The role of a functional variant of TYK2 in vasculitides and infections

L. Ortiz-Fernández[1], R. López-Mejias[2], F.D. Carmona[3], A.L. Castaño-Nuñez[4], on behalf of the Spanish GCA Study Group, IgAV Study Group, AAV Study Group, and HIV Study Group, P.A. Lyons[5], A. Caruz[6], M.F. Gónzalez-Escribano[4], K.G.C. Smith[5], M.A. González-Gay[2], J. Martin[1]

[1]Instituto de Parasitología y Biomedicina López-Neyra, CSIC, Granada, Spain; [2]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain; [3]Departamento de Genética e Instituto de Biotecnología, Universidad de Granada, Spain; [4]Department of Immunology, Hospital Universitario Virgen del Rocío (IBiS, CSIC, US), Sevilla, Spain; [5]Departments of Medicine, University of Cambridge School of Clinical Medicine, Cambridge Biomedical Campus, UK; [6]Immunogenetics Unit, Department of Experimental Biology, University of Jaén, Spain.

Abstract

Objective

The TYK2 gene encodes a tyrosin kinase which is involved in multiple immune functions. A functional variant of this gene has been identified to play a protective role in multiple autoimmune diseases. The goal of this study was to evaluate the involvement of this variant of TYK2 in vasculitides [giant cell arteritis (GCA), ANCA-associated vasculitis (AAV) and IgA vasculitis (IgAV)] and viral infections [hepatitis C virus (HCV) and human immunodeficiency virus type I (HIV-1)].

Methods

The study sample was composed of 13,745 European individuals. The genotyping was performed by Immunochip and TaqMan 5' allele discrimination assays and the allele frequencies were compared using PLINK.

Results

Although the results obtained did not reach the genome-wide level of significance, p-values at nominal significance were observed, suggesting that the TYK2 variant provides protection against two vasculitides: GCA (p=5.94E-3; OR (95%CI) = 0.56 (0.37–0.85) and AAV (p=6.79E-3; OR (95%CI) = 0.65 (0.47–0.89). However, this variant was not found to be associated with IgAV. No evidence was gained that the TYK2 variant confers susceptibility to HCV and HIV-1 infection.

Conclusion

This is the first study to propose the association between the TYK2 and both GCA and AAV. Our findings also suggest that TYK2 does not play a relevant role in IgAV or in susceptibility to HCV and HVI-1.

Key words

giant cell arteritis, TYK2, ANCA-associated vasculitis, IgA vasculitis, hepatitis C virus, HVI-1

Lourdes Ortiz-Fernández, PhD
Raquel López-Mejias, PhD
Francisco D. Carmona, PhD
Angel L. Castaño-Nuñez, PhD
Paul A. Lyons, PhD
Antonio Caruz, PhD
Maria F. Gónzalez-Escribano, PhD
Kenneth G.C. Smith, FMedSci, PhD
Miguel A. González-Gay, MD, PhD
Javier Martin, MD, PhD

Please address correspondence to:
Lourdes Ortiz Fernández,
Instituto de Parasitología
y Biomedicina López-Neyra,
Consejo Superior de Investigaciones
Científicas, Parque Tecnológico
Ciencias de la Salud,
Avenida del Conocimiento 17,
18016-Armilla, Granada, Spain.
E-mail: lurortiz.fernandez@gmail.com
and
Javier Martín
(same postal address as above)
E-mail: javiermartin@ipb.csic.es

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Introduction

The aetiology of autoimmune diseases is not well understood, although there is evidence that interaction between multiple susceptibility genes and environmental factors influences the predisposition and prognosis of these diseases (1). Occasionally, immune disorders share some genetic components, thereby suggesting that some molecular pathways may be common to these disorders (2).

An example of a common risk locus for autoimmune diseases is *TYK2*. This gene encodes a tyrosine kinase member of the Janus kinase (JAKs) family, which role in many immunological processes has been widely reported (3, 4). It is known that TYK2 is involved in type I interferon (IFN) and interleukin (IL12 and IL23) signalling (4). TYK2 is also implicated in Th1 and Th17 cell differentiation and is engaged in natural killer (NK) cell and B-cell maturation (5, 6). In the last decade, several studies have described the association between different polymorphisms in this locus and multiple autoimmune diseases such as systemic lupus erythematosus (SLE), Crohn's disease (CD), rheumatoid arthritis (RA) and systemic sclerosis (SSc) (7-10). To identify genetic associations within the *TYK2* region, Dendrou *et al*. carried out a thorough analysis that revealed that *TYK2* plays a protective role in autoimmunity. The authors also found that rs34536443 (P1104A) is the only polymorphism with a demonstrable impact on TYK2 function by causing an imbalance in cytokine signalling (11).

Systemic vasculitides are a heterogeneous group of autoimmune diseases by which inflammation in the blood vessel walls leads to tissue injury and eventually organ failure (12, 13). Despite the considerable progress made during the last decade in the understanding of the genetic basis of systemic vasculitides, the number of identified risk loci for most types of vasculitis remains significantly low as compared to other immune-mediated diseases (14, 15). Based on the existing evidence that *TYK2* is an interesting candidate gene, we investigated if a reported functional variant of *TYK2* (rs34536443, P1104A) plays a role in systemic vasculitis. Three clinical patterns of vasculitides were analysed, namely: giant cell arteritis (GCA), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immunoglobulin A (IgA) vasculitis (IgAV).

Interestingly, there is evidence of loss-of-function mutations in *TYK2* that increase susceptibility to microorganisms by inhibiting the cytokine-like type I IFN-signalling pathway (16, 17). Several studies have assessed the association between the *TYK2* locus and different infectious conditions including Chagas disease (18) and tuberculosis (19). However, no studies have been conducted to analyse the specific role of the functional *TYK2* variant in viral infections. Considering the above and taking into account that type I IFN pathway is essential for the anti-viral immune system (20), we decided to investigate the potential association between the functional variant of *TYK2* and two common and severe viral infections, *i.e*. hepatitis C virus (HCV) and human immunodeficiency virus type I (HIV-1).

In summary, the aim of this study was to determine the role of the functional *TYK2* variant rs34536443 in autoimmunity and viral infections. To such purpose we analysed the association between *TYK2* and three clinical patterns of vasculitides (GCA, AAV and IgAV) and two types of viral infections (HCV and HVI-1).

Material and methods

Study cohorts

The study population used to investigate the association between the *TYK2* variant rs34536443 and clinically distinct patterns of vasculitides was composed of 11,892 individuals. The GCA sample consisted of 763 Spanish individuals diagnosed in accordance with the 1990 American College of Rheumatology classification criteria (21). Only patients with a positive temporal artery biopsy were enrolled, as described elsewhere (22). IgAV data were collected from 315 patients from Spain diagnosed according to the guidelines established by Michel *et al*. (23) and the American College of Rheumatology classification criteria for IgAV (24). AAV data were compiled from 685 patients from UK diagnosed using the EMEA clinically-based

Table I. Genotype and minor allele frequency of rs3456443 in patients diagnosed with vasculitis and healthy individuals.

Disease	Population	Subgroup (n)	Genotype, n (%)			Allele test			
			CC	CG	GG	MAF (%)	*p*-value*	OR	95% CI
Giant cell arteritis (GCA)	Spanish	GCA patients (794)	0 (0)	29 (3.66)	761 (95.84)	1.84			
		Controls (1516)	0 (0)	98 (6.46)	1418 (93.54)	3.24	5.94E-3	0.56	0.37-0.85
IgAV vasculitis (IgAV)	Spanish	IgAV patients (311)	0 (0)	16 (5.14)	295 (94.86)	2.57			
		Controls (1516)	0 (0)	98 (6.46)	1418 (93.54)	3.23	3.88E-1	0.79	0.46-1.35
ANCA-associated vasculitis (AAV)	UK	AAV patients (670)	1 (0.15)	40 (5.97)	629 (93.88)	3.13			
		Controls (8604)	31 (0.36)	755 (8.77)	7818 (90.86)	4.70	6.79E-3	0.65	0.47-0.89

MAF: minor allele frequency; OR: odds ratio for the minor allele. *All *p*-values have been calculated for the allelic model.

algorithm (25). In total, 1,517 healthy subjects from Spain and 8,612 from UK were included as healthy controls. A more detailed description of each cohort is provided elsewhere (26-28).

A total of 1,853 individuals from two independent cohorts from Spain were included for analysis of viral infections (HCV and HIV-1). HCV data were collected from 253 subjects with persistent HCV infection (chronic hepatitis C) and 347 non-infected individuals, as described elsewhere (29). The HIV-1 sample was composed of 893 subjects exposed to HIV-1 infection by two distinct routes of exposure (sexual and injection drug use), 567 HIV-1 infected patients, and 326 HIV-1 exposed uninfected (EUI) subjects. In total, 360 healthy individuals who tested negative for HIV-1 and HCV were used as healthy controls. The inclusion criteria have been described in detail elsewhere (30).

The study was approved by the local ethical committees of the different participating centers in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment in the study.

Genotyping methods and quality controls

Genotyping of vasculitis samples was performed using the Immunochip platform. Case and control genotypes were obtained from previously published Immunochip studies (26, 28, 31). The same stringent quality controls were applied to all Immunochip datasets, as described before (26, 31).

Genotyping of viral infection cohorts was performed using TaqMan SNP genotyping technology. Genomic DNA was extracted from peripheral blood samples by standard methods. Genotyping was performed by 5' allele discrimination predesigned assays (assay_ID: C 60866522_10), Thermo Fisher Scientific (Waltham, Massachussetts, USA) in a LightCycler 480 Real-Time PCR System (Roche Applied Science, Mannheim, Germany), and in a MX3005 thermocycler (Stratagene) for HVC and HIV-1, respectively.

Statistical analysis

All statistical analyses were performed using PLINK V1.07 (http://zzz.bwh.harvard.edu/plink/) software (32). The χ^2 test was used to assess Hardy-Weinberg equilibrium (HWE), which was determined at a significance level of 0.01 for all groups of individuals. To establish associations, we compared allelic and genotypic frequencies in patients vs. healthy controls. To avoid any statistical error arising from the use of different genotyping platforms, comparisons were performed using the same platform. Statistical significance for these comparisons was determined using 2x2 contingency tables and χ^2 or Fisher's exact test, when necessary. Odds ratios (OR) and 95% confidence intervals (CI) were calculated according to Woolf's method. The genome-wide level of significance (5.00E-08) was set as cut-off *p*-value to define significant associations. Since the association between the polymorphism analysed in the current study and multiple autoimmune diseases has been previously confirmed in several independent studies (7-10), we used the term "nominal significance" to report findings with *p*-value <0.008, interpreting them as suggestive associations. This *p*-value is obtained by performing a multiple testing correction for six independent comparisons that have been made in this work. The statistical power of our study is shown in Supplementary Table S1 and was calculated using Power Calculator for Genetic Studies 2006 software under an additive model (33).

Ethics approval

Consent was obtained from all patients, and ethical approval obtained from Comité de Bioética del Consejo Superior de Investigaciones Científicas and the local ethical committees of the different participating centres.

Results

The genotyping success rate exceeded 95% for all datasets. No divergence from HWE was observed in any of the groups tested.

Firstly, in order to explore whether the *TYK2* variant rs34536443 was associated with the three clinically distinct patterns of vasculitides (GCA, AAV and IgAV), a comparison of allele frequencies was performed in patients vs. healthy controls. As shown in Table I, the frequencies of the minor allele of the *TYK2* variant were lower in patients than in healthy individuals in all comparisons. Although the results revealed no association at a genome-wide level of significance, suggestive associations at a nominal significance were observed for GCA [*p*=5.94E-3; OR (95%CI) = 0.56 (0.37–0.85)] and AAV [*p*=6.79E-3; OR (95%CI) = 0.65 (0.47–0.89)]. In both cases, the studied polymorphism potentially conferred protection against GCA and AAV, showing similar ORs.

Table II. Genotype and minor allele frequency of rs34536443 in HCV or HIV-1 infected patients and healthy individuals.

Infection	Population	Genotype, n (%)				Allele test			
		Subgroup (n)	CC	CG	GG	MAF (%)	*p*-value*	OR	95% CI
Hepatitis C virus (HCV)	Spanish	HCV patients (248)	1 (0.40)	14 (5.65)	233 (93.95)	3.23			
		Controls (342)	1 (0.30)	25 (7.30)	316 (92.40)	3.95	5.14E-1	0.81	0.43-1.52
Human immunodeficiency virus (HIV-1)	Spanish	HIV-1 patients (563)	1 (0.17)	39 (6.93)	523 (92.90)	3.64			
		EUI (321)	0 (0)	23 (7.17)	298 (92.83)	3.58	9.50E-1†	1.02	0.60-1.71
		Controls (343)	1 (0.29)	22 (6.41)	320 (93.29)	3.50	8.74E-1‡	1.04	0.62-1.74

MAF: minor allele frequency; OR; odds ratio for the minor allele.
*All *p*-values have been calculated for the allelic model. † *p*-value for the HIV-1 *vs*. EUI comparison; ‡ *p*-value for the HIV-1 *vs*. controls comparison.

Regarding IgAV, although the direction of the OR was consistent with the other two vasculitides, the differences in minor allele frequency did not reach any statistical significance [*p*=3.88E-1; OR (95%CI) = 0.79 (0.46–1.35)].

Secondly, we investigated whether *TYK2* may influence the risk for viral infections. To such purpose, we analysed the association between the rs34536443 variant and both HCV and HIV-1 infection. The results obtained did not reveal any statistically significant differences in allele frequencies between HCV-infected individuals and healthy controls [*p*=5.14E-1; OR (95%CI) = 0.81 (0.43–1.52)] (Table II). We also checked for the association between the functional *TYK2* variant rs34536443 and the risk for HIV-1 infection. A comparison was performed of allele frequencies in healthy controls, infected patients [*p*=9.50E-1; OR (95%CI) =1.02 (0.60–1.71)], and individuals exposed to the HIV-1 virus who remained uninfected (EUI) [*p*=8.74E-1; OR (95%CI) =1.04 (0.62-1.74)]. We did not find any significant differences (Table II). Therefore, our results suggested that the functional *TYK2* variant rs34536443 does not represent a risk factor for infection by HCV or HIV-1.

Discussion

While *TYK2* has been associated with multiple immune-mediated diseases, this is the first study to assess the role of *TYK2* in genetic predisposition to GCA and AAV. The results of our study identify the functional *TYK2* variant rs34536443 (P1104A) as a new potential protective factor against GCA and AAV. In contrast, *TYK2* rs34536443 does not seem to play a relevant role in IgAV. Finally, no evidence has been obtained that *TYK2* rs34536443 is a risk factor for HIV-1 or HCV infection.

In line with the results of previous studies on autoimmune diseases, our study suggested that *TYK2* has a protective role in GCA and AAV (8-10, 34). Of the multiple immune mechanisms in which TYK2 is involved, it has been described to play a key role in the regulation of multiple cytokines (16). The functional *TYK2* variant rs34536443 encodes a proline to alanine substitution at position 1,104 in the kinase domain of the protein. This substitution of highly conserved residues reduces TYK2 activity by decreasing pro-inflammatory cytokine signalling, such as type I IFN, IL12 and IL23 (11). Interestingly, one or more of these cytokine pathways are involved in the pathophysiology of GCA and AAV (35, 36). In addition, it has been described that TYK2 is implicated in Th1 and Th17 cell differentiation (6). In this sense, recent studies have revealed that both cell types are directly involved in the main immunological pathways which serve as mechanism effectors in the pathogenesis of both types of vasculitides (35, 37). Moreover, genes that encode proteins related to IL12 and IL23 have been associated with vasculitides in previous studies. More specifically, *IL12B* and *IL12RB2* have been recently described as susceptibility factors for GCA (38, 39). *IL12B* encodes a subunit shared by IL12 and IL23, and *IL12RB2* encodes a transducing component of the heterodimeric IL12 receptor (40). IL23 promotes Th-17 differentiation and function. IL12 recruits tyrosine kinases such as TYK2 and is an essential cytokine in Th1 response (41). Therefore, in agreement with previous studies, we provide further evidence of the involvement of IL12/IL23 cytokine signalling pathways and Th-1 and Th-17 cells in the pathophysiology of these disorders. However, given that the results of our study only have detected associations at a nominal significance, replication studies will be needed to confirm the protective effect of this variant in GCA and AAV.

Our results do not support that *TYK2* plays a relevant role in the development of IgAV. Other genes functionally related to *TYK2* have not been found to be associated with IgAV either (14, 15). However, a possible association cannot be definitely discarded, given the low statistical power of this study to detect moderate effects (OR=0.8). Despite been the largest cohort of IgAV European patients published to date, further investigations will be required to elucidate if *TYK2* is involved in the pathogenesis of this form of vasculitis.

The lack of TYK2 function has been related to the mild immunodeficiency that characterises susceptibility to viral infection (16). However, no significant association was observed between *TYK2* and susceptibility to HCV and HIV-1 infection. Although the statistical power of this study to detect low effects is moderate, our findings are consistent with the results of similar studies on the association between *TYK2* and different infectious diseases. A recent study investigated the role of *TYK2* in susceptibility to tuberculosis in a West African population (19). Another study was undertaken to determine the associ-

ation between TYK2 and HIV-1 control (42). Although no studies have been conducted to examine the role of the functional variant *TYK2* rs34536443, no evidence has been obtained on a genetic association between HIV-1 and *TYK2* (19, 42). In a recent work, no relationship was observed between *TYK2* and Chagas (18).

Given that the functional *TYK2* variant rs34536443 seems to confer protection against autoimmunity without increasing the risk of infection, TYK2 could be an excellent candidate for drug targeting in therapies for autoimmune diseases (11). In fact, the therapeutic inhibition of JAK kinases is attracting increasing interest from research groups (43).

In conclusion, the present study identifies *TYK2* as a potential protective factor against GCA and AAV. In addition, our results suggest that *TYK2* does not play a relevant role in IgAV and is not a risk factor for HIV-1 or HCV infection. Yet, larger studies are necessary to completely discard the involvement of *TYK2* in viral infections.

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Collaborating authors

Spanish GCA Study Group members

Juan J. Alegre-Sancho[7], Ricardo Blanco[8], José Luis Callejas[9], Luis Caminal-Montero[10], Santos Castañeda[11], M C. Cid[12], Marc Corbera-Bellalta[13], Eugenio de Miguel[14], J. Bernardino Díaz-López[10], Begoña Escalante[11], Patricia Fanlo Mateo[16], Benjamín Fernández-Gutiérrez[17], Antonio Fernández-Nebro[18], María Jesús García-Villanueva[19], Carmen Gómez-Vaquero[20], Elena Grau[21], Mercedes Guijarro Rojas[22], José Hernández-Rodríguez[12], Ana Hidalgo-Conde[23], Francisco J. López-Longo[24], Ana Belén Madroñero Vuelta[25], Begoña Marí-Alfonso[26], Lina Martínez[24], Agustín Martínez-Berriochoa[27], Víctor Manuel Martínez-Taboada[8], Aleida Martínez-Zapico[10], José A. Miranda-Filloy[28], Jordi Monfort[29], Inmaculada C. Morado[17], Javier Narváez[30], M. Carmen Ordóñez-Cañizares[18], Norberto Ortego-Centeno[9], Mercedes Pérez-Conesa[31], Sergio Prieto-González[12], Marc Ramentol-Sintas[32], Enrique Raya[17], Raquel Ríos-Fernández[9], Luis Rodríguez-Rodríguez[17], José A. Román[21], Luis Sáez-Comet[31], Julio Sánchez-Martín[34], Olga Sánchez-Pernaute[35], Roser Solans[32], Bernardo Sopeña[36], Laura Tío[29], Ainhoa Unzurrunzaga[37], Esther F. Vicente[11]

IgAV Study Group members

Maximiliano Aragües[38], Ricardo Blanco[8], Juan María Blanco-Madrigal[39], Santos Castañeda[11], Diego de Argila[38], Eva Galíndez-Aguirregoikoa[40], Fernanda Genre[2], Manuel León Luque[39], Javier Llorca[41], Verónica Mijares[3], José A. Miranda-Filloy[28], Antonio Navas Parejo[42], Norberto Ortego-Centeno[9], Trinitario Pina[3], Sara Remuzgo-Martínez[3], Esteban Rubio[39], Belén Sevilla-Perez[43], Begoña Ubilla[3]

AAV Study Group members

Paul Brenchley[44], Afzal N Chaundrhy[45], David G Clayton[46], Panos Deloukas[47], Lorraine Harper[48], David RW Jayne[45], Mark A Little[49], Sandosh Padmanabhan[50], Charles D Pusey[51], Tim F Rayner[45], Alan D Salamana[49], Caroline O Savage[52], Sapna Trivedi[45], Richard A Watts[53]

HIV Study Group members

Luis Miguel Real[54], Antonio Rivero-Juárez[55], Marina Laplana[56*]

Affiliations

[7]Dept. of Rheumatology, Hospital Universitario Doctor Peset, Valencia, Spain.
[8]Dept. of Rheumatology, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain.
[9]Dept. of Internal Medicine, Hospital Clínico San Cecilio, Granada, Spain.
[10]Dept. of Internal Medicine, Hospital Central de Asturias, Oviedo, Spain
[11]Dept. of Rheumatology, Hospital Universitario La Princesa, IIS-I Princesa, Madrid, Spain.
[12]Vasculitis Research Unit, Dept. of Autoimmune Diseases, Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain.
[13]Vasculitis Research Unit, Dept. of Autoimmune and Systemic Diseases, Hospital Clinic, University of Barcelona, Centre de Recerca Biomèdica Cellex (IDIBAPS), Barcelona, Spain.
[14]Dept. of Rheumatology, Hospital Universitario de La Paz, Madrid, Spain.
[15]Dept. of Internal Medicine, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain.
[16]Dept. of Internal Medicine, Hospital Virgen del Camino, Pamplona, Spain; Dept.of Rheumatology, Hospital Universitario Marqués de Valdecilla, Facultad de Medicina, Universidad de Cantabria, Santander, Spain.
[17]Dept. of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain.
[18]Dept. of Rheumatology, Hospital Carlos Haya, Málaga, Spain.
[19]Dept. of Rheumatology, Hospital Ramón y Cajal, Madrid, Spain.
[20]Dept. of Rheumatology, Hospital Universitario de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain.
[21]Dept. of Rheumatology, Hospital Universitario y Politécnico La Fe, Valencia, Spain.
[22]Dept. de Pathology, Hospital de La Princesa, IISIP, Madrid, Spain.
[23]Dept. of Internal Medicine, Hospital Universitario Virgen de la Victoria, Málaga, Spain.
[24]Dept. of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain.
[25]Dept. of Internal Medicine, Hospital Universitario Arnau de Vilanova, Lleida, Spain.
[26]Dept. of Internal Medicine, Corporació Sanitaria Parc Taulí, Instituto Universitario Parc Taulí, UAB, Sabadell, Barcelona, Spain.
[27]Dept. of Internal Medicine, Hospital de Cruces, Barakaldo, Spain.
[28]Dept. of Rheumatology, Hospital Xeral-Calde, Lugo, Spain.
[29]Dept. of Rheumatology, Grup de Recerca Cellular en Inflamació i Cartílag, IMIM (Institut de Recerca Hospital del Mar), Barcelona, Spain.
[30]Dept. of Rheumatology, Hospital Universitario de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain.
[31]Dept. of Internal Medicine, Hospital Universitario Miguel Servet, Zaragoza, Spain.
[32]Autoimmune Systemic Diseases Unit, Dept.of Internal Medicine, Hospital Vall d'Hebron, Autonomous University of Barcelona, Spain.
[33]Dept. of Rheumatology, Hospital de La Princesa, IISIP, Madrid, Spain.

[34]Dept. of Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain.
[35]Rheumatology Division, Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain.
[36]Dept. of Internal Medicine, Complejo Hospitalario Universitario de Vigo Xeral-Chuvi, Spain.
[37]Dept. of Internal Medicine, Hospital de Galdakao, Vizcaya, Spain.
[38]Dept. of Dermatology, Hospital Universitario La Princesa, IIS-IPrincesa, Madrid, Spain.
[39]Hospital Universitario Virgen del Rocío, Sevilla, Spain.
[40]Dept. of Rheumatology, Hospital Universitario de Basurto, Bilbao, Spain.
[41]Epidemiology and Computational Biology Department, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain.
[42]Dept. of Nephrology, Hospital Universitario San Cecilio, Granada, Spain.
[43]Medicine Department, Hospital Universitario San Cecilio, Granada, Spain.
[44]Cardiovascular Research, School of Biomedicine, University of Manchester, UK.
[45]Dept. of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK.
[46]Cambridge Institute for Medical Research, and Dept. of Medical Genetics, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK.
[47]Welcome Trust Sanger Institute, Hinxton, Cambridge, UK.
[48]School of Immunity and Infection, University of Birminngham, Edgbaston, Birmingham, UK.
[49]University College London Center for Nephrology, Royal Free Hospital, London, UK.
[50]Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK.
[51]Dept. of Medicine, Renal Section, Imperial College London, UK.
[52]Cambridge Institute for Medical Research, and Dept. of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK.
[53]Dept. of Rheumatology, Ipswich Hospital National Health Service Trust, Ipswich, UK.
[54]Unidad de Enfermedades Infecciosas y Microbiología Clínica, Hospital de Valme, Sevilla, Spain.
[55]Instituto Maimónides de Investigación Biomédica de Córdoba, Hospital Reina Sofía, Córdoba, Spain.
[56]Grup de Recerca en Genètica i Biodiversitat, Departament de Ciències Mèdiques Bàsiques, Universitat de Lleida, Catalonia, Spain; *present address: Institut de Biotecnologia i Biomedicina, Departament de Genètica i Microbiologia, Cerdanyola, Barcelona, Spain.

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