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Association between a Functional HLA-G 14-bp Insertion/deletion Polymorphism and Susceptibility to Autoimmune Diseases: A Meta-analysis

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Abstract

The aim of this study was to determine whether a functional human leukocyte antigen-G (HLA-G) 14-bp insertion (I)/deletion (D) polymorphism is associated with susceptibility to autoimmune diseases. A meta-analysis was conducted to assess the association between an HLA-G 14-bp I/D polymorphism and autoimmune diseases using 1) allele contrast, as well as 2) recessive, 3) dominant, and 4) codominant models. Sixteen articles that included 20 comparative studies with 3,555 patients and 5,225 controls were included in the meta-analysis. These studies were performed on nine Caucasian, six South American, three Asian, one Arab, and one African population samples. Our meta-analysis revealed no association between autoimmune diseases and the HLA-G 14-bp I/D polymorphism [odds ratio (OR) for allele I = 1.055; 95% confidence interval (CI) = 0.963–1.156; $p = 0.251$)]. However, meta-analysis according to autoimmune disease type revealed an association between systemic lupus erythematosus (SLE) and the II+ID genotype of the HLA-G 14-bp I/D polymorphism (OR = 1.205; 95% CI = 1.036–1.403; $p = 0.016$). Furthermore, analysis using a codominant model revealed an association between this polymorphism and SLE (OR for ID vs. DD = 1.203; 95% CI = 1.024–1.413; $p = 0.024$). In contrast, our meta-analysis revealed no association between rheumatoid arthritis (RA), multiple sclerosis (MS), or Crohn's disease (CD) and the HLA-G 14-bp I/D polymorphism. This meta-analysis showed that the HLA-G 14-bp I/D polymorphism is associated with susceptibility to a subgroup of autoimmune diseases such as SLE, but not RA, MS, or CD. These results support the existence of an association between the *HLA-G* gene and a subgroup of autoimmune diseases.

Key words: Autoimmune diseases, HLA-G, Polymorphism, Meta-analysis.

Introduction

Autoimmune diseases are a diverse group of complex diseases that affect up to 5% of the population, and are characterized by loss of self-tolerance that leads to immune-mediated tissue destruction (23). These diseases are multifactorial and are known to be caused by interactions between genetic and environmental factors. Furthermore, autoimmune diseases share a number of characteristics that suggest common etiologic mechanisms. Although the etiology of different autoimmune diseases has not been determined, genetic studies have established that susceptibility has a genetic component (3,21).

Human leukocyte antigen-G (HLA-G) is a non-classical major HLA class Ib molecule, which exerts immunotolerance-related effects by suppressing the cytotoxicity of natural killer (NK) cells and dendritic cell, CD4+, and CD8+ lymphocyte functions (2,9). HLA-G plays an important role in the regulation of autoimmunity by mediating immunosuppressive functions. The *HLA-G* gene, which is located in chromosome 6p21.31, contains a 14-bp insertion (I)/deletion (D) (rs1704) polymorphism in exon 8 in the 3′ untranslated region (3′UTR). HLA-G expression is influenced by an HLA-G 14-bp I/D polymorphism. This polymorphism affects HLA-G function by influencing the stability and splicing pattern of HLA-G mRNA isoforms (31). In particular, the 14-bp insertion has been associated with lower levels of HLA-G expression.

Some evidence has provided support to the idea that susceptibility to many autoimmune diseases may share common alleles or pathways. Studies have shown that the functional HLA-G 14-bp I/D polymorphism is associated with several autoimmune diseases; however, other reports have failed to find such associations (5,7,11,12,15,16,22,28-30,34-39). These disparities are probably a consequence of small sample sizes, low statistical power, and/or clinical heterogeneity. Therefore, to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false-positive or false-negative associations, we used meta-analysis (17,19,20). The aim of the present study was to determine, using meta-analysis, whether the HLA-G 14-bp I/D polymorphism is associated with susceptibility to autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and Crohn's disease (CD).

Methods

Identification of eligible studies and data extraction

We performed a search for studies that examined the association between the HLA-G 14-bp I/D polymorphism and autoimmune diseases. We searched the literature using PUBMED and EMBASE citation databases in order to identify available articles in which the HLA-G 14-bp I/D polymorphism was analyzed in patients with conditions such as SLE, RA, MS, and CD. Combinations of keywords such as "HLA-G", "polymorphism", "autoimmune diseases", together with names of individual diseases were entered as Medical Subject Heading (MeSH) and text words. References in

identified studies were also investigated to find additional studies not indexed in PUBMED or EMBASE. No restrictions were placed regarding language, race, ethnicity, or geographic area. Autoimmune diseases were diagnosed according to the classification criteria of each disease (1,12,14,24,25,27,32). Studies were included if: (1) they were published before April 2015, (2) contained original data, and (3) provided sufficient genotype data to calculate odds ratios (ORs). The following types of studies were excluded: (1) studies containing overlapping data, (2) studies in which the number of null and wild genotypes could not be ascertained, and (3) studies in which family members had been studied using for example the transmission disequilibrium test, because the analyses conducted were based on linkage considerations. We conducted a meta-analysis in accordance with the guidelines provided by PRISMA statement (26). Data were extracted from original studies by two independent reviewers (YH Lee and SC Bae) regarding the methods and results of meta-analysis. Discrepancy between the reviewers was resolved by consensus or a third reviewer (GG Song). The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, and number of cases and controls. Frequency of alleles was calculated from genotype distributions.

Evaluation of statistical associations

A chi-square test was used to assess whether observed genotype frequencies conformed to the Hardy-Weinberg (H-W) expectations. Meta-analyses were performed using (i) allelic contrast, as well as (ii) recessive, (iii) dominant, and (iv) codominant models. Subgroup analysis was performed by ethnicity and disease type in order to evaluate ethnic- and disease-specific effects. Point estimates of risks, ORs, and 95% confidence intervals (CIs) were estimated for each study. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities. This heterogeneity test assesses the null hypothesis that all studies evaluated the same effect. I^2 values were used to quantify the effect of heterogeneity. In this test values range between 0 and 100%, and represent the proportion of between-study variability attributable to heterogeneity rather than to chance (13). I^2 values of 25%, 50%, and 75% were nominally defined as low, moderate, and high estimates, respectively. The fixed effects model assumes that a genetic factor has the same effect on disease susceptibility across all studies investigated, and that variations between studies are due to chance alone. On the other hand, the random effects model assumes that different studies show substantial diversity, and assesses both within-study sampling error and between-study variance. When study groups are homogeneous the two models are similar, otherwise, the random effects model usually provides wider CIs than the fixed effects model. Furthermore, the random effects model is used in the presence of significant between-study heterogeneity (8). Statistical analysis was performed using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA). The power of each study was defined as the probability of detecting an association between the HLA-G polymorphism and autoimmune disease at a level of significance of 0.05, assuming a small effect size (convention w = 0.1). Power analysis was performed using G*Power statistical program (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower).

Evaluation of heterogeneity and publication bias

Subgroup analysis was performed according to ethnicity, autoimmune disease type, and HWE status in order to assess the influence of each of them on the heterogeneity of this meta-analysis in each group. Funnel plots are often used to detect publication bias. However, because of the limitations of funnel plotting, which requires a range of studies of varying sizes involving subjective judgments, publication bias was evaluated using Egger's linear regression test (10), which measures funnel plot asymmetry using a natural logarithm scale of ORs.

Results

Studies included in the meta-analysis

Ninety-eight reports were identified by electronic and manual search. After 53 duplicate and 24 irrelevance reports removed. and 22 were finally selected for full-text review based on title and abstract details. Of these, six reports were excluded due to lack of genotype data or because they were reviews; therefore, 16 reports met the inclusion criteria (5,7,11,12,15,16,22,28-30,34-39). In addition, four of these reports contained data on two different groups; therefore, we analyzed these studies independently (12,22,34,35). Therefore, a total of 20 separate studies were considered for this meta-analysis, which contained 3,555 patients and 5,225 controls, as well as nine Caucasian, six South American, three Asian, one Arab, and one African population samples (Table 1). Ethnicity-specific meta-analysis was conducted for the Caucasian, South American, and Asian populations. These studies encompassed SLE (n = 8), RA (n = 3), MS (n = 3), CD (n = 2), juvenile idiopathic arthritis (JIA; n = 1), vitiligo (n = 1), and ulcerative colitis (UC; n = 1). Disease-specific meta-analysis was performed in SLE, RA, MS, and CD. Select characteristics of these studies related to the association between the HLA-G 14-bp I/D polymorphism and diseases are summarized in Table 1. The statistical power of these studies ranged between 10.4% and 91.4%, and two studies had statistical power higher than 80% (Table 1).

Meta-analysis of the HLA-G 14-bp I/D polymorphism in autoimmune diseases

A summary of meta-analysis findings on the association between the HLA-G 14-bp I/D polymorphism and autoimmune diseases is provided in Table 2. Our meta-analysis revealed no association between autoimmune diseases and the HLA-G 14-bp allele I (OR = 1.055; 95% CI = 0.963–1.156; p = 0.251; Table 2), and stratification by ethnicity showed no association between HLA-G 14-bp allele I and autoimmune diseases in Caucasian, South American, and Asian ethnic groups (Table 2). Furthermore, no association was found between the HLA-G 14-bp I/D polymorphism and autoimmune diseases on using the recessive, dominant, and codominant models (Table 2, Figure 1).

Table 1. Characteristics of the studies included in the meta-analysis.

Author (Ref)	Ethnicity	Disease	Number of cases		Genotyping method	Case			Control			Association *p*-value	Power (%)[a]
			Case	Control		DD	DI	II	DD	DI	II		
Favoino, 2015(7)	Caucasian	SSc	20	26	PCR	12	8	0	11	15	0	0.334	10.4
Xidi, 2015(21)	Arab	CD	44	71	PCR	11	21	12	21	36	14	0.371	18.8
Chen, 2014(8)	Asian	SLE	206	212	PCR	94	91	21	115	79	18	0.103	53.3
Jeong, 2014(9)	Asian	Vitiligo	184	491	PCR	109	62	13	276	198	17	0.912	73.8
Veit-1, 2014(10)	South American	RA	339	294	PCR	110	170	59	105	136	53	0.635	71.0
Veit-2, 2014(10)	South American	RA	198	188	PCR	69	99	30	66	97	25	0.764	50.1
Lucena-Silva-1, 2013(11)	South American	SLE	140	147	PCR	43	61	36	57	60	30	0.107	39.5
Lucena-Silva-2, 2013(11)	South American	SLE	50	127	PCR	19	17	14	51	56	20	0.213	26.4
Rizzo, 2012(19)	Caucasian	MS	69	162	PCR	21	31	17	64	69	29	0.115	33.0
Consiglio, 2011(12)	South American	SLE	193	121	PCR	51	114	28	40	60	21	0.641	42.5
Wisniewski, 2010(20)	Caucasian	MS	227	288	PCR	75	110	42	96	147	45	0.609	62.1
Wu, 2009(13)	Asian	SLE	231	367	PCR	94	97	40	137	171	59	0.714	68.6
Veit-1, 2009(14)	Caucasian	SLE	197	356	PCR	65	129	3	122	175	59	0.024	65.2
Veit-2, 2009(14)	African	SLE	67	104	PCR	25	31	11	45	48	11	0.268	25.7
Rizzo, 2008(15)	Caucasian	SLE	200	451	PCR	56	97	47	165	221	65	0.003	72.2
Veit, 2008(22)	South American	JIA	106	85	PCR	46	50	10	25	38	22	0.003	28.2
Kroner, 2007(18)	Caucasian	MS	300	95	PCR	112	144	44	35	51	9	0.561	51.1
Rizzo, 2006(16)	Caucasian	RA	156	162	PCR	62	66	28	64	69	29	0.980	42.9
Glas-1, 2007(17)	Caucasian	CD	371	739	PCR	142	167	62	266	373	100	0.838	91.4
Glas-2, 2007(17)	Caucasian	UC	257	739	PCR	91	139	27	266	373	100	0.624	88.4

[a]Assuming a small effect size (convention w = 0.1) at a level of significance of 0.05.

Abbreviations: D, deletion; I, insertion; Ref, reference; SSc, systemic sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; MS, multiple sclerosis; JIA, juvenile idiopathic arthritis; CD, Crohn's disease; UC, ulcerative colitis; PCR, polymerase chain reaction.

Table 2. Meta-analysis of association between the HLA-G 14-bp I/D polymorphism and autoimmune diseases.

Polymorphism	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*P-val*	Model	*P-val*	I^2
HLA-G 14bp I vs. D	Overall	20	3,555	5,225	1.055	0.963-1.156	0.251	R	0.015	45.1
	Caucasian	9	1,797	3,018	1.042	0.906-1.198	0.567	R	0.025	54.4
	South American	6	1,026	92	1.028	0.826-1.278	0.807	R	0.021	62.4
	Asian	3	621	1,070	1.055	0.903-1.232	0.500	F	0.309	14.9
II vs. ID + DD (Recessive)	Overall	20	3,555	5,225	1.113	0.891-1.390	0.345	R	0.000	63.4
	Caucasian	9	1,797	3,018	1.039	0.700-1.542	0.850	R	0.000	76.9
	South American	6	1,026	92	0.978	0.651-1.470	0.917	R	0.017	63.7
	Asian	3	621	1,070	1.279	0.921-1.777	0.142	F	0.320	12.3
II + ID vs. DD (Dominant)	Overall	20	3,555	5,225	1.057	0.964-1.159	0.241	F	0.368	7.10
	Caucasian	9	1,797	3,018	1.046	0.921-1.189	0.487	F	0.450	0
	South American	6	1,026	92	1.102	0.912-1.330	0.314	F	0.196	31.9
	Asian	3	621	1,070	1.002	0.817-1.228	0.988	F	0.118	53.1
II vs. DD	Overall	20	3,555	5,225	1.147	0.908-1.448	0.249	R	0.200	59.7
	Caucasian	9	1,797	3,018	1.067	0.707-1.609	0.759	R	0.000	74.1
	South American	6	1,026	92	1.030	0.656-1.616	0.898	R	0.018	63.2
	Asian	3	621	1,070	1.254	0.885-1.777	0.203	F	0.308	15.1
ID vs. DD	Overall	20	3,555	5,225	1.038	0.942-1.145	0.450	F	0.402	4.44
	Caucasian	9	1,797	3,018	1.036	0.906-1.184	0.608	F	0.362	8.74
	South American	6	1,026	92	1.115	0.912-1.363	0.290	F	0.457	0
	Asian	3	621	1,070	0.963	0.680-1.364	0.832	R	0.076	61.1

D, deletion; I, insertion; R, random effects model; F, fixed effects model; OR, odds ratio; CI, confidence interval.

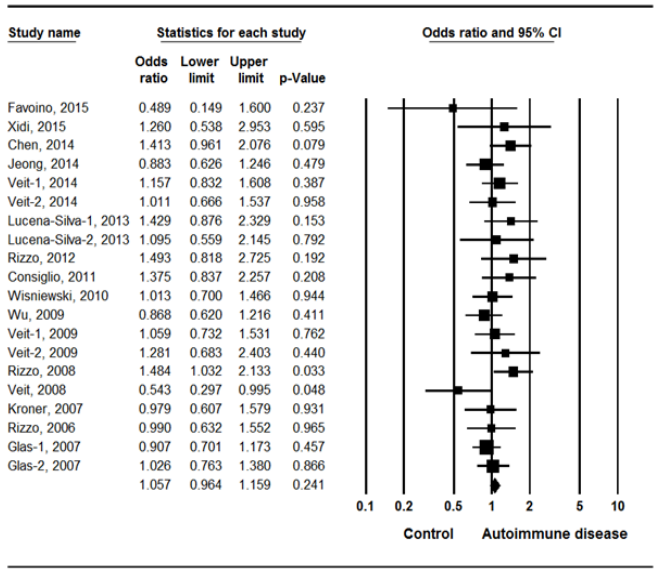

Figure 1. Odds ratio (OR) and 95% coefficient interval (CI) of individual studies and pooled data for the association between the II+ID genotype of the HLA-G 14-bp I/D polymorphism and autoimmune diseases.

Meta-analysis of the relation between the HLA-G 14-bp I/D polymorphism and autoimmune disease type

Meta-analysis findings regarding the association between the HLA-G 14-bp I/D polymorphism and SLE, RA, MS, or CD are summarized in Table 3. Our meta-analysis revealed no association between SLE and HLA-G 14-bp allele I (OR = 1.137; 95% CI = 0.953–1.356; p = 0.154; Table 3). However, meta-analysis under the dominant model revealed an association between SLE and II+ID genotype of the HLA-G 14-bp I/D polymorphism (OR = 1.205; 95% CI = 1.036–1.403; p = 0.016; Table 3, Figure 2). Furthermore, analysis using a codominant model revealed an association between HLA-G 14-bp I/D polymorphism and SLE (OR for ID vs. DD = 1.203; 95% CI = 1.024–1.413; p = 0.024; Table 3). In contrast, meta-analysis according to autoimmune disease type revealed no association between RA, MS, or CD and the HLA-G 14-bp I/D polymorphism (Table 3).

Heterogeneity and publication bias

Deviation from HWE among controls indicates potential bias during control selection, or genotyping errors. In one study, distribution of genotypes in normal control groups was not consistent with HWE (15); however, exclusion of this study did not markedly affect the results of our meta-analysis on the association between the HLA-G 14-bp I/D polymorphism and autoimmune diseases. Some between-study heterogeneity was observed in meta-analysis of the relation between HLA-G polymorphism and autoimmune diseases in all

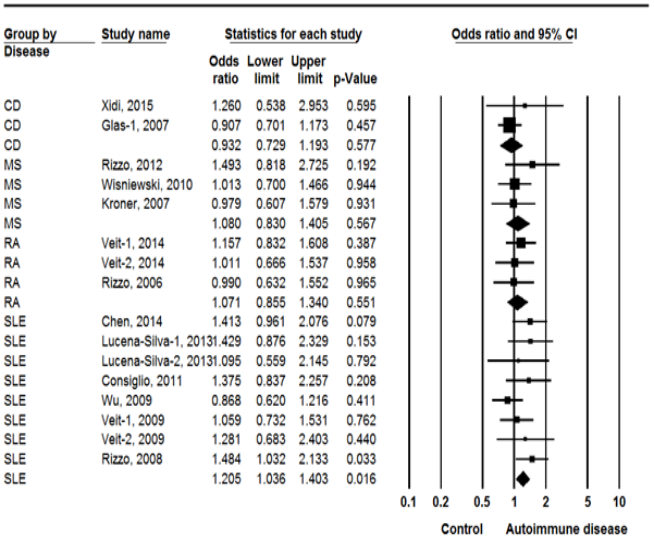

Figure 2. Odds ratio (OR) and 95% coefficient interval (CI) of individual studies, and pooled data for the association between the II+ID genotype of the HLA-G 14-bp I/D polymorphism and systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), or Crohn's disease (CD).

Table 3. Meta-analysis of the association between the HLA-G 14-bp I/D polymorphism and systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and Crohn's disease (CD).

Polymorphism	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*P-val*	Model	*P-val*	I^2
SLE	I vs. D	8	1,284	1,885	1.137	0.953-1.356	0.154	R	0.011	61.6
	II vs. ID + DD	8	1,284	1,885	1.079	0.686-1.696	0.742	R	0.000	75.8
	II + ID vs. DD	8	1,284	1,885	1.205	1.036-1.403	0.016	F	0.442	0
	II vs. DD	8	1,284	1,885	1.180	0.740-1.883	0.486	R	0.001	72.5
	ID vs. DD	8	1,284	1,885	1.203	1.024-1.413	0.024	F	0.405	3.18
RA	I vs. D	3	693	644	1.038	0.890-1.212	0.633	F	0.957	0
	II vs. ID + DD	3	693	644	1.018	0.764-1.358	0.902	F	0.862	0
	II + ID vs. DD	3	693	644	1.071	0.855-1.340	0.551	F	0.820	0
	II vs. DD	3	693	644	1.066	0.775-1.466	0.694	F	0.952	0
	ID vs. DD	3	693	644	1.074	0.847-1.364	0.555	F	0.724	0
MS	I vs. D	3	596	545	1.135	0.948-1.358	0.167	F	0.556	0
	II vs. ID + DD	3	596	545	1.369	0.973-1.925	0.071	F	0.775	0
	II + ID vs. DD	3	596	545	1.080	0.830-1.405	0.567	F	0.500	0
	II vs. DD	3	596	545	1.389	0.950-2.032	0.090	F	0.676	0
	ID vs. DD	3	596	545	0.996	0.755-1.315	0.979	F	0.552	0
CD	I vs. D	2	415	810	1.043	0.879-1.238	0.630	F	0.434	0
	II vs. ID + DD	2	415	810	1.312	0.952-1.809	0.097	F	0.718	0
	II + ID vs. DD	2	415	810	0.932	0.729-1.193	0.577	F	0.469	0
	II vs. DD	2	415	810	1.207	0.846-1.721	0.299	F	0.551	0
	ID vs. DD	2	415	810	0.859	0.661-1.116	0.254	F	0.557	0

D, deletion; I, insertion; R, random effects model; F, fixed effects model; OR, odds ratio; CI, confidence interval.

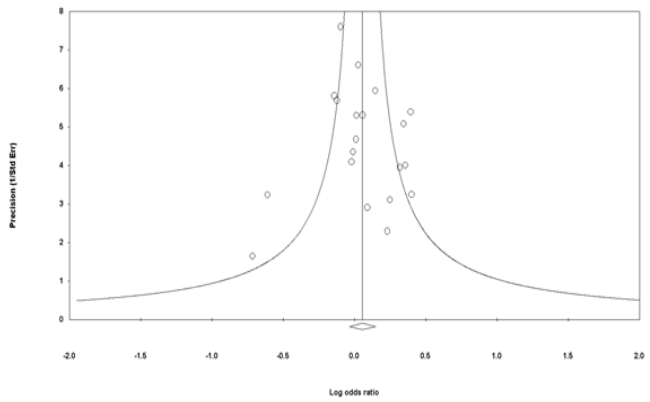

Figure 3. Funnel plot of studies that examined the association between the II+ID genotype of the HLA-G 14-bp I/D polymorphism and autoimmune diseases (Egger's regression p-value = 0.809).

study subjects, but no heterogeneity was found in meta-analyses of the relation between the polymorphism and the autoimmune diseases SLE, RA, MS, or CD under the dominant model (Tables 2, 3). No evidence of publication bias was found in our meta-analysis ($p > 0.1$ according to Egger's regression test; Fig. 3).

Discussion

HLA-G plays a key role in immunosuppression by inhibiting cytotoxic activity of NK and cytotoxic T cells, alloproliferative response of CD4+ T cells, and maturation and function of antigen-presenting cells (2,9). Taking into account the importance of HLA-G in immune modulation, the link between HLA-G expression and autoimmune diseases (29), and the fact that the *HLA-G* gene is located at a strong linkage region for autoimmune diseases (6,18), *HLA-G* has been considered a candidate gene in the context of autoimmune diseases.

The present study addressed the association between the HLA-G 14-bp I/D polymorphism and susceptibility to autoimmune diseases. Our meta-analysis did not find an association between the HLA-G 14-bp I/D polymorphism and autoimmune diseases. However, stratification by disease type revealed an association between SLE and the HLA-G 14-bp I/D polymorphism. The results of our study are consistent with an immunosuppressive role for HLA-G in SLE. However, we found no association between RA, MS, or CD and HLA-G polymorphism. Our results suggest an association between the *HLA-G* gene and a subgroup of autoimmune diseases, but do not provide further evidence for the existence of a common gene underlying multiple autoimmune diseases. However, taking into account the limited number of studies on some diseases included in the present meta-analysis, our results need to be interpreted with caution.

SLE is a prototypical autoimmune disease, and is characterized by multiple organ involvement, polyclonal B cell activation, and autoantibody production. HLA-G expression may be a mechanism of protection against autoimmune responses through downregulation of inflammatory processes and involvement in immune tolerance (4). The HLA-G 14-bp I/D polymorphism has been reported to be associated with sequence stability of HLA-G mRNA and patterns of alternative isoform splicing, which affect HLA-G mRNA expression and function of the HLA-G molecule (31). The HLA-G 14-bp I/D polymorphism may be implicated in SLE (31,33), and in our study we found over-representation of the HLA-G 14-bp ID+DD genotype in SLE patients compared to controls. The plausible mechanism on the association between the HLA-G 14-bp I/D polymorphism and SLE risk is that HLA-G 14-bp allele I carriers have lower expression of HLA-G and lower levels of soluble HLA-G (31,33), which leads to impaired immune tolerance and a shift the immune response in favor of a more autoimmunity. Lower level of HLA-G level in SLE has been also reported (29). Thus, decreased levels of soluble HLA-G in plasma due to the HLA-G 14-bp I/D polymorphism may lead to activation of inflammatory cells and contribute to the development of SLE.

RA is a chronic inflammatory autoimmune disease characterized by synovial cell proliferation and T lymphocyte accumulation within the synovial tissue, and is associated with immune dysregulation. MS is a demyelinating inflammatory disease of the central nervous system that affects young adults and has a relapsing or progressive course. CD is an idiopathic inflammatory bowel disease characterized by chronic segmental, transmural, and, typically, granulomatous inflammation of any region of the gastrointestinal tract. Our results showed that the HLA-G 14-bp I/D polymorphism was associated with susceptibility to SLE, but not RA, MS, or CD. This could be explained through the following mechanisms: (1) HLA-G transcription, translation, or mRNA stability may be regulated by HLA-G polymorphisms other than the HLA-G 14-bp I/D polymorphism; (2) different susceptibility to autoimmune diseases may be reflected as different HLA-G 14-bp I/D polymorphism distribution patterns in various populations; (3) autoimmune diseases are caused by interaction between genetic and environmental factors, but gene-environment interactions are not the same in different populations; and (4) this discrepancy may indicate a different role of HLA-G polymorphisms in different autoimmune diseases or the existence of underpowered studies with small sample sizes in subgroup analysis.

Our study has some limitations that require consideration. First, heterogeneity and confounding factors may have distorted the analysis. In particular, publication bias could have affected our findings, because studies reporting negative results may have not been published, or may have been missed. Second, our ethnic-specific meta-analysis included data from Caucasian, South American, and Asian patients; thus, our results are applicable only to these ethnic groups. Further studies performed in different ethnic populations are required. Third, we did not stratify and analyze factors such as sex, or clinical or environmental variables, because lack of data; HLA-G polymorphism may be associated with clinical manifestations in addition to disease susceptibility. Fourth, the number of studies and subjects in the subgroup analysis of disease types was relatively small; thus, our analysis may be underpowered. Fifth, several diseases such as, vitiligo, JIA, and UC were not analyzed in the present study. Therefore, additional studies are needed to explore the association between these autoimmune diseases and the HLA-G 14-bp I/D polymorphism.

This meta-analysis of 3,555 patients and 5,225 controls showed that the HLA-G 14-bp I/D polymor-

phism is associated with susceptibility to SLE, but not with RA, MS, or CD, suggesting that this polymorphism has disease-dependent functionality. The HLA-G 14-bp I/D polymorphism may be not a common genetic factor for multiple autoimmune diseases, and different pathogenic mechanisms could be involved in the development of polygenic autoimmune diseases. Further studies are needed to elucidate the role of the *HLA-G* gene in autoimmune pathogenesis.

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