# The Functional Polymorphism 844 A>G in $Fc_{\alpha}RI$ *(CD89)* Does Not Contribute to Systemic Sclerosis or Rheumatoid Arthritis Susceptibility

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***ABSTRACT.*** ***Objective.*** To investigate the role of the $Fc_{\alpha}RI$ 844 A>G functional polymorphism in the genetic predisposition to rheumatoid arthritis (RA) and systemic sclerosis (SSc) susceptibility.

***Methods.*** The study population was composed of 1401 patients with SSc, 642 patients with RA, and 1317 healthy controls. The $Fc_{\alpha}RI$ (*CD89*) single-nucleotide polymorphism rs16986050 was genotyped by pyrosequencing.

***Results.*** We observed no significant deviation of the genotype and allele frequencies in RA and SSc compared to controls. A metaanalysis and a recessive and dominant model yielded similar negative results.

***Conclusion.*** Our data show that the $Fc_{\alpha}RI$ 844 A>G polymorphism is not associated with SSc or RA susceptibility. (First Release Dec 15 2010; J Rheumatol 2011;38:446–9; doi:10.3899/jrheum.100427)

*Key Indexing Terms:*
SYSTEMIC SCLEROSIS RHEUMATOID ARTHRITIS IgA *CD89* $Fc_{\alpha}RI$

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Fc receptors (FcR) play a pivotal role in linking humoral and cellular components of immunity by bringing about the recognition of antigens bound to immunoglobulins (Ig). There is a large body of evidence describing genetic variations in FcR that were found to be associated with a wide range of autoimmune pathologies, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)[1]. Although disease-specific IgA is present in autoimmune disease, its effect remains the least scrutinized. IgA exhibits its immunoregulatory functions mainly by triggering cellular effector functions through the Fc-α receptor ($Fc_\alpha R$) on the cell surface. $Fc_\alpha RI$ (*CD89*) is the functionally most important IgA receptor and is expressed on various cells of the immune system[2]. Serum IgA regulates secretion of interleukin 1ß (IL-1ß), IL-10, tumor necrosis factor-α (TNF-α), IL-6, and IL-1RA. To mediate these effects, the FcR-associated signal-transducing transmembrane γ-chain (FCGR) needs to be present in complex with $Fc_\alpha RI$[3]. Intriguingly, a polymorphism (844 A>G, rs16986050) in the coding region of $Fc_\alpha RI$ leads to an amino acid change of serine 248 to glycine (S248G), which stimulates IL-6 production and induces cytokine release in the absence of the FCGR chain[4]. This variant was found to be enriched in 2 populations with SLE compared to healthy controls[5]. In other autoimmune diseases, specific IgA antibodies are also present. For instance, antitopoisomerase IgA and rheumatoid factor (RF) IgA and anti-citrullinated protein (ACPA) IgA are present in systemic sclerosis (SSc) and RA[6,7]. Although the exact role of IgA in these diseases remains to be elucidated, we hypothesized that an increased inflammatory response upon disease-specific IgA binding caused by this polymorphism could contribute to these diseases. For this reason we investigated the frequency of this variant in patients with SSc and RA.

## MATERIALS AND METHODS

*Study population.* The study population was composed of 1401 patients with SSc, 642 Dutch patients with RA, and 1317 healthy controls derived from blood donors. The subjects were matched demographically and by age and sex. Because SSc is a rare disease, we composed a cohort of 5 case-control sets of Europeans (Table 1). All patients fulfilled the American College of Rheumatology (ACR) 1980 classification criteria for SSc[8]. The local ethics committee from each center approved the study. Patients and controls provided written informed consent. All patients included in our study were classified as having limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc), using the criteria proposed by LeRoy, *et al*[9]. Further information on clinical phenotype was recorded as well. Autoantibody testing was performed in every center separately using either ELISA or immunofluorescence microscopy (Table 1). Our study included RA patients who met the ACR 1987 revised criteria for RA[10] (Table 2).

*Genotyping.* The $Fc_\alpha RI$ 844 A>G variant was genotyped by pyrosequencing, congruent with our previous reports. Pyrosequencing reactions were performed according to the manufacturer's instructions on a PSQ-HS96A system (Biotage, Uppsala, Sweden)[5,11].

*Statistical analysis.* Significance levels were calculated with Fisher's exact test. P values < 0.05 were considered significant after Bonferroni adjustment. Homogeneity of OR was assessed with Breslow-Day statistics. Pooled OR were calculated under a fixed-effects model (Mantel-Haenszel). In the SSc population (n = 1401), our study reaches a power of 80% to detect an OR of 1.21. The estimation of the power for the RA population (n = 645) is 80% to detect an OR of 1.31.

## RESULTS

After genotyping, no divergence in Hardy-Weinberg equilibrium was observed. We observed no significant deviation in genotype and allele frequencies of the $Fc_\alpha RI$ 844 A>G polymorphism in Dutch patients with RA compared to Dutch controls and when comparing patients who were ACPA-positive or negative and patients with RA who were RF-positive or negative (Table 3). No significant hetero-

*Table 2.* Clinical characteristics of the study patients with rheumatoid arthritis (n = 642).

| Characteristic | |
|---|---|
| Age, yrs (SD) | 65 (13) |
| Women, % | 66.5 |
| RF-positive, % | 78 |
| Anti-CCP-positive, %* | 65 |

* Status available for 155 patients. RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide.

*Table 1.* Clinical characteristics of the study patients with systemic sclerosis.

| Population | Netherlands | Spain | Germany | Sweden | Italy |
|---|---|---|---|---|---|
| No. | 143 | 231 | 422 | 161 | 444 |
| Age, yrs (SD) | 56 (13) | 55 (13) | 57 (12) | 53 (15) | 54 (13) |
| Disease duration, mo (SD) | 132 (87) | 143 (90) | 112 (109) | 83 (73) | 146 (138) |
| Women, % | 73.2 | 83.8 | 83.2 | 78.8 | 89.0 |
| Limited phenotype, % | 74.8 | 73.7 | 61.2 | 72.0 | 74.4 |
| ANA-positive, % | 73.2 | 85.4 | 83.2 | 75.1 | 81.6 |
| Anti-topo I-positive, % | 22 | NA | 24.8 | 16.7 | 25.2 |
| ACA-positive, % | 26.8 | 46.7 | 41.3 | 26.1 | 47.1 |
| Controls | | | | | |
| Age, yrs (SD) | 45 (12) | 56 (14) | 48 (9) | 52 (11) | 52 (14) |
| Women, % | 69.3 | 85.1 | 82.4 | 80.2 | 85.0 |

ANA: antinuclear antibodies; anti-topo I: antitopoisomerase I antibodies; ACA: anticentromere antibodies.

geneity was detected between the 5 European populations, justifying a metaanalysis. Initially, we observed a divergence in genotype distribution in the Swedish (p = 0.034) and Spanish (p = 0.019) populations with SSc. The same was observed for lcSSc susceptibility in both the Swedish (p = 0.016) and Spanish (p = 0.022) populations with SSc. The $Fc_{\alpha}RI$ 844G allele was associated with an increased risk of SSc, lcSSc, and anticentromere antibody (ACA)-positive SSc in the Swedish cohort (respectively, p = 0.019, 0.030, and 0.032). The 844G allele was found less frequently in the Italian ACA-positive patients with SSc (p = 0.042; Table 3). However, after correction for multiple testing, no result remained significant. In addition, a metaanalysis and recessive and dominant models yielded similar negative results (Table 3 and data not shown).

## DISCUSSION

We show that a common polymorphism in the coding region of $Fc_{\alpha}RI$ is not associated with RA or SSc susceptibility in 2 large cohorts. Considering the power of our study to detect significant deviations in allele frequencies of the $Fc_{\alpha}RI$ 844G variant between cases and controls, it is unlikely that the lack of association is due to a type 2 error. This indicates that the $Fc_{\alpha}RI$ 844 A>G polymorphism does not play a role in the susceptibility to RA and SSc and does not influence clinical phenotype. This is in contrast to the previous association of the $Fc_{\alpha}RI$ 844 A>G polymorphism with SLE susceptibility[5]. A number of polymorphisms have been found to influence susceptibility to RA as well as SSc and SLE[12,13]. These polymorphisms therefore form merely a genetic foundation for autoimmunity in general. Intriguingly, the poly-

*Table 3.* Genotype frequencies of the $Fc_{\alpha}RI$ 844 A>G polymorphism in 5 European systemic sclerosis populations and a Dutch rheumatoid arthritis population.

| Origin | Subtype | Total, n | AA, % | AG, % | GG, % | P vs Control | A, % | G, % | p vs Control |
|---|---|---|---|---|---|---|---|---|---|
| Italy | SSc | 444 | 0.76 | 0.22 | 0.02 | 0.484 | 0.87 | 0.13 | 0.277 |
| | lcSSc | 327 | 0.75 | 0.24 | 0.01 | 0.253 | 0.87 | 0.13 | 0.211 |
| | dcSSc | 112 | 0.74 | 0.21 | 0.05 | 0.409 | 0.85 | 0.15 | 0.903 |
| | ACA+ | 144 | 0.80 | 0.19 | 0.01 | 0.123 | 0.90 | 0.10 | 0.042 |
| | Anti-topo+ | 146 | 0.71 | 0.27 | 0.01 | 0.631 | 0.85 | 0.15 | 0.923 |
| | Control | 362 | 0.73 | 0.25 | 0.02 | | 0.85 | 0.15 | |
| Sweden | SSc | 161 | 0.58 | 0.30 | 0.12 | 0.034 | 0.73 | 0.27 | 0.019 |
| | lcSSc | 116 | 0.60 | 0.26 | 0.14 | 0.016 | 0.73 | 0.27 | 0.030 |
| | dcSSc | 45 | 0.53 | 0.40 | 0.07 | 0.252 | 0.73 | 0.27 | 0.107 |
| | ACA+ | 44 | 0.55 | 0.32 | 0.13 | 0.055 | 0.70 | 0.30 | 0.039 |
| | Anti-topo+ | 25 | 0.64 | 0.28 | 0.08 | 0.712 | 0.78 | 0.22 | 0.591 |
| | Control | 165 | 0.67 | 0.29 | 0.04 | | 0.81 | 0.19 | |
| Spain | SSc | 231 | 0.66 | 0.26 | 0.08 | 0.019 | 0.79 | 0.21 | 0.639 |
| | lcSSc | 157 | 0.66 | 0.25 | 0.09 | 0.022 | 0.79 | 0.21 | 0.794 |
| | dcSSc | 56 | 0.62 | 0.29 | 0.09 | 0.274 | 0.76 | 0.24 | 0.900 |
| | ACA+ | 89 | 0.66 | 0.28 | 0.06 | 0.388 | 0.80 | 0.20 | 0.525 |
| | Anti-topo+ | NA | NA | NA | NA | | NA | NA | |
| | Control | 250 | 0.60 | 0.36 | 0.04 | | 0.78 | 0.22 | |
| Germany | SSc | 422 | 0.64 | 0.31 | 0.05 | 0.564 | 0.79 | 0.21 | 0.680 |
| | lcSSc | 261 | 0.68 | 0.29 | 0.03 | 0.532 | 0.82 | 0.18 | 0.612 |
| | dcSSc | 160 | 0.63 | 0.32 | 0.05 | 0.642 | 0.79 | 0.21 | 0.722 |
| | ACA+ | 78 | 0.69 | 0.25 | 0.06 | 0.936 | 0.81 | 0.19 | 0.825 |
| | Anti-topo+ | 50 | 0.58 | 0.34 | 0.08 | 0.616 | 0.75 | 0.25 | 0.507 |
| | Control | 266 | 0.66 | 0.28 | 0.06 | | 0.80 | 0.20 | |
| Netherlands | SSc | 143 | 0.69 | 0.28 | 0.03 | 0.434 | 0.83 | 0.17 | 0.769 |
| | lcSSc | 98 | 0.72 | 0.24 | 0.04 | 0.983 | 0.84 | 0.16 | 0.999 |
| | dcSSc | 33 | 0.61 | 0.39 | 0.00 | 0.09 | 0.80 | 0.20 | 0.484 |
| | ACA+ | 34 | 0.76 | 0.24 | 0.00 | 0.455 | 0.88 | 0.12 | 0.383 |
| | Anti-topo+ | 33 | 0.70 | 0.27 | 0.03 | 0.860 | 0.83 | 0.17 | 0.862 |
| | RA | 642 | 0.71 | 0.26 | 0.03 | 0.593 | 0.84 | 0.16 | 0.582 |
| | Control | 274 | 0.72 | 0.24 | 0.04 | | 0.84 | 0.16 | |
| Total Mantel-Haenszel | SSc | 1401 | 0.68 | 0.27 | 0.05 | 0.662 | 0.82 | 0.18 | 0.675 |
| | lcSSc | 959 | 0.68 | 0.26 | 0.06 | 0.842 | 0.81 | 0.19 | 0.825 |
| | dcSSc | 406 | 0.63 | 0.32 | 0.05 | 0.102 | 0.79 | 0.21 | 0.192 |
| | ACA+ | 389 | 0.72 | 0.24 | 0.04 | 0.278 | 0.84 | 0.16 | 0.287 |
| | Anti-topo+ | 254 | 0.68 | 0.28 | 0.04 | 0.394 | 0.82 | 0.18 | 0.547 |
| | Control | 1317 | 0.68 | 0.28 | 0.04 | | 0.82 | 0.18 | |

SSc: systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; RA: rheumatoid arthritis; ACA: anticentromere antibodies; anti-topo: antitopoisomerase antibodies; NA: not analyzed.

morphism we investigated seems to be specific for SLE. An explanation for this can perhaps be found in the properties of IgA in these 3 conditions. In contrast to RA and SSc, mean total IgA has been found to be significantly elevated in SLE compared to controls, and IgA-mediated inflammation may thus play a proportionally larger role in SLE[14,15]. IgA ACPA antibodies are present in 29% of the overall patients with RA and in 47% of the patients with RA who have IgG anti-CCP antibodies. In SSc, IgA anti-topoisomerase antibodies have been described in 26.6% in a study containing 45 patients[15,16]. However, this implies that in a subgroup of patients with SSc or RA who have high IgA antibody titers, which has been described in patients with RA who smoke, an effect of this variant may still be present[15]. These data were not available from the cohorts described in our study. In addition, autoantibody measurements have been performed in separate centers with either ELISA or immunofluorescence microscopy. Caution is warranted when comparing outcomes from these techniques[17]. Future investigations into the role of IgA and the $Fc_{\alpha}RI$ gene might therefore benefit from taking this observation into account and focusing on subgroups with high IgA titers. Altogether, we could not demonstrate a role for the $Fc_{\alpha}RI$ 844 A>G variant in SSc and RA.


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