Letter

$5HT_{2A}$ polymorphism His452Tyr in a German Caucasian systemic sclerosis population - authors' response

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Published: 26 March 2009
This article is online at http://arthritis-research.com/content/11/2/404

Arthritis Research & Therapy 2009, **11:**404 (doi:10.1186/ar2635)

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The variance of results between our recent article [1] and the replication study by Kirsten and colleagues [2] in German patients may prompt the reader to ask the simple question: what conclusion can be drawn from these contradictory results?

One possible answer is that one of the two studies is wrong and all the clues would indicate the first report as the one describing a spurious finding. This is consistent with a general overestimate of the role of a gene in the first association study of it [3] and, indeed, we have always been aware of the possibility of false positive findings. Hence, we provided the reader a mean (for example, the false probability report probability) with which to gauge the strength of the association and the chance of having described a spurious result [1].

A second possible answer is that the variance of results stems from methodological differences between the two studies. It has been argued that replication studies should be viewed as tools to uncover heterogeneity rather than tools to test the hypothesis generated by the initial association [3] and, in a more extreme view, the relevance of replication has been questioned [4]. Our and Kirsten and colleagues' studies are heterogeneous with regard to many aspects, starting with 'phenotype definition'. In our report we included only patients fulfilling the American College of Rheumatology criteria for the classification of systemic sclerosis (SSc), while Kristen and colleagues also included 19% of early SSc patients according to LeRoy's definition [5]; we also had 75% limited cutaneous SSc patients compared to 50% in the German population. This different phenotype definition implies that the sets of causative loci or traits underlying the different definitions are likely to be different [3]. Moreover, the prevalence of females in our population was much higher (93.9% versus 50%) and it is well-known that platelets differently aggregate in males and females due to hormonal and gender-specific influences [6]. As we hypothesized that the rs6314 polymorphism does not act as a causative genetic mutation *per se*, but rather it is important in amplifying SSc-causative and coagulative pathological processes once they have already been triggered by other factors [1], all the above-mentioned and other hidden differences in the genetic background are likely to be of particular relevance. In this sense, it is reductive to consider the importance of the studied single nucleotide polymorphism on SSc susceptibility only for its main independent effect, but it should more appropriately be viewed in the context of a broader gene-gene or gene-environmental frame.

Competing interests

The authors declare that they have no competing interests.

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SSc = systemic sclerosis.