EXTENDED REPORT

Study of the role of functional variants of *SLC22A4*, *RUNX1* and *SUMO4* in systemic lupus erythematosus

G Orozco*, E Sánchez*, L M Gómez, M A González-Gay, M A López-Nevot, B Torres, N Ortego-Centeno, J Jiménez-Alonso, E de Ramón, J Sánchez Román, J M Anaya, G Sturfelt, I Gunnarsson, E Svennungsson, M Alarcón-Riquelme, M F González-Escribano, J Martín

Ann Rheum Dis 2006;**65**:791–795. doi: 10.1136/ard.2005.044891

See end of article for authors' affiliations

Correspondence to: Dr Javier Martín, Instituto de Parasitología y Biomedicina, CSIC, Parque Tecnológico de Ciencias de la Salud, Avenida del Conocimiento s/n 18100-Armilla, Granada, Spain; martin@ipb.csic.es

*These authors contributed equally to the study

Accepted 15 October 2005
Published Online First 25 October 2005

Background: Functional polymorphisms of the solute carrier family 22, member 4 (*SLC22A4*), runt related transcription factor 1 (*RUNX1*) and small ubiquitin-like modifier 4 (*SUMO4*) genes have been shown to be associated with several autoimmune diseases.
Objective: To test the possible role of these variants in susceptibility to or severity of systemic lupus erythematosus (SLE), on the basis that common genetic bases are shared by autoimmune disorders.
Methods: 597 SLE patients and 987 healthy controls of white Spanish origin were studied. Two additional cohorts of 228 SLE patients from Sweden and 122 SLE patients from Colombia were included. A case–control association study was carried out with six single nucleotide polymorphisms (SNP) spanning the *SLC22A4* gene, one SNP in *RUNX1* gene, and one additional SNP in *SUM04* gene.
Results: No significant differences were observed between SLE patients and healthy controls when comparing the distribution of the genotypes or alleles of any of the *SLC22A4*, *RUNX1*, or *SUMO4* polymorphisms tested. Significant differences were found in the distribution of the *SUMO4* genotypes and alleles among SLE patients with and without nephritis, but after multiple testing correction, the significance of the association was lost. The association of *SUMO4* with nephritis could not be verified in two independent SLE cohorts from Sweden and Colombia.
Conclusions: These results suggest that the *SLC22A4*, *RUNX1*, and *SUMO4* polymorphisms analysed do not play a role in the susceptibility to or severity of SLE.

Systemic lupus erythematosus (SLE) is a chronic complex inflammatory disease that is thought to have an autoimmune origin. Although the precise aetiology of SLE is unknown, a strong genetic component is well established.[1] The genetic background of systemic autoimmune diseases such as SLE is complex and probably involves multiple genes encoding proteins with significant functions in the regulation of the immune system.

The co-localisation of susceptibility loci in genome-wide scan studies have led to the hypothesis that common genes may contribute to the susceptibility to autoimmune diseases.[2 3] In addition, case–control and family based association studies support this hypothesis. Recent findings have proposed the *CTLA4* and *PTPN22* genes, as well as HLA, as ''general'' autoimmune disease loci.[4 5] Therefore, investigation of genes shown to be associated with autoimmune diseases, on the basis of an increased susceptibility to related autoimmune traits, seems a good way of studying the genetic basis of autoimmunity.

A recent study in a Japanese population reported an association between rheumatoid arthritis and a functional variant of the *SLC22A4* (solute carrier family 22, member 4) gene, which encodes the organic cation transporter 1 (OCT1).[6] This polymorphism disrupts a RUNX1 transcription factor binding site and affects the expression of *SLC22A4*. Furthermore, in the same study, an association between rheumatoid arthritis and a single nucleotide polymorphism (SNP) located in the *RUNX1* gene was also found. Recently, regulatory polymorphisms mapping in *RUNX1* binding sites have been independently reported to be associated with SLE and psoriasis.[7 8] In addition, *SLC22A4* polymorphisms have been reported to be associated with Crohn's disease in a white population.[9] However, the physiological function of OCT1 is not as yet completely understood; therefore, the role it might play in the pathogenesis of autoimmunity remains uncertain.

Other papers have recently reported evidence for the association of a *SUMO4* common non-synonymous SNP, 163 A→G resulting in the amino acid substitution M55V, with susceptibility to type 1 diabetes in several white and Asian populations.[10 11] SUMO4 protein conjugates to IκBα and negatively regulates NFκB transcriptional activity.[10] NFκB activates transcription of different genes encoding proteins involved in the immune response. Thus the impaired ability to control NFκB function correctly may lead to the development of autoimmune inflammatory disorders. The *SUMO4* M55V substitution has been shown to result in increase in NFκB transcriptional activity and in the expression of the *IL12B* gene.[10] This SNP might therefore play an important role in the development of SLE because of the involvement of NFκB and interleukin 12.

Bearing in mind these recent findings, we sought to test the possible role of these *SLC22A4*, *RUNX1*, and *SUMO4* polymorphisms in the susceptibility to and severity of SLE. Moreover, as SUMO4 is expressed at various levels in immune tissues, and particularly in the kidney,[10] we

Abbreviations: SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism

Table 1 Genotype and allele frequencies of different *SLC22A4*, *RUNX1*, and *SUMO4* single nucleotide polymorphisms among Spanish patients with systemic lupus erythematosus and healthy controls

Genotypes and alleles		SLE patients (%) (n = 597)	Healthy controls (%) (n = 987)	p Value	OR (95% CI)
SLC22A4 rs3763112 (slc2-E1)	G/G	181 (30.3)	273 (27.6)	0.14	
	G/A	315 (52.8)	509 (51.6)		
	A/A	101 (16.9)	205 (20.8)		
	G	677 (56.7)	1055 (53.4)	0.07	1.14 (0.98 to 1.3)
	A	517 (43.3)	919 (46.6)		
SLC22A4 rs1007602 (slc2-1)	C/C	227 (38)	360 (36.5)	0.78	
	C/T	301 (50.4)	515 (52.2)		
	T/T	69 (11.6)	112 (11.3)		
	C	755 (63.2)	1235 (62.6)	0.71	1.03 (0.88 to 1.20)
	T	439 (36.8)	739 (37.4)		
SLC22A4 rs3792876 (slc2-F2)	C/C	516 (86.5)	862 (87.3)	0.86	
	C/T	78 (13)	120 (12.2)		
	T/T	3 (0.5)	5 (0.5)		
	C	1110 (93)	1844 (93.4)	0.62	0.93 (0.69 to 1.25)
	T	84 (7)	130 (6.7)		
SLC22A4 rs2073838 (slc2-F1)	G/G	516 (86.5)	862 (87.3)	0.86	
	G/A	78 (13)	120 (12.2)		
	A/A	3 (0.5)	5 (0.5)		
	G	1110 (93)	1844 (93.4)	0.62	0.93 (0.69 to 1.25)
	A	84 (7)	130 (6.7)		
SLC22A4 rs1050152 (SLC22A4*L503F)	C/C	176 (29.5)	313 (31.7)	0.60	
	C/T	319 (53.5)	504 (51.1)		
	T/T	102 (17)	170 (17.2)		
	C	671 (56.2)	1130 (57.2)	0.56	0.96 (0.83 to 1.11)
	T	523 (43.8)	844 (42.8)		
SLC22A4 rs2269822 (slc2-3)	C/C	472 (79)	751 (76.1)	0.11	
	C/T	113 (19)	199 (20.2)		
	T/T	12 (2)	37 (3.7)		
	C	1057 (88.5)	1701 (86.2)	0.06	1.24 (0.99 to 1.55)
	T	137 (11.5)	273 (13.8)		
RUNX1 rs2268277	C/C	84 (14)	147 (14.9)	0.90	
	C/G	302 (50.7)	494 (50)		
	G/G	211 (35.3)	346 (35.1)		
	C	470 (39.3)	788 (39.9)	0.75	0.98 (0.84 to 1.13)
	G	724 (60.7)	1186 (60.1)		
SUMO4 163A→G	A/A	153 (25.6)	217 (22.0)	0.25	
	G/A	275 (46)	481 (48.7)		
	G/G	169 (28.4)	289 (29.3)		
	A	581 (48.7)	915 (46.4)	0.21	1.10 (0.95 to 1.27)
	G	613 (51.3)	1059 (53.6)		

CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism.

hypothesised that the *SUMO4* M55V variation might be implicated in the development of lupus nephritis.

METHODS

Subjects

In the present study 597 Spanish SLE patients meeting the American College of Rheumatology (ACR) criteria for SLE[12] were recruited from Hospital Universitario Virgen de las Nieves (Granada), Hospital Clínico Universitario San Cecilio (Granada), Hospital Xeral-Calde (Lugo), Hospital Carlos Haya (Málaga), and Hospital Universitario Virgen del Rocio (Sevilla).

The mean (SD) age of the SLE patients at diagnosis was 43 (13.3) years and at the onset of SLE symptoms, 32 (15) years. The clinical manifestations studied were articular manifestations, renal involvement, cutaneous lesions, serositis, neurological disease, and haematological disturbances. In addition, clinical activity or severity was assessed every six months by the SLE disease activity index (SLEDAI) score. In all, 987 Spanish blood bank and bone marrow donors of the corresponding cities were included as healthy controls. All the subjects—patients and controls—were of white Spanish origin and were included in the study after giving their written informed consent. We obtained approval for the study from all local ethics committees of the corresponding hospitals.

We also included two independent cohorts of 228 Swedish and 122 Colombian SLE patients meeting the ACR criteria,[12] in order to carry out a study of the *SUMO4* polymorphism with respect to nephritis susceptibility in SLE patients. Colombian patients were collected from Clínica Universitaria Bolivariana (Medellín). Swedish SLE patients were recruited from the Karolinska University Hospital in the Stockholm area and from the southern city of Lund. All patients were of self reported white European origin or had great grandparents born in Sweden. Controls were recruited partly from the blood bank at the Uppsala University Hospital and from a population cohort in Lund.

Genotyping

DNA from patients and controls was obtained from peripheral blood using standard methods. SNPs were selected

Table 2 Frequencies of the most common haplotypes (frequency >5%) formed by the SNPs rs3763112 (slc2-E1), rs1007602 (slc2-1), rs3792876 (slc2-F2), rs2073838 (slc2-F1), and rs2269822 (slc2-3) in patients with systemic lupus erythematosus and healthy controls

Haplotype	SLE patients (%) (n = 597)	Healthy controls (%) (n = 987)	p Value	OR (95% CI)
GCCGC	514 (43)	830 (42)	0.58	1.04 (0.9 to 1.21)
ATCGC	454 (38)	730 (37)	0.56	1.05 (0.9 to 1.22)
ACCGC	72 (6)	138 (7)	0.29	0.85 (0.63 to 1.16)
GCCGT	60 (5)	118 (6)	0.26	0.83 (0.60 to 1.16)

CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus.

according to previous studies of autoimmune diseases including those studied in Japanese rheumatoid arthritis patients spanning the *SLC22A4* region (rs(reference SNP ID)3763112 [slc2-E1], rs1007602 [slc2-1], rs3792876 [slc2-F2], rs2073838 [slc2-F1], and rs2269822 [slc2-3]),[6] and the *SLC22A4* SNP associated with Crohn's disease in a white population (rs1050152 [SLC22A4*L503F]).[9] In addition, we also tested the *RUNX1* rs2268277 variant which has been reported to be associated with rheumatoid arthritis [6] and the *SUMO4* 163 A→G polymorphism previously shown to be associated with type 1 diabetes.[10] Samples were genotyped for *SLC22A4*, *RUNX1* and *SUMO4* polymorphisms using a TaqMan 5′ allelic discrimination Custom TaqMan® SNP genotyping assays method (Applied Biosystems, Foster City, California, USA). Allele specific probes were labelled with the fluorescent dyes VIC and FAM, respectively. Polymerase chain reaction (PCR) was carried out in a total reaction volume of 8 µl with the following amplification protocol: denaturation at 95℃ for 10 minutes, followed by 40 cycles of denaturation at 95℃ for 15 seconds, and finished with annealing and extension at 60℃ for one minute. Post-PCR, the genotype of each sample was attributed automatically by measuring the allelic specific fluorescence on the ABI PRIM 7000 sequence detection system using the SDS 1.1 software for allelic discrimination (Applied Biosystems).

Statistical analysis

Allelic and genotypic frequencies of all the genetic variants were obtained by direct counting. Statistical analysis to compare allelic and genotypic distributions was done using the χ^2 test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated according to Woolf's method. The software used was the Statcalc program (Epi Info 2002; Centers for Disease Control and Prevention, Atlanta, Georgia, USA). Probability (p) values less than 0.05 were considered significant. Uncorrected p values are presented in all the tables. For non-parametric data analysis, the Mann–Whitney U test was used for ordinal variables and Fisher's exact test for dichotomous variables. For the haplotype analysis, pairwise linkage disequilibrium measures were investigated and haplotypes constructed by the expectation-maximisation (EM) algorithm implemented in UNPHASED software.[13]

Sample sizes were estimated a priori by Quanto 0.5 software (Department of Preventive Medicine, University of Southern California) according to previously reported allele frequencies,[6 9 10] so that each association study had at least 80% power to detect an association with the same odds ratio as detected in previous studies (odds ratios of 1.5 to 2.0) at the 5% significance level assuming a dominant inheritance model.

RESULTS

SLC22A4 genotypes were in Hardy–Weinberg equilibrium in patients and controls. We observed that the *SLC22A4* rs3792876 and rs2073838 SNPs were in complete linkage disequilibrium, as previously described in a Japanese population. No significant differences in the allele and genotype frequencies of the different SNPs tested in the *SLC22A4* region were found between SLE patients and controls (table 1).

Of note, the frequencies of these *SLC22A4* polymorphisms in our population differed significantly from those found in the Japanese population.[6]

We also estimated the *SLC22A4* haplotype frequencies and evaluated associations between these variants with SLE (table 2). However, we found no association of *SLC22A4* haplotypes with SLE in our population.

With regard to the rs2268277 *RUNX1* polymorphism, genotypes were in Hardy–Weinberg equilibrium in patients and controls. Similarly, no significant differences between SLE patients and healthy controls were observed when the distributions of the genotypes or alleles of this *RUNX1* SNP were compared (table 1).

Genotype and allele frequencies of the *SUMO4* 163A→G SNP in SLE patients and healthy controls are shown in table 1. The genotype frequencies were not found to be significantly different from those predicted by Hardy–Weinberg equilibrium testing in healthy controls. The observed allele frequencies in our control population were in accord with those found in other white populations.[10 11 14] However, they differ significantly from those described in Asian populations (Spanish *v* Taiwanese, $p<10^{-7}$; Spanish *v* Chinese, $p = 6.10^{-6}$; Spanish *v* Korean, $p = 12.10^{-6}$).[10] No significant differences in the distribution of the alleles or genotypes of the *SUMO4* 163A→G polymorphism were found when we compared SLE patients with the control group (table 1).

We then analysed the demographic and clinical characteristics of SLE patients (age at disease onset, sex, articular manifestations, renal involvement, cutaneous lesions, serositis, neurological disease, and haematological disturbance) according to their *SLC22A4*, *RUNX1*, and *SUMO4* genotypes. However, no significant differences were observed except for the presence of renal involvement according to *SUMO4* genotype (table 3).

The overall distribution of genotypes among SLE patients with and without nephritis yielded significant differences ($p = 0.04$ by χ^2 test from a 2×3 contingency table). Also, the G/G genotype was found at a higher frequency ($p = 0.03$, OR = 1.54 (95% CI, 1.03 to 2.31)) and the A/A genotype at a lower frequency ($p = 0.04$, OR = 0.64 (95% CI, 0.41 to 1.00)) in SLE patients with nephritis compared to those without. In addition, we found a greater frequency of the *SUMO4* G163 allele among SLE patients with nephritis compared with those without nephritis ($p = 0.008$, OR = 1.41 (95% CI, 1.08 to 1.82)). Nonetheless, these differences turned out to be non-significant after Bonferroni correction for multiple testing. To test further the implications of the *SUMO4* 163A→G SNP in the development of nephritis in SLE patients, we studied two additional independent SLE cohorts,

Table 3 Distribution of *SUMO4* 163A→G genotypes and alleles in Spanish, Swedish, and Colombian patients with systemic lupus erythematosus, according to the presence of nephritis

	SLE patients with nephritis	SLE patients without nephritis	p Value	OR (95% CI)
Spanish	**(n = 189)**	**(n = 351)**		
A/A	39 (20.5)	101 (28.8)	0.04*	0.64 (0.41 to 1.00)
G/A	87 (46.0)	164 (46.6)	0.88	0.97 (0.67 to 1.41)
G/G	63 (33.5)	86 (24.6)	0.03*	1.54 (1.03 to 2.31)
A	165 (43.5)	366 (52.2)	0.008*	0.71 (0.55 to 0.92)
G	213 (56.5)	336 (47.8)	0.008*	1.41 (1.08 to 1.82)
Swedish	**(n = 68)**	**(n = 160)**		
A/A	22 (32.4)	49 (30.6)	0.8	1.08 (0.56 to 2.08)
G/A	37 (54.4)	83 (51.9)	0.7	1.11 (0.60 to 2.04)
G/G	9 (13.2)	28 (17.5)	0.42	0.72 (0.29 to 1.72)
A	81 (59.6)	181 (56.6)	0.55	1.13 (0.74 to 1.74)
G	55 (40.4)	139 (43.4)	0.55	0.88 (0.58 to 1.36)
Colombian	**(n = 63)**	**(n = 59)**		
A/A	17 (27)	19 (32.2)	0.52	0.78 (0.33 to 1.82)
G/A	31 (49.2)	28 (47.5)	0.85	1.07 (0.5 to 2.32)
G/G	15 (23.8)	12 (20.3)	0.64	1.22 (0.48 to 3.15)
A	65 (51.6)	66 (55.9)	0.5	0.84 (0.49 to 1.43)
G	61 (48.4)	52 (44.1)	0.5	1.19 (0.7 to 2.04)

Values are n (%).
*Corrected p value non-significant.
CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus.

from Sweden and Colombia. When we compared the genotype and allele frequencies of the *SUMO4* 163A→G polymorphism between SLE patients with and without nephritis in both populations, we found no significant differences (table 3).

DISCUSSION

In this study we have tried to establish for the first time the relation of *SLC22A4* and *RUNX1* polymorphisms previously associated with rheumatoid arthritis and Crohn's disease (in the case of *SLC22A4*) with a related autoimmune inflammatory disease, SLE. In addition, this study constitutes the first attempt to assess the potential implication of the functional variant 163 A→G of the *SUMO4* gene—which has been shown to be associated with type 1 diabetes—with susceptibility to SLE. We found no evidence of an association of the alleles and genotypes of any of the polymorphisms under study with SLE.

With regard to *SLC22A4*, the lack of association in our study could have arisen because of a type 2 error (false negative). According to the a priori calculation, our sample size reached at least 80% power to detect the relative risk for the individual SNPs reported in the Japanese study at the 5% significance level. Although an association of the *SLC22A4* gene with Crohn's disease has been reported in both Japanese[15] and white populations,[9] the associated disease polymorphism in the Japanese was the rs3792876, while in the Europeans it was rs1050152. It is possible that disease relevant genes or alleles may be specific for certain populations and vary among different ethnic groups.

With regard to the *RUNX1* rs2268277 polymorphism, the lack of association with SLE was not caused by a lack of power. Thus our SLE sample size (597 patients) was large enough to reach >90% statistical power to detect a relative risk similar to the Japanese study at the 5% significance level. It will be of interest to analyse the influence of *RUNX1* in Japanese patients with SLE, in addition to replicating the reported *RUNX1* rheumatoid arthritis association in a white rheumatoid arthritis cohort.

No evidence of association of the *SUMO4* 163 A→G SNP with susceptibility to SLE was found. This lack of association is not attributable to the sample size because the power of our study to detect a difference considering OR = 1.5 at $\alpha = 0.05$ was >99%. The allele and genotype frequencies observed in our study were similar to those described previously in other white populations.[10 11 14] The reported association of the *SUMO4* gene with type 1 diabetes is now under debate.[16 17] Of note, Guo *et al* did not find association between the *SUMO4* polymorphism and type 1 diabetes in a case–control study carried out in a Spanish population.[10]

However, our results show that the frequency of the *SUMO4* 163G allele, encoding Val55, is higher among SLE patients with nephritis than in the remaining SLE patients without nephritis, suggesting a role for this polymorphism in the development of renal disease in SLE. However, the differences in the distribution of the genotypes and alleles of *SUMO4* between SLE with and without nephritis turned out to be non-significant after multiple test correction. In addition, we were unable to confirm the association of lupus nephritis in two additional populations of SLE patients from Sweden and Colombia.

Several recent findings prompted us to speculate about a possible role of *SUMO4* in the development of nephritis in SLE patients. *SUMO4* mRNA has been detected mainly in the kidney.[11] Furthermore, the 163G variant of the *SUMO4* gene has been shown to produce a greater NFκB transcriptional activity, and as a result, a higher expression of IL12p40.[10] In this sense, there are increasing data to suggest that NFκB plays a pivotal role in many nephropathies.[18 19] Thus further investigation into the role of *SUMO4* polymorphisms in the development of renal involvement should be of interest, using SLE patients from different populations.

Finally, it is possible that the genes evaluated do not play a major role in the development of SLE, although they may be associated with the development of other related autoimmune diseases.

ACKNOWLEDGEMENTS

This work was supported by Plan Nacional de I+D (grant SAF03-3460), Fondo de Investigaciones Sanitarias (PI 04 0067), and in part by Junta de Andalucía, grupo CTS-180. We thank M[a] Paz Ruiz and Sonia Morales for their excellent technical assistance.

Supported also by grants from the Alliance for Lupus Research, the Swedish Research Council (grant 12673) and the Torsten and Ragnar Söderbergs Foundation to MEAR.

Authors' affiliations

G Orozco*, E Sánchez*, J Martín, Instituto de Parasitología y Biomedicina, CSIC, Granada, Spain
L M Gómez, Unidad de Biología Celular e Inmunología, Corporación Para Investigaciones Biológicas (CIB) and Universidad de Antioquia, Medellin, Colombia
M A González-Gay, Servicio de Reumatología, Hospital Xeral-Calde, Lugo, Spain
M A López-Nevot, Servicio de Inmunología, Hospital Virgen de las Nieves, Granada, Spain
B Torres, M F González-Escribano, Servicio de Inmunología, Hospital Virgen del Rocío, Sevilla, Spain
N Ortego-Centeno, Servicio de Medicina Interna, Hospital San Cecilio, Granada, Spain
J Jiménez-Alonso, Servicio de Medicina Interna, Hospital Virgen de las Nieves, Granada, Spain
E de Ramón, Servicio de Medicina Interna, Hospital Carlos Haya, Málaga, Spain
J Sánchez Román, Servicio de Medicina Interna, Hospital Virgen del Rocio, Sevilla, Spain
J M Anaya, Unidad de Biología Celular e Inmunología, CIB, Universidad del Rosario, Medellin, Colombia
G Sturfelt, Department of Rheumatology, Lund University Hospital, Lund, Sweden
I Gunnarsson, E Svennungsson, Unit for Rheumatology, Karolinska University Hospital, Solna, Sweden
M Alarcón-Riquelme, Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, Uppsala, Sweden

*These authors contributed equally to the study.

REFERENCES

1 **Tsao BP**. The genetics of human systemic lupus erythematosus. *Trends Immunol* 2003;**24**:595–602.
2 **Wandstrat A**, Wakeland E. The genetics of complex autoimmune diseases: non- MHC susceptibility genes. *Nat Immunol* 2001;**2**:802–9.
3 **Marrack P**, Kappler J, Kotzin BL. Autoimmune disease: why and where it occurs. *Nat Med* 2001;**7**:899–905.
4 **Ueda H**, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, *et al*. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* 2003;**423**:506–11.
5 **Siminovitch KA**. PTPN22 and autoimmune disease. *Nat Genet* 2004;**36**:1248–9.
6 **Tokuhiro S**, Yamada R, Chang X, Suzuki A, Kochi Y, Sawada T, *et al*. An intronic SNP in a RUNX1 binding site of SLC22A4, encoding an organic cation transporter, is associated with rheumatoid arthritis. *Nat Genet* 2003;**35**:341–8.
7 **Prokunina L**, Castillejo-Lopez C, Oberg F, Gunnarsson I, Berg L, Magnusson V, *et al*. A regulatory polymorphism in PDCD1 is associated with susceptibility to systemic lupus erythematosus in humans. *Nat Genet* 2002;**32**:666–9.
8 **Helms C**, Cao L, Krueger JG, Wijsman EM, Chamian F, Gordon D, *et al*. A putative RUNX1 binding site variant between SLC9A3R1 and NAT9 is associated with susceptibility to psoriasis. *Nat Genet* 2003;**35**:349–56.
9 **Peltekova VD**, Wintle RF, Rubin LA, Amos CI, Huang Q, Gu X, *et al*. Functional variants of OCTN cation transporter genes are associated with Crohn disease. *Nat Genet* 2004;**36**:471–5.
10 **Guo D**, Li M, Zhang Y, Yang P, Eckenrode S, Hopkins D, *et al*. A functional variant of SUMO4, a new I kappa B alpha modifier, is associated with type 1 diabetes. *Nat Genet* 2004;**36**:837–41.
11 **Bohren KM**, Nadkarni V, Song JH, Gabbay KH, Owerbach D. A M55V polymorphism in a novel SUMO gene (SUMO-4) differentially activates heat shock transcription factors and is associated with susceptibility to type I diabetes mellitus. *J Biol Chem* 2004;**279**:27233–8.
12 **Tan EM**, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25**:1271–7.
13 **Dudbridge F**. Pedigree disequilibrium tests for multilocus haplotypes. *Genet Epidemiol* 2003;**25**:115–21.
14 **Owerbach D**, Pina L, Gabbay KH. A 212-kb region on chromosome 6q25 containing the TAB2 gene is associated with susceptibility to type 1 diabetes. *Diabetes* 2004;**53**:1890–3.
15 **Yamazaki K**, Takazoe M, Tanaka T, Ichimori T, Saito S, Iida A, *et al*. Association analysis of SLC22A4, SLC22A5 and DLG5 in Japanese patients with Crohn disease. *J Hum Genet* 2004;**49**:664–8.
16 **Smyth DJ**, Howson JM, Lowe CE, Walker NM, Lam AC, Nutland S, *et al*. Assessing the validity of the association between the SUMO4 M55V variant and risk of type 1 diabetes. *Nat Genet*. 2005;37: 110–11; author's reply, 112–13.
17 **Qu H**, Bharaj B, Liu XQ, Curtis JA, Newhook LA, Paterson AD, *et al*. Assessing the validity of the association between the SUMO4 M55V variant and risk of type 1 diabetes. *Nat Genet*. 2005;37: 111–12; author's reply, 112–13.
18 **Sakurai H**, Hisada Y, Ueno M, Sugiura M, Kawashima K, Sugita T. Activation of transcription factor NF-kappa B in experimental glomerulonephritis in rats. *Biochim Biophys Acta* 1996;**1316**:132–8.
19 **Tomita N**, Morishita R, Lan HY, Yamamoto K, Hashizume M, Notake M, *et al*. In vivo administration of a nuclear transcription factor-kappaB decoy suppresses experimental crescentic glomerulonephritis. *J Am Soc Nephrol* 2000;**11**:1244–52.