Relationship between the HLA-G 14bp insertion/deletion polymorphism and susceptibility to autoimmune disease: a meta-analysis

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ABSTRACT. Numerous studies have investigated the potential relationship between the human leukocyte antigen (HLA)-G 14-bp insertion/deletion (INS/DEL) polymorphisms and autoimmune disease (AID). However, published results are inconclusive. Our aim was to determine whether the 14-bp INS/DEL polymorphism in the HLA-G gene contributes to the risk of AID. A systemic literature search of the PubMed and EMBASE databases was conducted to identify eligible studies investigating the association of the HLA-G 14-bp INS/DEL polymorphism with AID. Our analysis included 11 publications involving a total of 6462 individuals. Overall, no significant association between the HLA-G 14-bp INS/DEL polymorphism and AID was detected in any comparison model. Further subgroup analyses based on AID types and ethnicity also revealed no significant associations. Our results suggest that the HLA-G 14-bp INS/DEL polymorphism is unrelated

to the development of AID. Further studies including larger sample sizes are warranted to confirm these results.

Key words: Autoimmune disease; Human leukocyte antigen-G; Indel polymorphism; Meta-analysis; Susceptibility

INTRODUCTION

The immune system plays an important role in recognizing foreign antigens and protecting against infections, facilitating species survival. However, when the body reacts to itself, immunity can become problematic. Autoimmunity is defined as a misdirected attack made by the immune system against the host as a result of a failing to recognize a self-antigen. This phenomenon is typically an innocuous finding, but has the potential to lead to a broad spectrum of complex autoimmune diseases (AIDs) (Amur et al., 2012).

AID generally refers to a clinically distinct illness caused by an immune reaction to an otherwise normal molecule or tissue component of the subject's body (Cohen, 2014). A total of 5-8% of the general population is affected by AIDs and at least 80 medical conditions are known to be associated with AIDs (Gleicher and Barad, 2007). Recurrent and chronic courses and multiple organ involvement are commonly observed in AIDs.

Human leukocyte antigen (HLA)-G, a non-classical major histocompatibility complex class I molecule, plays an important role in regulating immune responses. HLA-G expression was initially thought to be restricted to the placenta. Recently, however, HLA-G expression has been detected in thymic epithelium, pancreas, intestine, and peripheral blood monocytes (Kovats et al., 1990; Crisa et al., 1997). HLA-G molecules are generated through alternative splicing of the primary transcript of the gene (Ishitani and Geraghty, 1992); HLA-G has 7 isoforms, including 4 membrane-bound (HLA-G1-G4) isoforms and 3 secreted, soluble isoforms (HLA-G5-G7).

HLA-G exhibits immunotolerance functions, inducing apoptosis of activated $CD8^+$ T cells (Fournel et al., 2000), interactions with T regulatory cells (Du et al., 2011), modulation of the activity of natural killer cells (Marchal-Bras-Goncalves et al., 2001) and dendritic cells (Liang et al., 2008), and blocking of the allo-cytotoxic T lymphocyte response (Kapasi et al., 2000).

Recent studies have revealed that HLA-G is expressed in numerous pathological conditions, such as psoriatic skin lesions, atopic dermatitis, pemphigus vulgaris, myositic lesions, multiple sclerosis, ulcerative colitis, and some cancers (Larsen and Hviid, 2009; Donadi et al., 2011).

HLA-G production is controlled by several polymorphisms in the promoter (or 5'-upstream regulatory) region as well as a 14-bp insertion (INS)/deletion (DEL) in the 3'untranslated region. These polymorphisms modify interactions between the gene and transcriptional or post-transcriptional factors, respectively (Hviid et al., 2006). Many association studies have focused on the 3'-untranslated region polymorphic sites that appear to play a pivotal role in the regulation of HLA-G expression by influencing the binding of specific microRNAs, affecting the stability of the HLA-G mRNA (Sabbagh et al., 2014). The relationships between the HLA-G 14-bp INS/DEL polymorphism and many AIDs have been previously examined. However, the results of many of the association studies published to date have been inconclusive.

In this study, we performed a meta-analysis using all data published to date to assess the statistical evidence of the association between the HLA-G 14-bp INS/DEL polymorphism and AID risk.

MATERIAL AND METHODS

Search strategy

Case and control studies were searched in the PubMed, EMBASE, and Korean Studies Information Service System databases up to May 2014 without language restrictions. Relevant studies were identified using the terms: “HLA-G 14-bp or HLA-G insertion or HLA-G deletion” AND “polymorphism or polymorphisms or variant” AND “autoimmune or autoimmunity or autoimmune disease”. Studies were restricted to humans. Additional studies were identified by a manual search of reference lists in original or review articles. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

Inclusion criteria

Studies were included if they met the following criteria: 1) studies that evaluated the association between the HLA-G 14-bp INS/DEL polymorphism (rs66554220) and autoimmune disease, 2) case-control study design, and 3) had detailed genotype frequencies for cases and controls.

Data extraction

Two investigators independently extracted data and reached consensus on all items. If the 2 investigators generated different results, they rechecked the data and reached a consensus through discussion. Data extracted from the selected articles included the first author’s name, year of publication, country of origin, ethnicity of the study population, and numbers of cases and controls. Ethnicity was divided into Asian and Caucasian populations.

Statistical analysis

Before the effect estimation of HLA-G 14-bp INS/DEL polymorphism in AID, we first calculated the Hardy-Weinberg equilibrium of the HLA-G 14-bp INS/DEL polymorphism using the χ^2 test (http://www.had2know.com/academics/hardy-weinberg-equilibrium-calculator-2-alleles.html). The meta-analysis was performed using the Comprehensive Meta-Analysis software (BioStat, Inc., Englewood, NJ, USA). The pooled odds ratio (OR) and 95% confidence interval (CI) were used to investigate the association between autoimmune disease and the rs66554220 polymorphism in the HLA-G gene. A random-effect or fixed-effect model was used. OR, with the corresponding 95%CI, was calculated for the additive model (INS/INS *vs* INS/DEL *vs* DEL/DEL), dominant model (INS/INS and INS/DEL *vs* DEL/DEL), and recessive model (INS/INS *vs* INS/DEL and DEL/DEL), and allele (INS *vs* DEL).

A χ^2 test-based Q statistic test was performed to assess heterogeneity. We also assessed the effects of heterogeneity using the I^2 test. A significant Q test ($P < 0.05$) or $I^2 > 50\%$ indicated heterogeneity among the studies. The random-effect Mantel Haenszel method was used if the result of the Q test was $P < 0.05$ or the I^2 statistic was > 50 %, indicating statistically significant heterogeneity between studies. Otherwise, the fixed-effect Mantel Haenszel method was used. P values < 0.05 were considered to indicate statistical significance.

RESULTS

Study characteristics

A total of 70 studies were screened from the databases. Figure 1 shows that 11 articles, including 2704 cases and 3758 controls, were ultimately selected. The characteristics of the studies selected regarding the HLA-G 14-bp INS/DEL polymorphism and AID are summarized in Table 1. The types of AID included systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIR), multiple sclerosis, ulcerative colitis, Crohn's disease, idiopathic dilated cardiomyopathy, pemphigus vulgaris, and non-segmental vitiligo. The INS allele showed a higher frequency in AID groups in Caucasian populations than in Asian populations (INS allele frequency = 0.31 and 0.41 in Asian and Caucasian populations, respectively; Figure 2). However, in the control group, the INS allele frequencies were similar in the Caucasian and Asian populations (INS allele frequency = 0.35 and 0.40 in Asian and Caucasian populations, respectively).

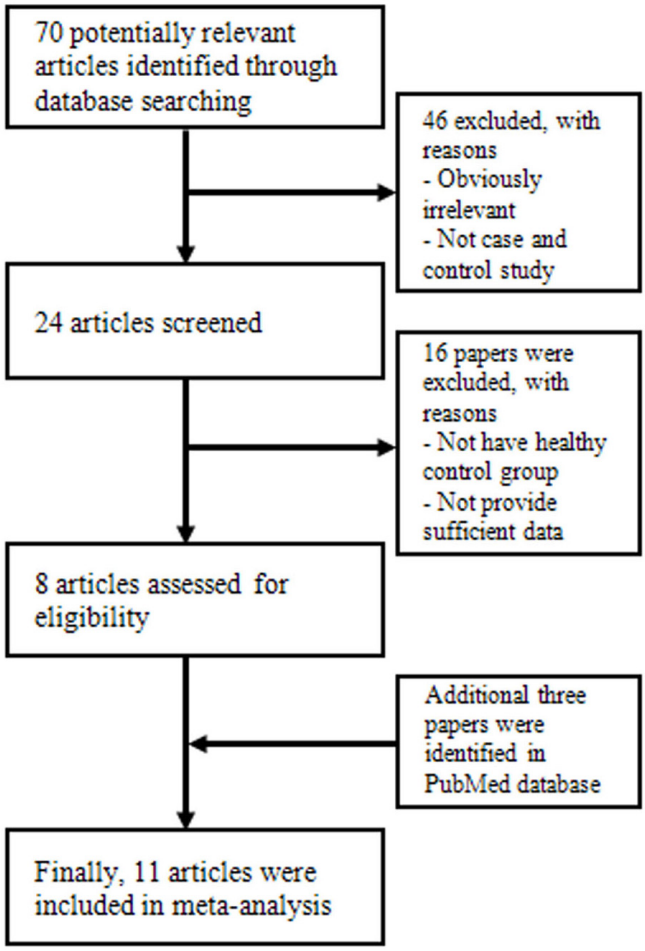

Figure 1. Flow chart illustrating the search strategy used to identify relevant studies.

Table 1. Genotype and allele distribution of the HLA-G 14-bp INS/DEL polymorphism in patients with autoimmune diseases and controls.

Study	Type of autoimmune disease	Ethnicity	Case			Control			Case		Control		HWE
			INS/INS	INS/DEL	DEL/DEL	INS/INS	INS/DEL	DEL/DEL	INS	DEL	INS	DEL	P
Veit et al. (2009)	SLE	Caucasian	41	161	91	70	223	167	243	343	363	557	0.44
Consiglio et al. (2011)	SLE	Caucasian	28	114	51	21	60	40	170	216	102	140	0.85
Wu et al. (2009)	SLE	Asian	40	97	94	59	171	137	177	285	289	445	0.65
Rizzo et al. (2008)	SLE	Caucasian	47	97	56	65	221	165	191	209	351	551	0.51
Gazit et al. (2004)	Pemphigus vulgaris	Caucasian	11	12	7	19	11	0	34	26	49	11	0.22
Veit et al. (2008)	RA	Caucasian	49	132	84	59	175	122	230	300	293	419	0.78
Rizzo et al. (2006)	RA	Caucasian	28	66	62	29	69	64	122	190	127	197	0.18
Veit et al. (2008)	JIA	Caucasian	10	50	46	22	38	25	70	142	82	88	0.33
Jeong et al. (2014)	Non-segmental vitiligo	Asian	13	62	109	17	198	276	88	280	232	750	0.01
Lin et al. (2007)	IDC	Asian	10	48	59	85	188	128	68	166	358	444	0.30
Kroner et al. (2007)	Multiple sclerosis	Caucasian	44	144	112	9	51	35	232	368	69	121	0.12
Glas et al. (2007)	Ulcerative colitis	Caucasian	27	139	91	100	373	266	193	321	573	905	0.09
Glas et al. (2007)	Crohn's disease	Caucasian	62	167	142	100	373	266	291	451	573	905	0.09

INS, insertion; DEL, deletion; HWE, Hardy-Weinberg equilibrium; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; IDC, idiopathic dilated cardiomyopathy.

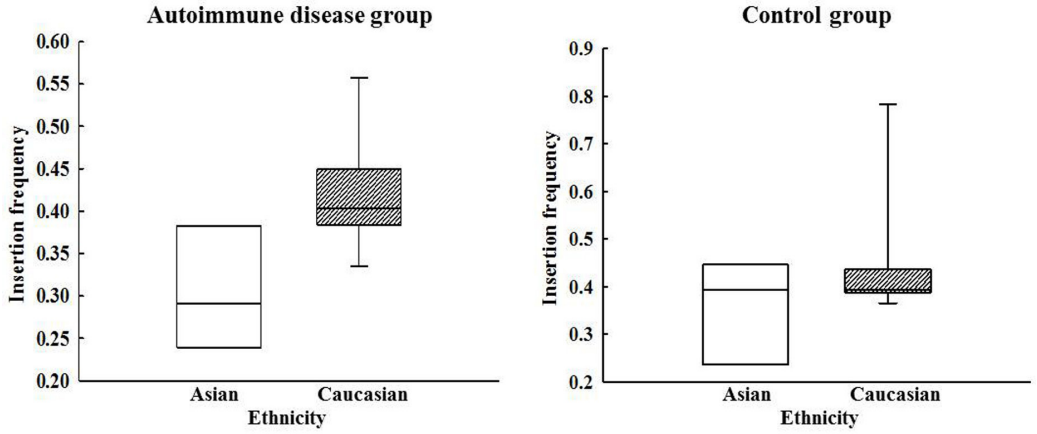

Figure 2. Insertion frequency of the HLA-G 14-bp insertion/deletion polymorphism in Asian and Caucasian populations.

Quantitative synthesis

Table 2 shows the results of the overall meta-analysis. The results indicated that the HLA-G 14-bp INS/DEL polymorphism was unrelated to the risk of AID (INS/INS *vs* INS/DEL + DEL/DEL, OR = 0.94, 95%CI = 0.70-1.20, P = 0.67; INS/DEL + INS/DEL *vs* DEL/DEL, OR = 0.95, 95%CI = 0.80-1.10, P = 0.59; INS/INS *vs* INS/DEL, OR = 0.99, 95%CI = 0.80-1.30, P = 0.93; INS/INS *vs* DEL/DEL, OR = 0.95, 95%CI = 0.70-1.30, P = 0.74; INS *vs* DEL, OR = 0.94, 95%CI = 0.80-1.10, P = 0.39; Table 2). In subanalyses, according to AID type, SLE and RA were analyzed. No association was detected between the HLA-G 14-bp INS/DEL polymorphism and SLE or RA (Table 3). These results suggest that the HLA-G 14-bp INS/DEL polymorphism does not contribute to the development of AID.

Table 2. Results of the meta-analysis in comparative genetic models.

Genetic comparison	Population	OR (95%CI)	P	Heterogeneity		Model
				P	I^2	
INS/INS *vs* INS/DEL + DEL/DEL	All	0.94 (0.70-1.20)	0.67	0.00008	69.82	Random
	Asians	0.93 (0.37-2.31)	0.87	0.0015	84.63	Random
	Caucasians	0.95 (0.72-1.27)	0.75	0.0017	66.08	Random
INS/DEL + INS/DEL *vs* DEL/DEL	All	0.95 (0.80-1.10)	0.59	0.002	61.69	Random
	Asians	0.72 (0.49-1.06)	0.10	0.033	70.51	Random
	Caucasians	1.06 (0.89-1.26)	0.52	0.063	44.38	Random
INS/INS *vs* INS/DEL	All	0.99 (0.80-1.30)	0.93	0.002	60.87	Random
	Asians	1.10 (0.48-2.51)	0.82	0.008	79.30	Random
	Caucasians	0.97 (0.74-1.26)	0.81	0.013	56.86	Random
INS/INS *vs* DEL/DEL	All	0.95 (0.70-1.30)	0.74	0.00002	72.18	Random
	Asians	0.79 (0.28-2.24)	0.66	0.0004	87.12	Random
	Caucasians	1.02 (0.74-1.40)	0.91	0.0023	64.89	Random
INS *vs* DEL	All	0.94 (0.80-1.10)	0.39	6.37E-06	74.04	Random
	Asians	0.80 (0.53-1.19)	0.27	0.0018	84.23	Random
	Caucasians	0.99 (0.85-1.16)	0.94	0.0011	67.35	Random

The random model was adopted if the result of the Q test was P < 0.05 or the I^2 statistic was > 50 %, and the fixed model was used if the result of the Q test was P > 0.05 or the I^2 statistic was <50%. OR, odds ratio; CI, confidence interval; INS, insertion; DEL, deletion.

Table 3. Results of the meta-analysis of different comparative genetic models in the SLE.

Genetic comparison	Population	OR (95%CI)	P	Heterogeneity		Model
				P	I^2	
INS/INS *vs* INS/DEL + DEL/DEL	All	1.13 (0.79-1.62)	0.51	0.066	58.36	Random
INS/DEL + INS/DEL *vs* DEL/DEL	All	1.19 (1.00-1.43)	0.05	0.154	42.85	Fixed
INS/INS *vs* INS/DEL	All	1.06 (0.73-1.54)	0.77	0.072	57.18	Random
INS/INS *vs* DEL/DEL	All	1.26 (0.86-1.83)	0.23	0.099	52.11	Random
INS *vs* DEL	All	1.13 (1.00-1.28)	0.05	0.114	49.64	Fixed

The random model was adopted if the result of the Q test was P < 0.05 or the I^2statistic was > 50%, and the fixed model was used if the result of the Q test was P > 0.05 or the I^2statistic was < 50%. OR, odds ratio; CI, confidence interval; INS, insertion; DEL, deletion.

DISCUSSION

Since the 14-bp INS/DEL polymorphism was first reported by Harrison et al. (1993), the association between the HLA-G 14-bp INS/DEL polymorphism and disease has been a research focus. Many studies have investigated the complications of pregnancy, such as recurrent spontaneous abortion and pre-eclampsia. Several studies have suggested that the HLA-G 14-bp INS/DEL polymorphism is associated with AIDs, such as SLE (Rizzo et al., 2008; Veit et al., 2009; Wu et al., 2009; Consiglio et al., 2011), RA (Rizzo et al., 2006; Veit et al., 2008), juvenile idiopathic arthritis (Veit et al., 2008), multiple sclerosis (Kroner et al., 2007), ulcerative colitis (Glas et al., 2007), Crohn's disease (Glas et al., 2007), idiopathic dilated cardiomyopathy (Lin et al., 2007), pemphigus vulgaris, and non-segmental vitiligo (Jeong et al., 2014).

Among polymorphisms in the HLA-G gene, the 14-bp INS/DEL polymorphism in the 3'-untranslated region of exon 8 has been shown to play an important role in the post-transcriptional regulation of HLA-G (Dahl and Hviid, 2012). The 14-bp INS/DEL polymorphism likely affects mRNA stability and expression; the presence of the 14-bp INS allele has been associated with lower levels of HLA-G mRNA and, to some extent, with lower levels of soluble HLA-G (Rebmann et al., 2001; Hviid et al., 2003, 2004). Decreased soluble HLA-G plasma concentrations may lead to chronic activation of inflammatory cells and contribute to the development of AIDs (Larsen and Hviid, 2009).

To explore the potential relationship between the HLA-G 14-bp INS/DEL polymorphism and AID risk, numerous case-control studies have been conducted. For SLE, the results obtained were inconclusive and even contradictory. Studies examining juvenile idiopathic arthritis, ulcerative colitis, Crohn's disease, idiopathic dilated cardiomyopathy, pemphigus vulgaris, and non-segmental vitiligo showed significant associations between the 14-bp INS/DEL and disease risk, while RA and multiple sclerosis showed no association. In SLE, to date, conflicting results have been reported. Rizzo et al. (2008) reported an increased frequency of the 14-bp INS among Italian patients, and Veit et al. (2009) and Consiglio et al. (2011) reported an excess of heterozygotes in Brazilian patients. However, Wu et al. (2009) detected no association between the HLA-G 14-bp INS/DEL polymorphism and SLE among Chinese patients. In the current meta-analysis, we found no association between this polymorphism and SLE. Rizzo et al. (2009) and Veit et al. (2008) studied the association between the 14-bp INS/DEL polymorphism and RA. Both studies showed consistent results: there was no difference between genotype and allelic frequencies for this polymorphism. A single study for each of the associations between this polymorphism and JIR, multiple sclerosis, ulcerative colitis, Crohn's disease, idiopathic dilated cardiomyopathy, pemphigus vulgaris, and non-segmental vitiligo has been reported (Gazit et al., 2004; Glas et al., 2007; Kroner et al., 2007; Lin et al., 2007; Veit et al., 2008; Jeong et al., 2014). Thus, we did not perform AID

subtype analyses of these cases, and the results should be interpreted cautiously.

This is the first meta-analysis to assess the relationship between polymorphisms in HLA-G 14-bp INS/DEL and the genetic susceptibility to AIDs. In the present meta-analysis, in total, 2704 cases and 3758 controls from 11 case control studies were included. Overall, our results showed no association between the HLA-G 14bp INS/DEL polymorphism and genetic susceptibility to AID, including SLE, RA, JIR, multiple sclerosis, ulcerative colitis, Crohn's disease, idiopathic dilated cardiomyopathy, pemphigus vulgaris, and non-segmental vitiligo.

The current meta-analysis had several limitations. First, the etiological mechanisms of AID are complex, in which gene-gene and gene-environment interactions are involved. It is possible that the current polymorphism has a partial effect of the development of AID, which would not be detected readily by meta-analysis. Second, the reports in this meta-analysis were obtained from the PubMed, EMBASE, and Korean Studies Information Service System databases. Thus, there is a possibility of publication bias. Third, the numbers of studies and individual sample sizes included in our pooled analysis were not sufficiently large for comprehensive analysis, particularly for AID subtype analyses, and further research is needed.

In conclusion, we conducted a meta-analysis of the HLA-G 14-bp INS/DEL polymorphism and the risk of AID development. Our results demonstrate that the HLA-G 14-bp INS/DEL polymorphism does not contribute to overall AID susceptibility. However, further well-designed studies with larger sample sizes are needed to confirm our results.

Conflicts of interest

The authors declare no conflict of interest.

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