Influence of IL2RA rs2104286 Polymorphism in the Risk of Biopsy-proven Giant Cell Arteritis

LUIS RODRÍGUEZ-RODRÍGUEZ, SANTOS CASTAÑEDA, TOMÁS R. VÁZQUEZ-RODRÍGUEZ, INMACULADA C. MORADO, BEATRIZ MARÍ-ALFONSO, CARMEN GÓMEZ-VAQUERO, JOSÉ A. MIRANDA-FILLOY, NORBERTO ORTEGO-CENTENO, JAVIER NARVAEZ, RICARDO BLANCO, BENJAMÍN FERNÁNDEZ-GUTIÉRREZ, JAVIER MARTÍN, and MIGUEL A. GONZÁLEZ-GAY

ABSTRACT. Objective. To assess the influence of the IL2RA rs2104286 A>G polymorphism on susceptibility to and clinical spectrum of manifestations of biopsy-proven giant cell arteritis (GCA).

Methods. Our study included 318 patients with biopsy-proven GCA. DNA from patients and healthy controls was obtained from peripheral blood. Samples were genotyped for the IL2RA rs2104286 A>G polymorphism using a predesigned TaqMan allele discrimination assay and by PCR amplification.

Results. Although GCA patients showed a higher frequency of the minor allele homozygote of IL2RA rs2104286 (GG) compared to controls (5.1% vs 2.8%, respectively; p = 0.06, odds ratio 1.84, 95% confidence interval 0.91–3.70), the allele distribution showed no significant differences between GCA patients and controls. Stratification of GCA patients according to sex or polymyalgia rheumatica, jaw claudication, visual ischemic manifestations, or other severe ischemic complications did not yield significant differences in the allele or genotype frequencies of the IL2RA rs2104286 polymorphism.

Conclusion. IL2RA rs2104286 polymorphism does not appear to be a genetic risk factor for susceptibility to biopsy-proven GCA. Also, this polymorphism does not seem to be implicated in the clinical expression of this vasculitis. (First Release September 1 2010; J Rheumatol 2010;37:2331–3; doi:3899/jrheum.100388)

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IL2RA GENE POLYMORPHISM

From Instituto de Parasitología y Biomedicina López-Neyra, C.S.I.C., Granada; Department of Rheumatology, Hospital Clínico San Carlos; Department of Rheumatology, Hospital de la Princesa, Madrid; Department of Rheumatology, Hospital Xeral-Calde, Lugo; Department of Internal Medicine, Corporació Sanitaria Parc Taulí, Universitat Autònoma de Barcelona, Sabadell; Department of Rheumatology, Hospital Universitari de Bellvitge-IDIBELL, L’Hospitalet de Llobregat, Barcelona; Department of Internal Medicine, Hospital Clínico San Carlos, Granada; and Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain.

L. Rodríguez-Rodríguez, MD, Instituto de Parasitología y Biomedicina López-Neyra, C.S.I.C., Granada, and Department of Rheumatology, Hospital Clínico San Carlos; S. Castañeda, MD, PhD, Department of Rheumatology, Hospital de la Princesa; T.R. Vázquez-Rodríguez, MD; J.A. Miranda-Filloy, MD, Department of Rheumatology, Hospital Xeral-Calde; I.C. Morrado, MD; B. Fernández-Gutiérrez, MD, PhD, Department of Rheumatology, Hospital Clínico San Carlos; B. Mari-Alfonso, MD, Department of Internal Medicine, Corporació Sanitaria Parc Taulí, Universitat Autònoma de Barcelona, Sabadell; C. Gómez-Vaquero, MD, PhD; J. Narvaez, MD, PhD, Department of Rheumatology, Hospital Universitari de Bellvitge-IDIBELL, L’Hospitalet de Llobregat; N. Ortego-Centeno, MD, PhD, Department of Internal Medicine, Hospital Clínico San Carlos; J. Martín, MD, PhD, Instituto de Parasitología y Biomedicina López-Neyra, C.S.I.C.; R. Blanco, MD, PhD; M.A. González-Gay, MD, PhD, Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, IFIMAV.

Dr. González-Gay and Dr. Martín shared senior authorship in this study.

Address correspondence to Dr. M.A. González-Gay, Rheumatology Service, Hospital Universitario Marqués de Valdecilla, IFIMAV, Avda. de Valdecilla, s/n, 39008 Santander, Spain.

E-mail: miguelaggay@hotmail.com

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Giant cell arteritis (GCA) is an inflammatory vasculopathy affecting medium-size and large arteries, with inflammatory lesions extending throughout all layers of the arterial wall. Vascular infiltrate is composed of T cells (the dominant cell population), highly activated macrophages and, in some cases, multinucleated giant cells. CD4 T cells undergo clonal proliferation, confirmed by the isolation of identical clones from separate and independent parts of the same artery, and from both temporal arteries of the same patient. This phenomenon supports an antigen-specific trigger within the affected arteries that induces production of interleukin 2 (IL-2) and interferon-γ.

IL-2 has a central role for T cell responses, by controlling the magnitude of clonal expansion, development of effector cells, and subsequent contraction of antigen-specific T cells. Also, this cytokine plays a role in activation-induced cell death and in the regulatory T cell homeostasis.

IL-2 receptor (IL-2R) is composed of 3 different subunit complexes, CD25, CD122, and CD132. CD25 is mostly limited to activated T cells, including regulatory T cells.

IL2RA rs2104286 (A>G) polymorphism has been associated with susceptibility to various autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, and type 1 diabetes. This polymorphism has shown no association with other autoimmune diseases such as systemic lupus ery...
thematous or antineutrophil cytoplasmic antibody-associated vasculitis7.

GCA is a complex polygenic disease in which more than 1 genetic locus is likely to contribute to disease susceptibility and severity8.

Taking these considerations together, the aim of our study was to assess the potential association between IL2RA rs2104286 polymorphism and GCA in a large series of patients with biopsy-proven disease. We also studied whether this polymorphism may be implicated in the clinical spectrum of manifestations of GCA.

MATERIALS AND METHODS

Patients. We recruited 318 Spanish patients who fulfilled the 1990 American College of Rheumatology classification criteria for GCA9. All patients had a positive temporal artery biopsy10. Subjects were from Departments of Rheumatology or Internal Medicine from 5 Spanish cities: Lugo, Madrid, L’Hospitalet de Llobregat, Sabadell, and Granada. A control population of 867 healthy controls from corresponding cities matched with GCA patients was also assessed. Approval from the local ethical committees and written informed consent from patients and controls were obtained.

Clinical manifestations including polymyalgia rheumatica, jaw claudication, visual ischemic manifestations, cerebrovascular accidents (including stroke and/or transient ischemic attacks), severe ischemic manifestations, and the presence of a “true” occlusive disease were assessed10,11,12.

Genotyping methods. DNA from patients and controls was obtained from peripheral blood, using standard methods. Samples were genotyped for IL2RA rs2104286 A>G polymorphism using a TaqMan 5’ allele discrimination assay (Applied Biosystems, Foster City, CA, USA), following the manufacturer’s specifications.

Statistical analysis. Power of the study was assessed using Quanto v1.2.3. We used the chi-square test and Fisher exact test for Hardy-Weinberg equilibrium and statistical analysis to compare allelic and genotypic distributions. Odds ratios (OR) and 95% confidence intervals (CI) were calculated according to Woolf’s method using the Statcalc program (Epi-Info 2002; US Centers for Disease Control, Atlanta, GA, USA).

RESULTS

Clinical features of patients with GCA are summarized in Table 1. No evidence of departure from Hardy-Weinberg equilibrium was observed in controls. The case:control ratio was 1:2.7. The power of our study to find a difference between GCA patients and controls with an estimated OR was 1:2.7. The power of our study to find a difference between GCA patients and controls with an estimated OR was 1:2.7. The power of our study to find a difference between GCA patients and controls with an estimated OR was 1:2.7.

Association of IL2RA rs2104286 polymorphism with GCA. Allele frequencies in controls were similar to those reported6. We found a nonsignificant trend towards a higher frequency of homozygotes for the minor allele G among GCA patients compared to controls (GG in GCA patients 5.1% vs 2.8% in controls; p = 0.06, OR 1.84, 95% CI 0.91–3.70; Table 2). However, no significant differences were found in the allelic distribution between GCA patients and controls.

Genotype and allele frequencies of IL2RA rs2104286 polymorphism according to patients’ clinical manifestations. No significant differences in the genotypic or allelic frequencies were found when GCA patients were stratified according to sex or presence or absence of specific features of the disease (Table 3).


discussion

We examined for the first time the contribution of the IL2RA rs2104286 polymorphism to GCA susceptibility in a large series of histologically confirmed patients. However, our results do not confirm a role of the IL2RA rs2104286 polymorphism in susceptibility to GCA or in the clinical expression of this vasculitis. In this regard, only a nonsignificant increased frequency of homozygotes for the minor allele G among GCA patients compared to healthy controls was found.

IL2RA rs2104286 polymorphism has been associated with other autoimmune diseases, especially with multiple sclerosis4,5. We aimed to establish the influence of this polymorphism in GCA because of the role that IL-2 has in CD4+ T cell regulation. Although IL-2 is dispensable for the generation of effective T cell-mediated immunity, several studies indicate that a failure in the production of CD4+CD25+ regulatory T cells is the underlying cause of autoimmunity.

Table 1. Main clinical features of 318 patients with biopsy-proven giant cell arteritis Data in parentheses are % unless otherwise indicated.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Variable</th>
</tr>
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<tbody>
<tr>
<td>Age at diagnosis, yrs, median (IQR)</td>
<td>75 (70–79)</td>
</tr>
<tr>
<td>Women</td>
<td>216 (68)</td>
</tr>
<tr>
<td>Headache</td>
<td>267 (84)</td>
</tr>
<tr>
<td>Abnormal temporal artery on examination</td>
<td>196 (62)</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>151 (48)</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>130 (41)</td>
</tr>
<tr>
<td>Visual ischemic manifestations*</td>
<td>68 (21)</td>
</tr>
<tr>
<td>Stroke</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Severe ischemic manifestation**</td>
<td>169 (53)</td>
</tr>
<tr>
<td>True occlusive disease***</td>
<td>44 (14)</td>
</tr>
</tbody>
</table>

* Transient visual loss including amaurosis fugax, permanent visual loss, diplopia. ** At least one of: visual manifestations, cerebrovascular accident (stroke and/or transient ischemic attacks), jaw claudication, limb claudication of recent onset. *** At least one of: permanent visual loss, stroke, limb claudication of recent onset.

Table 2. Genotype and allele frequencies of IL2RA rs2104286 polymorphism in healthy controls and patients with biopsy-proven GCA.

<table>
<thead>
<tr>
<th>Controls, n = 867 (%)</th>
<th>GCA, n = 318 (%)</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA 559 (64.5)</td>
<td>202 (63.5)</td>
<td>1 = reference</td>
<td></td>
</tr>
<tr>
<td>AG 284 (32.8)</td>
<td>100 (31.4)</td>
<td>0.86</td>
<td>0.97 (0.73–1.30)</td>
</tr>
<tr>
<td>GG 24 (2.8)</td>
<td>16 (5.1)</td>
<td>0.06</td>
<td>1.84 (0.91–3.70)</td>
</tr>
<tr>
<td>AA + AG 843 (97.3)</td>
<td>302 (94.9)</td>
<td>1 = reference</td>
<td></td>
</tr>
<tr>
<td>GG 24 (2.8)</td>
<td>16 (5.1)</td>
<td>0.06</td>
<td>1.86 (0.93–3.70)</td>
</tr>
<tr>
<td>A 1402 (80.9)</td>
<td>504 (79.2)</td>
<td>1 = reference</td>
<td></td>
</tr>
<tr>
<td>G 332 (19.1)</td>
<td>132 (20.8)</td>
<td>0.38</td>
<td>1.11 (0.88–1.39)</td>
</tr>
</tbody>
</table>
in the absence of IL-2. In GCA patients, the peripheral blood count of CD4+CD25+ regulatory T cells is not significantly different from that observed in healthy subjects. IL2RA rs2104286 polymorphism has no effect on the percentage of CD4+CD25+ regulatory T or memory CD4+CD25+ T cells. However, it is associated with a lower percentage of CD4+ naive cells expressing CD25+ on the cell surface; it is also associated with a lower proportion of CD69+CD4+ naive T cells that upregulate CD25 upon T cell activation. As a consequence, it is possible that this polymorphism might cause decreased production of IL-2, which would impair CD4+CD25+ regulatory T cell function, taking into account that these cells themselves do not secrete IL-22 and this cytokine seems to function as a T cell growth factor for them.

Our results do not confirm a major contribution of IL2RA rs2104286 polymorphism in GCA.

REFERENCES


