence of HLA-DR2, specifically the subtype HLA-DR15. The presence of HLA-DR2 is thus associated with increased $CD4^+$ T cell activity, leading to increased secretion of pro-inflammatory cytokines, including IL-17 and interferon-gamma (IFN-γ). These cytokines activate the adaptive immune response and play a major role in immune clearance. This might also explain in part the propensity for increased SLE risk in HLA-DR2 carriers.[61]

The results of our study are in contrast with that by Lu et al,[24] which showed no association of HLA-DRB1 with SLE susceptibility in Taiwan. The strength of our study is its relatively large sample size: a post-hoc analysis of test power using a two-tailed *z* test comparing HLA-DR2-positive and HLA-DR2-negative patients using G*Power revealed that a power of over 0.97 was achieved; however, a post-hoc analysis of test power using the same parameters as our study revealed a test power of less than 0.80 in Lu et al's[24] study group. In a similar study, Rudwaleit et al[62] examined HLA-DRB1 and HLA-DQB1 alleles in 26 Chinese SLE patients (with 77 controls) attending the National University Hospital in Singapore. The study revealed a lack of DR2 association with SLE in these patients, and the authors proposed two possible explanations: genetic admixture in the Singapore Chinese population, or ethnic heterogeneity among the southern Chinese.[62] It is also possible that this finding was due to sampling bias; however, due to the low number of patients enrolled (power = 0.27).

In conclusion, of the HLA-DR genotypes tested, HLA-DR2 was found to be positively correlated with susceptibility to SLE in Taiwanese, as well as an earlier and more severe clinical course. These findings contrast with that of Lu et al.[24] In addition, our study revealed that carriage of HLA-DR6 appeared to trend toward negative correlation with SLE, while carriage of HLA-DR8 appeared to trend toward positive correlation with SLE. SLE is a systemic disease with heterogeneous clinical manifestations, and the effects of different HLA-DR genotypes on disease susceptibility appear rather subtle; as a result, the discrepancy between our study and that by Lu et al[24] could be due to sampling bias. In any case, a relatively low number of cases might not be enough to reveal the true nature of this disease.

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REFERENCES

1. Klareskog L, Padyukov L, Alfredsson L. Smoking as a trigger for inflammatory rheumatic diseases. *Curr Opin Rheumatol* 2007;19:49–54.
2. Cooper GS, Gilbert KM, Greidinger EL, James JA, Pfau JC, Reinlib L, et al. Recent advances and opportunities in research on lupus: environmental influences and mechanisms of disease. *Environ Health Perspect* 2008;116:695–702.
3. Mak A, Tay SH. Environmental factors, toxicants and systemic lupus erythematosus. *Int J Mol Sci* 2014;15:16043–56.
4. Kamen DL. Environmental influences on systemic lupus erythematosus expression. *Rheum Dis Clin North Am* 2014;40:401–12, vii.
5. Gaffney PM, Kearns GM, Shark KB, Ortmann WA, Selby SA, Malmgren ML, et al. A genome-wide search for susceptibility genes in human systemic lupus erythematosus sib-pair families. *Proc Natl Acad Sci USA* 1998;95:14875–9.
6. Gaffney PM, Ortmann WA, Selby SA, Shark KB, Ockenden TC, Rohlf KE, et al. Genome screening in human systemic lupus erythematosus: results from a second Minnesota cohort and combined analyses of 187 sib-pair families. *Am J Hum Genet* 2000;66:547–56.
7. Tsao BP, Cantor RM, Kalunian KC, Chen CJ, Badsha H, Singh R, et al. Evidence for linkage of a candidate chromosome 1 region to human systemic lupus erythematosus. *J Clin Invest* 1997;99:725–31.
8. Moser KL, Neas BR, Salmon JE, Yu H, Gray-McGuire C, Asundi N, et al. Genome scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1q in African-American pedigrees. *Proc Natl Acad Sci USA* 1998;95:14869–74.
9. Karassa FB, Trikalinos TA, Ioannidis JPA; FcgammaRIIa-SLE Meta-Analysis Investigators. Role of the Fcgamma receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. *Arthritis Rheum* 2002;46:1563–71.
10. Grumet FC, Coukell A, Bodmer JG, Bodmer WF, McDevitt HO. Histocompatibility (HL-A) antigens associated with systemic lupus erythematosus: a possible genetic predisposition to disease. *N Engl J Med* 1971;285:193–6.
11. Fernando MMA, Stevens CR, Walsh EC, De Jager PL, Goyette P, Plenge RM, et al. Defining the role of the MHC in autoimmunity: a review and pooled analysis. *PLoS Genet* 2008;4:e1000024.
12. Reveille JD, Moulds JM, Ahn C, Friedman AW, Baethge B, Roseman J, et al. Systemic lupus erythematosus in three ethnic groups: I. The effects of HLA class II, C4, and CR1 alleles, socioeconomic factors, and ethnicity at disease onset. *Arthritis Rheum* 1998;41:1161–72.
13. Galeazzi M, Sebastiani GD, Morozzi G, Carcassi C, Ferrara GB, Scorza R, et al; European Concertee Action on the Immunogenetics of SLE. HLA class II DNA typing in a large series of European patients with systemic lupus erythematosus: correlations with clinical and autoantibody subsets. *Medicine (Baltim)* 2002;81:169–78.
14. Morris DL, Taylor KE, Fernando MMA, Nititham J, Alarcón-Riquelme ME, Barcellos LF, et al; International MHC and Autoimmunity Genetics Network. Unraveling multiple MHC gene associations with systemic lupus erythematosus: model choice indicates a role for HLA alleles and non-HLA genes in Europeans. *Am J Hum Genet* 2012;91:778–93.
15. Doherty DG, Ireland R, Demaine AG, Wang F, Veerapan K, Welsh KI, et al. Major histocompatibility complex genes and susceptibility to systemic lupus erythematosus in southern Chinese. *Arthritis Rheum* 1992;35:641–6.
16. Hashimoto H, Nishimura Y, Dong RP, Kimura A, Sasazuki T, Yamanaka K, et al. HLA antigens in Japanese patients with systemic lupus erythematosus. *Scand J Rheumatol* 1994;23:191–6.
17. Koskenmies S. Linkage mapping of systemic lupus erythematosus (SLE) in Finnish families multiply affected by SLE. *J Med Genet* 2004;41:2e–5.
18. Koskenmies S, Widén E, Onkamo P, Sevón P, Julkunen H, Kere J. Haplotype associations define target regions for susceptibility loci in systemic lupus erythematosus. *Eur J Hum Genet* 2004;12:489–94.
19. Forabosco P, Gorman JD, Cleveland C, Kelly JA, Fisher SA, Ortmann WA, et al. Meta-analysis of genome-wide linkage studies of systemic lupus erythematosus. *Genes Immun* 2006;7:609–14.
20. Tsuchiya N, Kawasaki A, Tsao B, Komata T, Grossman J, Tokunaga K. Analysis of the association of HLA-DRB1, TNFα promoter and TNFR2 (TNFRSF1B) polymorphisms with SLE using transmission disequilibrium test. *Genes Immun* 2001;2:317–22.
21. Fernando MMA, Stevens CR, Sabeti PC, Walsh EC, McWhinnie AJM, Shah A, et al. Identification of two independent risk factors for lupus within the MHC in United Kingdom families. *PLoS Genet* 2007;3:e192.
22. Lee YH, Bae SC, Choi SJ, Ji JD, Song GG. Genome-wide pathway analysis of genome-wide association studies on systemic lupus erythematosus and rheumatoid arthritis. *Mol Biol Rep* 2012;39:10627–35.
23. Alarcón-Riquelme ME, Ziegler JT, Molineros J, Howard TD, Moreno-Estrada A, Sánchez-Rodríguez E, et al. Genome-wide association study in an Amerindian ancestry population reveals novel systemic lupus erythematosus risk loci and the role of European admixture. *Arthritis Rheumatol* 2016;68:932–43.
24. Lu LY, Ding WZ, Fici D, Deulofeut R, Cheng HH, Cheu CC, et al. Molecular analysis of major histocompatibility complex allelic associations with systemic lupus erythematosus in Taiwan. *Arthritis Rheum* 1997;40:1138–45.
25. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:1151–9.
26. Vyas JM, Van Der Veen AG, Ploegh HL. The known unknowns of antigen processing and presentation. *Nat Rev Immunol* 2008;8:607–18.
27. Gaipl US, Voll RE, Sheriff A, Franz S, Kalden JR, Herrmann M. Impaired clearance of dying cells in systemic lupus erythematosus. *Autoimmun Rev* 2005;4:189–94.
28. Schiller M, Bekeredjian-Ding I, Heyder P, Blank N, Ho AD, Lorenz HM. Autoantigens are translocated into small apoptotic bodies during early stages of apoptosis. *Cell Death Differ* 2008;15:183–91.
29. Inaba K, Turley S, Yamaide F, Iyoda T, Mahnke K, Inaba M, et al. Efficient presentation of phagocytosed cellular fragments on the major histocompatibility complex class II products of dendritic cells. *J Exp Med* 1998;188:2163–73.
30. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR. Impaired phagocytosis of apoptotic cell material by monocyte-derived

macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum* 1998;41:1241–50.
31. Maniati E, Potter P, Rogers N, Morley B. Control of apoptosis in autoimmunity. *J Pathol* 2008;214:190–8.
32. Lee HS. Independent association of HLA-DR and FC receptor polymorphisms in Korean patients with systemic lupus erythematosus. *Rheumatol* 2003;42:1501–7.
33. Furukawa H, Kawasaki A, Oka S, Ito I, Shimada K, Sugii S, et al. Human leukocyte antigens and systemic lupus erythematosus: a protective role for the HLA-DR6 alleles DRB1*13:02 and *14:03. *PLoS One* 2014;9:e87792.
34. Bettencourt A, Carvalho C, Leal B, Brás S, Lopes D, Martins da Silva A, et al. The protective role of HLA-DRB1 13 in autoimmune diseases. *J Immunol Res* 2015;2015:1–6.
35. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. *Clin J Am Soc Nephrol* 2017;12:825–35.
36. Azizah MR, Ainoi SS, Kuak SH, Kong NC, Normaznah Y, Rahim MN. The association of the HLA class II antigens with clinical and autoantibody expression in Malaysian Chinese patients with systemic lupus erythematosus. *Asian Pac J Allergy Immunol* 2001;19:93–100.
37. Marchini M, Antonioli R, Lleò A, Barili M, Caronni M, Origgi L, et al. HLA class II antigens associated with lupus nephritis in Italian SLE patients. *Hum Immunol* 2003;64:462–8.
38. Wadi W, Elhefny NEAM, Mahgoub EH, Almogren A, Hamam KD, Al-Hamed HA, et al. Relation between HLA typing and clinical presentations in systemic lupus erythematosus patients in Al-Qassim Region, Saudi Arabia. *Int J Health Sci* 2014;8:159–65.
39. Bhallil O, Ibrahimi A, Ouadghiri S, Ouzeddoun N, Benseffaj N, Bayahia R, et al. HLA class II with lupus nephritis in Moroccan patients. *Immunol Invest* 2017;46:1–9.
40. de Holanda MI, Klumb E, Imada A, Lima LA, Alcântara I, Gregório F, et al. The prevalence of HLA alleles in a lupus nephritis population. *Transpl Immunol* 2018;47:37–43.
41. Gunawan A, Handono K, Kalim H, Susianti H, Eko MH, Lawrence GS, et al. The importance of HLA-DRB1 alleles in patients with lupus nephritis. *Turk J Immunol* 2018;6:118–22.
42. Diaz-Gallo L, Oke V, Lundström E, Elvin K, Ling Wu Y, Eketjäll S, et al. Four systemic lupus erythematosus subgroups, defined by autoantibodies status, differ regarding HLA-DRB1 genotype associations and immunological and clinical manifestations. *ACR Open Rheumatol* 2022;4:27–39.
43. Bastian HM, Alarcon GS, Roseman JM, McGwin G, Vila LM, Fessler BJ, et al; LUMINA Study Group. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA) XL II: factors predictive of new or worsening proteinuria. *Rheumatol* 2006;46:683–9.
44. Chung SA, Brown EE, Williams AH, Ramos PS, Berthier CC, Bhangale T, et al; International Consortium for Systemic Lupus Erythematosus Genetics. Lupus nephritis susceptibility loci in women with systemic lupus erythematosus. *J Am Soc Nephrol* 2014;25:2859–70.
45. Niu Z, Zhang P, Tong Y. Value of HLA-DR genotype in systemic lupus erythematosus and lupus nephritis: a meta-analysis. *Int J Rheum Dis* 2015;18:17–28.
46. Morimoto S, Hashimoto H, Yamanaka K, Tokano Y, Nishimura Y, Sawada S, et al. Multicenter cooperative study of HLA class II alleles in Japanese patients with systemic lupus erythematosus. *Mod Rheumatol* 2000;10:235–9.
47. Chang C, Greenspan A, Gershwin ME. Osteonecrosis. In: Firestein GS, editor. *Firestein & Kelley's textbook of rheumatology*. 11th ed. Elsevier; 2021, p. 1852–3.
48. Mok MY, Farewell VT, Isenberg DA. Risk factors for avascular necrosis of bone in patients with systemic lupus erythematosus: is there a role for antiphospholipid antibodies? *Ann Rheum Dis* 2000;59:462–7.
49. Prasad R, Ibanez D, Gladman D, Urowitz M. The role of non-corticosteroid related factors in osteonecrosis (ON) in systemic lupus erythematosus: a nested case-control study of inception patients. *Lupus* 2007;16:157–62.
50. Jones LC, Mont MA, Le TB, Petri M, Hungerford DS, Wang P, et al. Procoagulants and osteonecrosis. *J Rheumatol* 2003;30:783–91.
51. Smikle M, Christian N, DeCeulaer K, Barton E, Roye-Green K, Dowe G, et al. HLA-DRB alleles and systemic lupus erythematosus in Jamaicans. *South Med J* 2002;95:717–9.
52. Selvaraja M, Chin VK, Abdullah M, Arip M, Amin-Nordin S. HLA-DRB1*04 as a risk allele to systemic lupus erythematosus and lupus nephritis in the Malay population of Malaysia. *Front Med* 2021;7:598665.
53. Bang SY, Choi JY, Park S, Choi J, Hong SJ, Lee HS, et al. Influence of susceptibility HLA-DRB1 alleles on the clinical subphenotypes of systemic lupus erythematosus in Koreans: HLA-DRB1 associated with SLE. *Arthritis Rheumatol* 2016;68:1190–6.
54. Bell DA, Rigby R, Stiller CR, Clark WF, Harth M, Ebers G. HLA antigens in systemic lupus erythematosus: relationship to disease severity, age at onset, and sex. *J Rheumatol* 1984;11:475–9.
55. Davies EJ, Hillarby MC, Cooper RG, Hay EM, Green JR, Shah S, et al. HLA-DQ, DR and complement C4 variants in systemic lupus erythematosus. *Br J Rheumatol* 1993;32:870–5.
56. Webb R, Kelly JA, Somers EC, Hughes T, Kaufman KM, Sanchez E, et al. Early disease onset is predicted by a higher genetic risk for lupus and is associated with a more severe phenotype in lupus patients. *Ann Rheum Dis* 2011;70:151–6.
57. Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases? *Autoimmune Dis* 2012;2012:1–7.
58. Psarras A, Wittmann M, Vital EM. Emerging concepts of type I interferons in SLE pathogenesis and therapy. *Nat Rev Rheumatol* 2022;18:575–90.
59. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al; TULIP-2 Trial Investigators. Trial of anifrolumab in active systemic lupus erythematosus. *N Engl J Med* 2020;382:211–21.
60. Stickler M, Valdes AM, Gebel W, Razo OJ, Faravashi N, Chin R, et al. The HLA-DR2 haplotype is associated with an increased proliferative response to the immunodominant CD4+ T-cell epitope in human interferon-β. *Genes Immun* 2004;5:1–7.
61. Mangalam AK, Taneja V, David CS. HLA Class II molecules influence susceptibility versus protection in inflammatory diseases by determining the cytokine profile. *J Immunol* 2013;190:513–8.
62. Rudwaleit M, Gibson K, Wordsworth P, Pile K, Oh V. HLA associations of systemic lupus erythematosus in Chinese from Singapore. *Ann Rheum Dis* 1995;54:686–7.