## Dr. Petrek replies

*To the Editor:*

It was interesting to read comments[1] on the results of a candidate gene association study carried out in my laboratory 10 years ago[2]. All 3 explanations that Peng and colleagues suggest to account for discordant data on possible associations between *IL-1A* –889 gene variants and systemic sclerosis (SSc) reported between 2003 and 2007 by investigators from different countries — former Czechoslovakia[2], Italy[3], and Japan[4] — are tangible. However, especially from the perspective of the 10-year period since our original data were obtained, I would like to expand on the following general points.

In the last decade the field of gene study, either determining the susceptibility to or protection from complex diseases or modifying their course, has undergone substantial progress in terms of high-throughput genotyping methodologies enabling parallel determination of many gene variants or in the shift from pathogenetically based candidate gene studies to genome-wide association studies (GWAS). However, in my opinion the most significant change appeared in the area of genetic epidemiology, where statements were published guiding design, conduct, and interpretation of genetic association studies (e.g., Little, *et al*[5], Janssens, *et al*[6]).

Looking at the report on the association between *IL-1A* –889 and SSc in the Slovak population[2] from the viewpoint of these guidelines published a few years later[5,6], the study complies with most of the items on their checklists. The patient and control populations were ethnically matched; despite relatively low patient numbers given the disease prevalence, the study was adequately powered; the statistical methods were adequate; the observed genotype frequencies were in Hardy-Weinberg equilibrium — the genotyping errors were improbable; and the study limitations were discussed.

Thus, the most plausible cause for the discrepant data remains phenotypical heterogeneity among the patients enrolled into the 3 studies under comparison. Especially in the Japanese patient group[4], there was a different distribution of the limited and diffuse forms of SSc, and also the proportion of the patients with organ involvement (namely lung) was not fully comparable between the studies[2,3,4]. Although the data in the 3 reports do not allow complete comparisons, the study groups also differed by their autoantibody profiles. Further, as Peng, *et al*[1] point out, the different ethnicities could be another substantial factor contributing to the controversial findings. There have been reports on differences in distributions of cytokine polymorphisms including *IL-1A* –889 even within Europe[7], and existence of distinct frequency profiles of polymorphisms in immune response genes, including *IL-1A* –889, between white and Asian populations is well recognized, as exemplified in populations from Toronto, Canada, and Korea[8].

My coauthors and I concluded in our report that *IL-1A* –889 polymorphism could be one genetic factor predisposing to development of SSc, and at the same time we stated that "further studies with larger numbers of patients with this rare disease in populations of different ethnic background are required to confirm this association"[2]. If we considered the study by our Italian colleagues[3] as a replication and agreed that it showed adequate replicative power, a conclusion might be made that this particular gene variant is not likely to be involved in susceptibility to SSc in white subjects. This speculation would be supported also by the results of current GWAS and their metaanalyses (reviewed by Romano, *et al*[9]), which did not report the polymorphic genes of the *IL1/IL1RN* gene complex to be associated with the disease. This interpretation, however, does not discriminate the products of the IL-1 gene family from their involvement in the pathogenesis of SSc. Current reports suggest that variants in the inflammasome *NLRP1* gene may contribute to SSc disease severity through mechanisms affecting pro-IL-1ß processing and maturation[10].

The lesson from this look at these older studies emphasizes the intensifying need for precise clinical phenotyping including assessment of disease severity and/or subphenotyping, where relevant. This development, and also the current possibility of reinterpreting the candidate role of IL-1 in the pathogenesis of SSc, e.g., in the context of epigenetic mechanisms, is yet another reflection of a Latin hexametric adage, *Tempora mutantur, nos et mutamur in illis* (Times change, and we change with them).

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