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Association of interferon-induced helicase C domain (*IFIH1*) gene polymorphisms with systemic lupus erythematosus and a relevant updated meta-analysis

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ABSTRACT. Systemic lupus erythematosus (SLE) is a complex autoimmune disorder presenting heterogeneous clinical manifestations. A number of genes involved in SLE susceptibility are related to the type

I interferon (IFN) pathway. IFN mediates innate immune responses and its increased levels contribute to the breakdown of peripheral tolerance. Interferon-induced helicase C domain 1 (IFIH1) activates and modulates IFN responses through its caspase recruitment domain. In this study, we analyzed four *IFIH1* single nucleotide polymorphisms (SNPs): rs6432714, rs10930046, rs1990760, and rs3747517, in 337 patients with SLE and 373 healthy individuals from southeast and northeast Brazil. Our results did not find an association between *IFIH1* SNPs and SLE (P value >0.025 after Bonferroni's adjustment). However, meta-analysis of peer-reviewed articles from 2008 to 2015 and data from this study indicated an association between rs1990760 and SLE onset ($P < 0.05$). This is the first association analysis on *IFIH1* polymorphisms and SLE susceptibility in Brazilian populations.

Key words: IFIH1; SLE; SNPs; SLE clinical manifestations; Meta-analysis

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by the formation of pathogenic autoantibodies against nuclear antigens and breakdown of self-tolerance. SLE etiology is not completely known, and genetic predisposition and environmental factors play a key role in its pathogenesis. Additionally, SLE presents extensive and heterogeneous clinical manifestations varying according to ancestry, geography, and particularly gender (Tsokos, 2011). Several of the genes associated with SLE seem related to the type I interferon (IFN) pathway, and lead to increased serum levels of IFN-inducible genes, known as "IFN-signature" (Tsokos, 2011; Choubey, 2012).

Interferon-induced helicase C domain 1 (*IFIH1*) gene, located at chromosome 2 (2q24), encodes the homonymous protein, which recognizes viral dsRNA in the cytoplasm of infected cells and modulates IFN responses, such as production of pro-inflammatory cytokines and apoptotic processes (Chistiakov, 2010). Genetic association studies have confirmed that *IFIH1* is involved in autoimmune disorders, such as type 1 diabetes and Graves' disease; recently a link to SLE has been investigated (Smyth et al., 2006; Sutherland et al., 2007; Gateva et al., 2009). These studies have revealed that high levels of IFIH1 in lupus-prone mice could accelerate autoimmune processes and exacerbate the disease by increasing the levels of antinuclear autoantibodies (Crampton et al., 2012). Moreover, increased levels of IFIH1 in tissue-specific regions of chronic discoid lupus erythematosus patients (Zahn et al., 2011) indicate a key role in predisposition to SLE.

The association between *IFIH1* polymorphisms and SLE has been investigated in different populations, but not in the Brazilian one. In this study, we assessed the association between four *IFIH1* polymorphisms (rs6432714, rs10930046, rs1990760, and rs3747517) and SLE pathogenesis, as well as its clinical manifestations in Brazilian patients from two different cohorts. In addition, we conducted a meta-analysis of recent literature involving *IFIH1* rs1990760 and SLE susceptibility.

MATERIAL AND METHODS

Subjects

We evaluated 337 SLE patients and 373 healthy controls from two Brazilian cohorts identified as Southeast - Division of Clinical Immunology, University Hospital of the School of Medicine of Ribeirão Preto, University of São Paulo; and Northeast - Division of Rheumatology of Hospital das Clínicas, Federal University of Pernambuco. All clinical features of the cohorts are reported in Table 1. The present study was approved by the local Ethics Committees: Southeast CEP/HCRP/FMRP #2234/2007 and Northeast CAAE 03065312.3.0000.5208. SLE diagnosis was performed according to the criteria of the American College of Rheumatology.

Table 1. Demographic and clinical features from the two Brazilian cohorts.

Healthy controls	Southeast (N = 186)	Northeast (N = 187)
Gender		
Male	49%	25%
Female	51%	75%
Mean age (± SD)	37 (11)	31 (13)
Systemic lupus erythematosus (SLE) patients	(N = 153)	(N = 184)
Gender		
Male	7%	1%
Female	93%	99%
Mean age (± SD)	37.8 (12)	32 (7)
Mean age at diagnosis (± SD)	NA	31 (8)
Ethnic group		
European derived	76%	11%
African derived	24%	89%
Clinical/laboratorial characteristics		
Malar rash	56%	58.9%
Discoid rash	16%	17.8%
Photosensitivity	28.5%	67.3%
Ulcers	NA	19.6%
Arthritis	43%	72%
Serositis	25%	22.4%
Nephritic disorder	55%	50.5%
Neuropsychiatric disorder	19%	7.5%
Hematological alterations	53%	68.2%
Antinuclear antibody	82%	93.5%
Anti-DNA antibody (anti-dsDNA)	21.5%	24.4%
Anti-Sm antibody	NA	8.42%
Antiphospholipid syndrome	21%	5.6%

NA, not available.

SNP selection and *IFIH1* genotyping

Genomic DNA was extracted from peripheral whole blood using a salting out procedure as described by Sambrook et al. (1989). We selected four single nucleotide polymorphisms (SNPs) within *IFIH1*: rs6432714 (A > T), rs10930046 (T > C), rs1990760 (C > T), and rs3747517 (A > G).

All SNPs presented a minor allele frequency of at least 10%. They were selected using the SNPbrowser software 4.0 (Applied Biosystems, Foster City, CA, USA) and the HapMap database (http://hapmap.ncbi.nlm.nih.gov/). The tag SNP rs6432714 was located at intron 7, covering the region from intron 6 to intron 7 by linkage disequilibrium. The non-synonymous

SNP rs10930046 was located at exon 7. SNP rs1990760 was located within exon 15 encoding an alanine to threonine amino acid change at codon 946 (Ala946Thr) (Zhao et al., 2007). SNP rs3747517 was located at exon 13, encoding a missense mutation (Wang et al., 2013).

Genotyping was performed with commercially available fluorogenic allele-specific probes (TaqMan Probes; Applied Biosystems) using the ABI 7500 real-time PCR platform (Applied Biosystems). Allelic discrimination followed manufacturer protocols. Data were analyzed using the SDS software 2.3 (Applied Biosystems).

Statistical and meta-analysis

Hardy-Weinberg equilibrium (HWE) and SNP association tests between genotypes were performed using the exact test and the likelihood ratio test, respectively. Association tests between alleles were performed applying the chi-square test with Yate's correction for continuity. Estimate of the best genetic model was made by Akaike's information criterion. All analyses were performed using SNPassoc package for R v.3.0.2 (González et al., 2007). Linkage disequilibrium was calculated using the Haploview software v. 4.2 (Barrett et al., 2005). *Post hoc* statistical power tests were performed using the G*Power software v.3.1.3 (Faul et al., 2009). P values <0.025 were considered statistically significant after Bonferroni's correction.

Meta-analysis searches were performed by two researchers, who separately entered the key words "IFIH1 and SLE" in the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Periodicals CAPES (http://www.periodicos.capes.gov.br/) databases. Eleven and 109 articles were retrieved, respectively. Finally, *IFIH1* rs1990760 was assessed in nine different association studies from six peer-reviewed articles, including a genome-wide association study (GWAS) (SLEGEN et al., 2008; Gateva et al., 2009; Gono et al., 2010; Cunninghame Graham et al., 2011; Cen et al., 2013a; Enevold et al., 2014). All articles ranged from 2008 to 2015 (Figure 1). Meta-analysis also included our data on rs1990760 from Northeast and Southeast Brazilian cohorts; workflow is shown in Figure 1. HWE was performed by applying the chi-square test. Allele and genotype frequencies, as well as sample size of SLE and control groups for each selected paper were analyzed. When the Q test for heterogeneity gave P values <0.10, the DerSimonian-Laird random-effects model was applied using the metafor package for R (Viechtbauer, 2010). Publication bias in meta-analyses was assessed for asymmetry using a funnel plot graph (Figure 2).

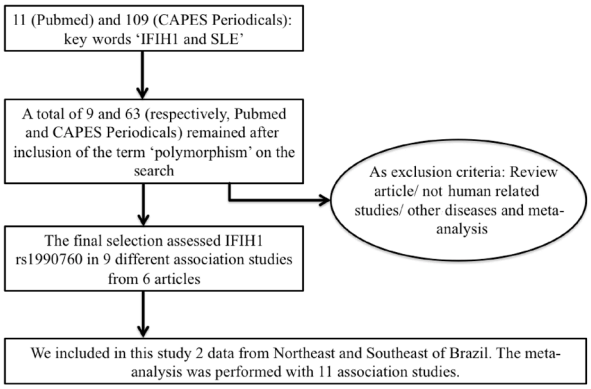

Figure 1. Schematic workflow indicating the criteria for meta-analysis.

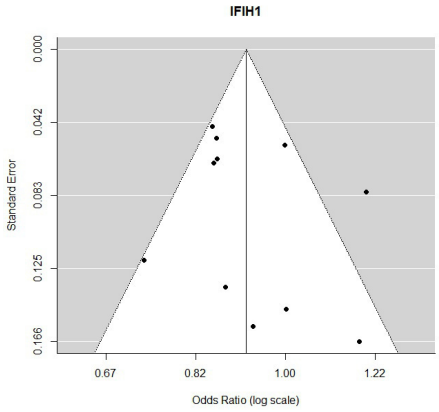

Figure 2. Asymmetry test funnel plot graph for meta-analysis.

RESULTS

We genotyped 337 SLE patients, 153 from Southeast (93% females, 7% males) and 184 from Northeast (99% females, 1% male) cohorts; and 373 healthy controls, 186 from Southeast (51% females, 49% males) and 187 from Northeast (75% females, 25% males) cohorts. The allele and genotype distributions from all tested SNPs within the *IFIH1* gene were in HWE, except for rs10930046 in patients from the Southeast cohort (P = 0.045). No associations were found in any population between the polymorphisms and SLE susceptibility or its clinical manifestations after Bonferroni's adjustment (Table 2). Power analysis indicated a variation 0.09-0.91. We considered an α error probability of 0.05 in the calculations.

Table 2. *IFIH1* SNP genotype frequencies in systemic lupus erythematosus patients (SLE) and healthy controls (HC) from two Brazilian cohorts.

SNP	Genotypes	SLE		HC		OR	CI(95%)	P
		N	%	N	%			
rs6432714	AA	209	62	247	68.6	1	-	-
	AT	114	33.8	99	27.5	0.72	0.5-1.03	0.07
	TT	14	4.2	14	3.9	0.94	0.42-2.12	0.88
rs10930046	TT	176	63.5	259	69.4	1	-	-
	TC	93	33.6	101	27.1	0.7	0.48-1.01	0.06
	CC	8	2.9	13	3.5	1.1	0.41-2.76	0.9
rs1990760	CC	97	30.3	93	30.3	1	-	-
	CT	163	50.9	151	49.2	0.93	0.65-1.35	0.71
	TT	60	18.8	63	20.5	1.13	0.71-1.79	0.61
rs3747517	CC	171	51.7	158	50.6	1	-	-
	CT	135	40.8	132	42.3	1.07	0.77-1.48	0.69
	TT	25	7.6	22	7.1	0.95	0.51-1.77	0.88

N = number of individuals; OR = odds ratio; CI = confidence interval. Binary logistic regression adjusted by gender and origin of sample is also shown.

Haplotype analysis indicated strong linkage disequilibrium between rs6432714 and rs10930046 (D' = 0.96) in the Southeast cohort, as well as among all studied polymorphisms in the Northeast cohort [D' = 0.99 (rs6432714 and rs10930046) and D' = 0.91 (rs1990769 and rs3747517), respectively]. However, no association was found with SLE in any of the studied populations.

In the meta-analysis study, we considered rs1990760 frequencies in 6613 patients with SLE worldwide and in 22,818 healthy controls. According to the allele model, we observed a statistically significant ($P < 0.05$) overall association with SLE protection (OR = 0.93, 95%CI = 0.85-0.99, P = 0.0266) when comparing C versus T alleles (Figure 3). The analysis also indicated heterogeneity (τ^2) of 0.01. Genotype distributions from all studies included in the meta-analysis were in HWE. In addition, sensitivity analysis was applied to estimate the influence of a specific study on meta-analysis. The results of removing each study, one by one, from the analysis are shown in Table 3. The asymmetry test did not identify a publication bias (P = 0.4462), as reported in Figure 2.

Table 3. Sensitivity analysis using *IFIH1* rs1990760 for meta-analysis.

OR	95%CI.lb	95%CI.ub	P|z|	I^2	P|Q|
0.9259	0.8492	1.0095	0.0808	64.7178	0.0025
0.9290	0.8508	1.0143	0.1005	62.1441	0.0047
0.9272	0.8490	1.0126	0.0929	63.9792	0.0030
0.9265	0.8504	1.0095	0.0810	64.4872	0.0026
0.9128	0.8425	0.9891	0.0258	64.9680	0.0023
0.9050	0.8339	0.9822	0.0169	59.0967	0.0089
0.8864	0.8362	0.9396	0.0001	31.5964	0.1556
0.9200	0.8481	0.9979	0.0445	65.5846	0.0019
0.9307	0.8619	1.0050	0.0670	60.7962	0.0063
0.9166	0.8456	0.9937	0.0345	65.6024	0.0019
0.9066	0.8400	0.9786	0.0119	61.7967	0.0051

OR = odds ratio; CI = confidence interval; lb = lower confidence interval bound; ub = upper interval bound; I^2 = measures the meta-analysis inconsistency.

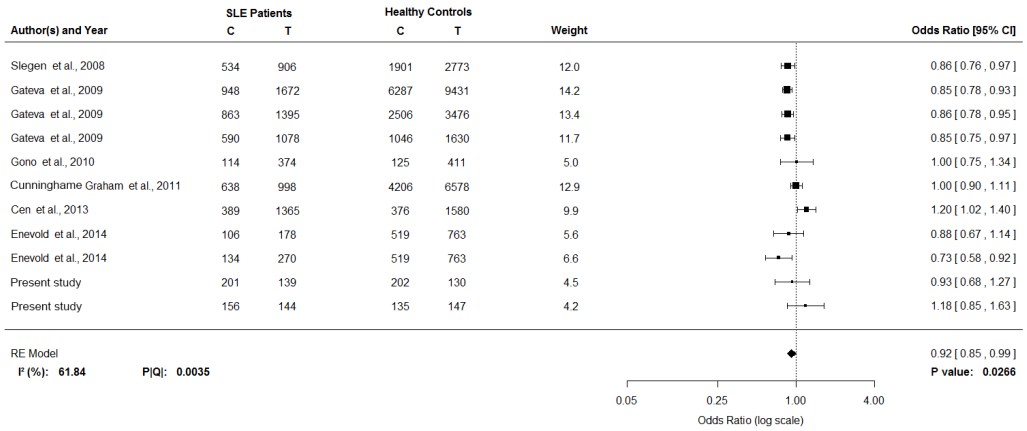

Figure 3. Allele model depicting all studies included in meta-analysis of SNP rs1990760.

DISCUSSION

IFN plays an important role in SLE pathogenesis by enhancing autoimmune processes and disease complications (Lenert, 2010). Studies on IFN-induced genes improve our understanding of the regulatory mechanisms involved in activity and development of SLE. IFIH1 acts as a cytoplasmic sensor for dsRNA, causing activation of NF-κB, IFN-regulatory factors 3 and 7, and increased IFN production (Enevold et al., 2014). Additionally, IFIH1 is expressed in different cells of the immune system, playing a significant role in autoimmune diseases (Cen et

al., 2013b). Herein, we performed a genetic association study between *IFIH1* polymorphisms and SLE predisposition, as well as its clinical manifestations, in two different Brazilian cohorts: Southeast and Northeast. We also carried out meta-analysis between *IFIH1* rs1990760 and SLE susceptibility, as this particular polymorphism is the focus of most attention worldwide.

In this study, we identified negative associations in both cohorts. The tested SNPs were located throughout *IFIH1*, mainly from intron 7 (rs6432714) to exon 15 (rs3747517). rs6432714 has never been investigated in patients with SLE; however, it has been associated with type 1 diabetes, an autoimmune disease, in the population of northeast Brazil (Moura et al., 2013). Recently, a whole-genome admixture mapping study identified *IFIH1* rs10930046 to be related to apoptosis, inflammation, and autoantibody production in patients with SLE (Molineros et al., 2013). In this study, we did not find any association between rs10930046 and SLE or its clinical features, confirming an earlier finding by Wang et al. (2013). However, the same study identified a protective effect against SLE development when performing a combined analysis with *IFIH1* rs78456138 and rs3747517.

IFIH1, which recognizes dsRNA viruses, has been proposed as a potential SLE activator. It has been implicated in the production of autoantigens, such as the RNA binding Ro60 KD antigen, and molecular mimicry (James et al., 1997; McClain et al., 2005; Stathopoulou et al., 2005). Viral infections may increase the level of lupus autoantigens by promoting cellular injury and apoptosis (Lenert, 2010). The first confirmed association involving *IFIH1* SNPs and SLE was made by Gateva et al. (2009), who identified the altered risk of SLE derived from the A946T polymorphism (rs1990760) in populations from Sweden and the USA. Later, these results were replicated by Cunninghame Graham et al. (2011), confirming that risk allele A or protective allele G were associated to SLE onset. Our results reinforced a previous GWAS, which reported a trend for association between rs1990760 and SLE susceptibility (SLEGEN et al., 2008).

rs1990760 is located within the RIG-1 regulatory domain encoded by exons 14-16 and was linked to increased IFN-α levels in patients with SLE positive for anti-dsDNA autoantibodies (Robinson et al., 2011; Molineros et al. 2013). rs1990760 is also the most studied *IFIH1* SNP associated with SLE, and has been demonstrated to increase *IFIH1* expression. This may lead to an IFN cascade initiated by nucleic acids (Guerra et al., 2012), and characteristic of SLE pathogenesis (Cen et al., 2013b).

The updated meta-analysis in our study showed association between rs1990760 and SLE, pointing towards a protective role for the C allele, thus reinforcing previous results by Gateva et al. (2009) and Enevold et al. (2014). Despite the overall divergent results obtained with rs1990760 in SLE (Figure 2), our meta-analysis indicates either a protective association for the C allele or no association at all. These differences might be explained by taking into account the heterogeneous genetic background of the populations included in this and other studies, as also proposed by Enevold et al. (2014). Sensitivity analysis estimates indicate that a large number of studies are required to produce more robust meta-analysis results.

In conclusion, our genetic association study on two different Brazilian cohorts, did not detect any association between the tested SNPs and SLE susceptibility or its clinical features. However, meta-analysis showed association between *IFIH1* rs1990760 and SLE, indicating that the rs1990760 C allele was linked to SLE.

Conflicts of interest

The authors declare no conflict of interest.

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