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A replication study confirms the association of TNFSF4 (OX40L) polymorphisms with Systemic Sclerosis in a large European cohort

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Introduction

The *TNFSF4* gene, which encodes OX40L, is considered as a potential autoimmunity candidate gene. OX40L is expressed on activated antigen presenting cells (APCs) and endothelial cells in acute inflammation [1]. Furthermore, it enhances B-cell proliferation and differentiation, and its binding to OX40 (CD134) promotes proliferation and survival of T-cells and predisposes them to a more permissive proliferative and survival condition [2]. Interestingly, four *TNFSF4* promoter single-nucleotide polymorphisms (SNP) were recently implicated in susceptibility to systemic sclerosis (SSc) [3].

Aim

The aim of this study was to confirm the influence of *TNFSF4* polymorphisms on SSc susceptibility and clinical subtypes or phenotypic features.

Patients and methods

Eight European populations of Caucasian ancestry were included, comprising a total of 3014 SSc patients and 3125 healthy controls. Four genetic variants of the *TNFSF4* gene (rs1234314, rs844644, rs844648 and rs12039904) were selected as genetic markers and genotyped using Taqman Allelic Discrimination Assays.

Results

A pooled-analysis revealed the association of rs1234314 and rs12039904 SNPs with SSc [OR=1.15,95%CI 1.02-1.31;OR=1.18,95%CI 1.08-1.29, respectively].

After subtype stratification, significant association of the four tested SNPs with the limited cutaneous SSc (lcSSc) subgroup of patients was revealed [rs1234314 OR=1.22,95%CI 1.07-1.38; rs844644 OR=0.91,95%CI 0.83-0.99; rs844648 OR=1.10,95%CI 1.01-1.20; and rs12039904 OR=1.20,95%CI 1.09-1.33]. Considering autoantibody status, the association of three of these variants, rs1234314, rs844648 and rs12039904 with anticentromere autoantibody (ACA) positive subset of patients remained significant [OR=1.23,95%CI 1.10-1.37; OR=1.12,95%CI 1.01-1.25; OR=1.22,95%CI 1.07-1.38, respectively]. Haplotype analysis confirmed the existence of a previously described protective haplotype and revealed a new risk haplotype with evidence of association with SSc [OR=0.88,95%CI 0.82-0.96;OR=1.14,95%CI 1.03-1.26, respectively], lcSSc [OR=0.88,95%CI 0.80-0.96; OR=1.20,95%CI 1.08-1.35, respectively] and ACA positive subgroups[OR=0.86,95%CI 0.77-0.97;OR=1.23, 95% CI 1.07-1.42, respectively].

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Conclusions

Our data confirm the influence of *TNFSF4* polymorphisms in SSc genetic susceptibility, especially with lcSSc and ACA positive subsets of patients.

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