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Evaluation of genetic association between an *ITGAM* non-synonymous SNP (rs1143679) and multiple autoimmune diseases

Juan-Manuel Anaya[1,*], **Xana Kim-Howard**[2,*], **Sampath Prahalad**[3], **Alejandra Cherñavsky**[4], **Carlos Cañas**[5], **Adriana Rojas-Villarraga**[1], **John Bohnsack**[6], **Roland Jonsson**[7], **Anne Isine Bolstad**[8,9], **Johan G Brun**[9,10], **Beth Cobb**[2], **Kathy L. Moser**[2], **Judith A. James**[2,11], **John B. Harley**[12], and **Swapan K. Nath**[2]

[1]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario, Bogotá, Colombia

[2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, USA

[3]Departments of Pediatrics and Human Genetics, Emory University School of Medicine, Atlanta, GA, USA

[4]Immunogenetic Laboratory, Hospital de Clínicas José de San Martín, Universidad de Buenos Aires, Buenos Aires, Argentina

[5]Fundación Valle de Lili, Cali, Colombia

[6]Pediatric Immunology-Department of University of Utah, Salt Lake City, UT

[7]Broegelmann Research Laboratory, The Gade Institute, University of Bergen, Bergen, Norway

[8]Department of Clinical Dentistry, University of Bergen, Bergen, Norway

[9]Department of Rheumatology, Haukeland University Hospital, Bergen, Norway

[10]Section for Rheumatology, University of Bergen, Bergen, Norway

[11]Departments of Medicine and Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

[12]Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Abstract

Many autoimmune diseases (ADs) share similar underlying pathology and have a tendency to cluster within families, supporting the involvement of shared susceptibility genes. To date, most of the genetic variants associated with systemic lupus erythematosus (SLE) susceptibility also show association with others ADs. *ITGAM* and its associated 'predisposing' variant (rs1143679, Arg77His), predicted to alter the tertiary structures of the ligand-binding domain of *ITGAM,* may

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Address for Correspondence: Swapan K. Nath, Ph.D., Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City, OK 73104, swapan-nath@omrf.org, Phone: 405-271-7765, Fax: 405-271-4110.
*Both authors contributed equally

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play a key role for SLE pathogenesis. The aim of this study is to examine whether the *ITGAM* variant is also associated with other ADs. We evaluated case-control association between rs1143679 and ADs (N=18,457) including primary Sjögren's syndrome, systemic sclerosis, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, celiac disease, and type-1 diabetes. We also performed meta-analyses using our data in addition to available published data. Although the risk allele 'A' is relatively more frequent among cases for each disease, it was not significantly associated with any other ADs tested in this study. However, the meta-analysis for systemic sclerosis was associated with rs1143679 (p_{meta}=0.008). In summary, this study explored the role of *ITGAM* in general autoimmunity in seven non-lupus ADs, and only found association for systemic sclerosis when our results were combined with published results. Thus *ITGAM* may not be a general autoimmunity gene but this variant may be specifically associated with SLE and systemic sclerosis.

Keywords

ITGAM; autoimmune diseases; genetic susceptibility

1. Introduction

Genetic susceptibility of multiple autoimmune diseases (ADs) often share underlying commonalities [1]. The hypothesis that clinically distinct ADs may be controlled by a common set of susceptibility genes was put forward [1], and there is a growing understanding that susceptibility to the ADs is due to complex interactions between multiple genes and environmental factors. Some of these underlying predisposing factors may be shared among many ADs.

Recently, applying a trans-ethnic mapping approach, we identified and replicated an association between a variant at exon-3 (rs1143679) of Integrin-α-M (*ITGAM*, also known as CD11b) and systemic lupus erythematosus (SLE) susceptibility in individuals with Caucasian, African, and Hispanic populations [2–3]. Our subsequent comprehensive imputation-based association analysis of the *ITGAM-ITGAX* region also demonstrated that this missense variant, which changes this amino acid from an arginine to histidine (R77H), explained SLE-association with *ITGAM* [4].

ITGAM encodes the α-chain subunit of the heterodimeric Integrin-$\alpha_M\beta_2$, a cell surface receptor expressed primarily on monocytes and neutrophils. It plays an important role in activation, adherence, and migration of leucocytes through stimulated endothelium, and also in the phagocytosis of complement coated particles and neutrophil apoptosis [5]. Using a computer model, we also speculated that substitution of the residue 77 at this coding variant (R77H) may alter the conformation of the αI domain of $\alpha_M\beta_2$ which might affect the binding capacity of various ligands (i.e., ICAM1), implicated in susceptibility to various inflammatory ADs.

Several recent reports have examined the relationship between rs1143679 and non-SLE ADs, in particular RA [6–7] and SSc [8–9]. Although association was not found with RA, SSc association results were contradictory. The goal of this study was to further study the role of the *ITGAM* variant R77H (rs1143679), in general autoimmunity. Since rs1143679 is robustly associated with SLE we hypothesize that this association could be replicated in other ADs including primary Sjögren's syndrome (pSS), systemic scleroderma (SSc), multiple sclerosis (MS), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), celiac disease (CED), and type 1 diabetes (T1D).

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2. Materials and Methods

2.1 Study Populations

We used de-identified DNA samples from 2050 cases from seven ADs (pSS, SSc, MS, RA, JIA, CED, T1D) and 2879 controls from ethnically matched populations (Table 1). All subjects were enrolled into their respective studies after obtaining their written informed consent and following protocols approved by the appropriate institutional review boards. All patients with ADs met the international classification criteria for their respective disease [10–14].

The entire Colombian sample comprised of 1286 individuals enrolled at the Center for Autoimmune Diseases Research (CREA) and the Fundación Clínica Valle de Lili. Controls for the Colombian analyses included 763 individuals without a history of chronic inflammatory autoimmune or infectious diseases and was unrelated to patients.

Argentinean 222 CED patients and 189 controls were recruited through the Hospital de Clínicas José de San Martín, Buenos Aires, Argentina. Controls were healthy volunteers and unrelated family friends.

JIA cases were 454 children from the Intermountain States Database of Childhood Rheumatic Diseases (USA). Patients were diagnosed as defined by the International League of Associations for Rheumatology (ILAR) classification criteria. Controls were 589 healthy adults without a history of autoimmunity. Cases and controls were very similar in ethnicity, and predominantly (>90%) were of Northern European ancestry. Subjects were enrolled under protocols approved by the Institutional Review Board at the University of Utah.

The MS dataset was comprised of 996 (505 MS cases and 491 controls) participants recruited at the University of California, San Francisco (kindly provided by Dr. Jorge Oksenberg). All MS cases met well-established disease criteria [15] and baseline clinical characteristics of this patient dataset are reported in [16].

The SSc dataset was comprised of 488 individuals (87 SSc patients and 401 controls). These individuals were either locally recruited at Oklahoma Medical Research Foundation (Oklahoma City, USA) or were provided through the NIH-sponsored Scleroderma Registry and Repository from the University of Houston. All SSc cases met the American College of Rheumatology disease criteria [17].

We studied a cohort of 259 European-derived independent pSS patients and 446 ethnically matched normal healthy controls (European-American and Norwegian). All patients fulfilled the American–European Consensus Group classification criteria for pSS [12].

2.2 Genotyping

RA, JIA, MS, CED, pSS, T1D, and SSc samples were genotyped using TaqMan assays (Applied Biosystems). SNP genotyping (rs1143679) was completed using ABI custom TaqMan assays designed on File Builder 2.0 software. TaqMan SNP genotyping assays are carried out in 384-well plates using Applied Biosystems TaqMan Universal PCR Master Mix on an ABI 7900HT Sequence Detection System using SDS 2.0 software.

2.3 Statistical analysis

Allele and genotype frequencies were calculated for each population and tested for Hardy–Weinberg equilibrium (HWE) in controls. Case-control association were assessed by χ^2 test using 2×3 (genotypic test) and 2×2 (allelic test) contingency tables. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated using PLINK [18]. To assess for population

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stratification of controls at this variant, the overall F_{ST} (measure of the proportion of genetic diversity due to allele frequency differences among populations) was calculated using all control populations.

2.4 Power analysis

We assessed the statistical power to detect the association with the present samples using a retrospective power analyses using CATS [19] for the available samples (cases and controls), with a fixed minor allele frequency (MAF)=11% (based on controls), disease prevalence=1%, type-I error p=0.05, and OR=1.4 or OR=1.6.

2.5 Meta-analysis

Meta-analysis for pSS was performed using the three data sets from this study. RA and SSc meta-analyses were performed using genotype data presented in this study as well as publically available, published data. Overall and disease specific meta-analyses were performed using R-meta (http://cran.r-project.org/web/packages/rmeta/index.html) and CatMap [20]. Data was used from this present study as well as from published studies.

3. Results

Cases and controls for all populations were in HWE ($p \geq 0.01$) for rs1143679. Disease allele (A) frequencies were consistent across populations, with the highest and lowest MAF estimated to be 10.1% and 15.9% in European-American and Argentine controls, respectively. Overall $F_{ST}=0.003$ for control from all populations were not stratified at this variant, i.e. allele frequencies were not different between controls.

Summary of allelic associations and relevant information are given in Table 1. In our genotype data no association was observed between rs1143679 and any of the AD groups (p-values between 0.115 and 0.726). Since there were three independent pSS case-control sets we performed a combined analysis for the three pSS samples (347 cases and 601 controls data). However, this did not yield a significant association (p=0.336). Likewise, the meta-analysis for RA (2685 cases and 2710 healthy controls) using Colombian (present study), New Zealand [6], and Spanish [7] did not show a significant association ($p_{meta}=0.18$) between rs1143679 and RA. However, meta-analysis for SSc (4337 cases and 5326 healthy controls) 8550/9907, European-American (present study) and European [8–9], showed significant association between SSc and rs1143679 ($p_{meta}=0.008$) (Figure 1).

Our retrospective power estimate demonstrated that most of our disease-specific analyses were underpowered to detect a statistically significant differences. For an OR=1.4 we would have between 0.23–0.73 power to detect statistical differences for most populations (Table 1). However, the combined sample sets for the disease specific meta-analysis, RA, SSC, and pSS, achieved sufficient power to detect association with an OR=1.4.

4. Discussion

The genetic risk factors for ADs might well consist of two forms: those common to many ADs and those specific to a given disorder [21–22]. Combinations of common and disease-specific alleles at HLA and non-HLA genes, in interaction with epigenetic and environmental factors over time may determine the final clinical autoimmune phenotype [1]. Since the *ITGAM* SNP rs1143679 has been consistently associated SLE across multiple, diverse populations, it is important to assess its relation with other ADs. We genotyped relatively homogenous samples with ethnically matched controls to assess association between the only “causal” (to date) SLE susceptibility variant of *ITGAM* and multiple ADs. Samples were collected from populations of Latin America and from European descent.

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While we did not find significant association between SSc and rs1143679, our meta-analysis incorporating published data revealed modest but significant association. The other ADs assessed in this study did not yield association with rs1143679. However, we observed higher MAF from the cases in most ADs. Many of our AD groups were relatively small and may have been under-powered to detect modest associations, especially CED and T1D. However, for RA, pSS, and SSc, our meta-analyses were large enough to detect association. Therefore, with modest ORs we are confident about these results. Additionally, since the samples are from different ethnic groups there may be an impact of admixture on this population. This issue is not yet thoroughly worked out. However, based on previous work on *ITGAM* association in Latin Americans samples we did not see an impact of admix on *ITGAM* association [3]. The association between *ITGAM* and SLE was replicated in Latin Americans as well as the major HLA genes associated with SLE and other ADs [23–24].

It has been postulated that patients with the ‘A’ allele of the non-synonymous coding SNP rs1143679 might express high amounts of ITGAM making these individuals prone to develop lupus nephritis or aggravate the inflammatory process by increasing initial kidney cellular infiltration [25–27]. On the other hand, there is not enough evidence concerning the implications of ITGAM in the pathogenesis of SSc or its sub-phenotypes. Monocytes CD11b (ITGAM) are the predominant cell population infiltrating skin and lungs in patients with early, rapidly progressive SSc [25]. Although ITGAM may play an important role in SSc [28–31], further functional studies are required to elucidate the relation between *ITGAM* polymorphism and disease outcome.

None of other ADs we assessed, including pSS, MS, RA, T1D, CED, and JIA were associated with rs1143679. Our results were consistent with recent reports which indicate that *ITGAM* is not associated with RA [6–7]. The first study examined the association in RA cases and controls from New Zealand and the UK [6], and the second study in RA cases and controls from Spain [7]. Despite sufficient power for both studies, neither study found an association between RA and *ITGAM*, even when patients were stratified by clinical features of RA. Additionally, meta-analysis using our data and published reports did not reveal significant association between RA and rs1143679.

A recent report [32] indicates that *ITGAM* SNP rs1143679 is associated with discoid lupus erythematosus (DLE) in a Finnish and Swedish cohort. DLE is a chronic skin condition of sores with inflammation and scarring favoring the face, ears, and scalp and at times on other body areas. Of interest, in addition to reporting strong association of rs1143679 with lupus related renal involvement, this SNP was also strongly related to skin manifestations beyond overall SLE susceptibility [33–34]. It is possible that CD11b could mediate the inflammatory processes in SLE as CD11b deficiency in mice enhanced differentiation of naive T cells to interleukin (IL) 17 producing T-helper type17 cells [35]. Additionally, serum IL-17 concentrations were higher in patients with discoid lupus and SLE compared with normal controls [36]. Thus far, the question for future research: what is the role of *ITGAM* in predisposition for lupus-related skin manifestations. Another research question would examine if this potential association is specific to European-derived populations only.

In summary, the current study explored the role of *ITGAM* in general autoimmunity in non-SLE ADs, and only found association for SSc when our results were combined with published results. ITGAM, as other SLE associated molecules such as complement C reactive protein, is involved in the immune opsonin pathway and in phagocytic clearing of nuclear antigens and apoptotic debris, which provide excessive exposure of lupus-related antigens to immune cells [37]. Analysis of gene-gene interactions in the opsonin pathway and its relationship to SLE and SSc may provide a system-based approach to identify additional candidate genes associated with these diseases [37]. Interestingly, the coexistence

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of SLE and SSc is not rare [38] and this association is part of a cluster of polyautoimmunity [38]. Although *ITGAM* could play an important role in SSc, further functional studies are required to elucidate the relation between *ITGAM* polymorphism and SSc course and outcome. Thus *ITGAM* may not be a general autoimmunity gene but this variant may be specifically associated with SLE, DLE, and SSc pathogeneses.

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Take-Home Messages

- An association between a variant at exon-3 (rs1143679) of Integrin-α-M (*ITGAM*) and SLE susceptibility has been described in multiple ethnic populations.
- ITGAM encodes the α-chain subunit of the heterodimeric Integrin-αMβ2, a cell surface receptor expresses primarily on monocytes and neutrophils. It plays an important role in different processes of leucocytes.
- Although genetic susceptibility of autoimmune diseases often share underlying commonalities, R77H (rs1143679) polymorphism of *ITGAM* gene appears to exclusively influence susceptibility towards SLE and SSc.
- Although *ITGAM* could play an important role in SSc, further functional studies are required to elucidate the relation between *ITGAM* polymorphism and SSc course and outcome.

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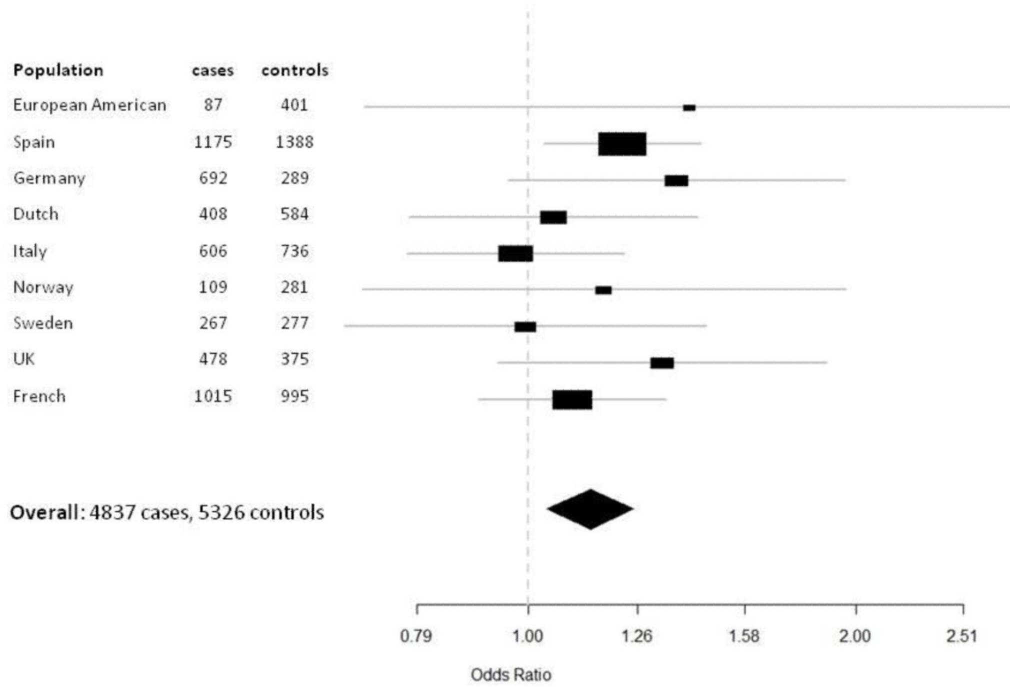

Fig. 1.
Meta-analysis for *ITGAM* variant rs1143679 and SSc in the current study and published data

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Table 1

Results of case-control association of rs1143679 and multiple autoimmune diseases.

Disease	Population	Ref	Case/Cont	MAF (A) Case	MAF (A) Ctrl	P-value	OR (L95-U95)	Power* OR=1.4	Power* OR=1.6
SSc	EA	present study	87/401	0.143	0.101	0.115	1.48 (0.91–2.41)	0.25	0.47
SSc	European	Carmona, et al., 2011	3735/3930	0.138	0.131	0.019	1.12 (1.02–1.23)	1.00	1.00
SSc	French	Coustet, et al., 2011	1015/995	0.135	0.126	0.387	0.92 (0.71–1.19)	0.97	1.00
SSc	***Meta-analysis***		***4337/5326***	---	---	***0.008***	***1.12 (1.03–1.22)***	***1.00***	***1.00***
RA	Columbian	present study	304/240	0.127	0.104	0.304	1.25 (0.82–1.89)	0.46	0.76
RA	New Zealand	Phipps-Green, et al., 2009	746/564	0.095	0.099	0.720	0.95 (0.73–1.24)	0.82	0.98
RA	Spanish	Suarez-Gestal, et al., 2009	1635/1906	0.172	0.160	0.244	1.09 (1.00–1.20)	0.71	1.00
RA	***Meta-analysis***		***2685/2710***	---	---	***0.178***	***1.08 (0.97–1.20)***	***0.87***	***1.00***
pSS	Colombian	present study	88/155	0.136	0.107	0.325	1.33 (0.76–2.32)	0.23	0.42
pSS	Norwegian	present study	133/136	0.134	0.114	0.491	1.20 (0.72–2.01)	0.26	0.47
pSS	EA	present study	126/310	0.143	0.134	0.726	1.08 (0.71–1.64)	0.31	0.56
pSS	***Meta-analysis***		***347/602***	---	---	***0.336***	***1.17 (0.88–1.55)***	***0.65***	***0.92***
T1D	Columbian	present study	131/368	0.128	0.107	0.386	1.23 (0.77–1.95)	0.32	0.59
CED	Argentine	present study	222/189	0.134	0.159	0.329	0.81 (0.54–1.23)	0.37	0.64
JIA	EA	present study	454/589	0.105	0.115	0.476	0.90 (0.68–1.20)	0.73	0.96
MS	EA	present study	505/491	0.120	0.106	0.320	1.15 (0.87–1.52)	0.72	0.95
Overall Sample Size			**8550/9907**						

Power based on minor allele frequency of 11%, disease prevalence of 1%, p-value 0.05; MAF=minor allele frequency

Abbreviations: MAF=minor allele frequency; EA: European ancestry, Ref: reference, Ctrl: control, SSc: scleroderma, JIA: juvenile idiopathic arthritis, MS: multiple sclerosis, CED: celiac disease, RA: rheumatoid arthritis, T1D: type 1 diabetes, pSS: primary Sjögren's syndrome.