Association of small ubiquitin-like modifier 4 gene polymorphisms with rheumatoid arthritis in a Tunisian population

Sirs,

Rheumatoid arthritis (RA) is a complex multifactorial disease caused by environmental influences and unknown number of predisposing genes. *SUMO4*, has been involved in the regulation of NF-kB, whish has a central role in the immune response (1, 2). The polymorphism (163A>G rs237025 M55V) down-regulates NF-κB signal, leading to decreased transcription of pro-inflammatory cytokines. It was associated with type 1 diabetes, autoimmune thyroid disease and rheumatoid arthritis disease in the USA (3), in North America (4) and rheumatoid arthritis without amyloidosis (5).

The aim of this study is to investigate association of the SUMO4 (+163A/G) single nucleotide polymorphism (SNP) with RA in a Tunisian population and its association to the main clinical manifestations in the disease. We compared the distribution of the 163A>G polymorphism of the *SUMO4* gene between a total of 292 subjects of Tunisian origin, including 108 RA and 184 control subjects laminate according to the age, the sex, disease duration and RA activity. A replication cohort was studied including 103 cases with RA and 157 healthy control subjects using PCR-RFLP analysis (6, 7). The genotype frequencies of RA patients and healthy controls are conformed to Hardy-Weinberg equilibrium.

Results of this distribution are presented in Table I. The SUMO4 +163 G allele is more frequent in controls than in RA patients, (p=0.018; χ^2=5.54; OR=1.5, 95% CI=1.05–2.14). The frequency of subjects with the GG genotype was significantly higher in controls than in RA patients, (p=0.036; χ^2 =6.6). A protective role of (+163A/G) polymorphism was found when the AA genotype was compared with (AG+GG) genotype, (p=0.016; χ^2=5.78; OR=0.52, 95% CI=0.29–0.92). The same result was obtained with Replication Cohort (data not shown) which confirms our finding in the initial study. Small numbers of stratification analysis of different RA activity according to the status of DAS28, G allele may tend to be protective among RA patients (p=0.00036; χ^2=15.85) (Table I) and was significantly increased among the RA patients in the subgroup analysis associated with lower RA activity (p=0.03).

This case-control study suggests a protective effect of allele +163 G in Tunisian Rheumatoid arthritis patients. In China, Hou *et al*. (6) identified a susceptible allele +438 C and two possible protective haplotypes of the *SUMO4* gene with Behçet's disease, an autoimmune disease. This result seems to be correlated with the protective role of SUMO4 gene. Contrary to our results, previous studies in North America (3) and in Japan (5) found evidence that SUMO4+163G (Valine) was associated with an increased risk of RA.

In conclusion, our data were the first in North Africa depicting the prevalence of the (+163A/G) Met55Val *SUMO4* gene polymorphism with RA, and indicated that SUMO4 +163G (Valine) contributes to RA protection. Our findings suggest that the functional SNP that controls *SUMO4* seems to be different in the North African population. A possible explanation might be caused by genetic heterogeneity in the Tunisian population, which is characterised by important genetic exchanges throughout history and frequent migration around the Mediterranean sea (8). Another possible explanation might be caused by other SNPs affecting the function of *SUMO4* rather than M55V SNP. Therefore, the *SUMO4* gene may be a protective factor to RA. However, the present work should be regarded as an hypothesis-testing study with its limitations, and further studies using larger samples are needed to pin-point the regulatory polymorphism or haplotype and its effects on the development of certain manifestations in RA.

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Table I. Distribution of SUMO4 M55V (+163A/G) SNP in RA (n=108) and healthy controls (n=184) and according to RA activity in Tunisia.

SNP	Genotype frequency (%)			χ^2	Allele frequency (%)		χ^2
+163A/G	AA	AG	GG	(p-value)	A	G	(p-value)
RA patients (n=108)	36 (33.3)	56 (51.85)	16 (14.81)	6.60	128 (59.25)	88 (40.74)	5.54
Controls (n=184)	38 (20.65)	105 (57.06)	41 (22.28)	**(0.036)**	181 (49.18)	18 (50.81)	**(0.018)**
Moderate RA activity	24 (45.2)	19 (35.8)	10 (18.8)	11.11	67 (63.2)	39 (36.7)	2.03
RA without this condition	11 (20)	37 (67.2)	7 (12.7)	**(0.0038)**	59 (53.6)	51 (46.3)	(0.15)
Low RA activity	1 (3.8)	22 (84.6)	3 (11.5)	15.85	24 (46.1)	28 (53.8)	0.5
RA without this condition	34 (41.9)	34 (41.9)	13 (16.04)	**(0.00036)**	102 (62.9)	60 (37.0)	**(0.03)**

p=0.018 for allele frequencies; p=0.036 for genotype frequencies and p=0.016 for genotype frequencies (obtained when comparing the controls frequency of the (AG+GG) genotype to RA patients).
Moderate RA activity: (3.2<DAS28<5.1); p=0.0038 for genotype frequencies and p=0.005 χ^2=7.8; OR=0.3; 95% CI=(0.12–0.77) for genotype frequencies (obtained when comparing the controls frequency of the (AG+GG) genotype to RA patients.
Low RA activity: DAS28 <3.2); p=0.03 for allele frequencies; p=0.00036 for genotype frequencies and p=0.00031; χ^2=13 for genotype frequencies (obtained when comparing the controls frequency of the (AG+GG) genotype to RA patients.