Letter in response to article 'Imputation-based analysis of MICA alleles in the susceptibility to ankylosing spondylitis'

A recent study has raised new questions about the independent association of MICA alleles with ankylosing spondylitis (AS).[1] This letter highlights some important issues to be discussed in response to this article.

The authors used imputation to genotype MICA and HLA-B27 in patients with AS and controls of European ancestry. The results appeared discordant with the previous report that showed a strong and human leukocyte antigen (HLA)-B27 independent association between MICA*007:01 and AS in US and Chinese cohorts.[2] A common finding was a significant high rate of MICA*007 in patient with AS. The debate is whether this observation is coming from linkage disequilibrium effect of HLA-B27. Although a trend was seen with an association of MICA*007 and AS in 1669 HLA-B27 negative AS cases and, 12 263 controls, it marginally lacked statistical significance (OR=1.32, p=0.07). However, it is noted that the experimental designs were different in two studies. The earlier study applied the sequencing genotyping of MICA gene and examined the association in two distinct ethnic populations of US Caucasian and Chinese Han. The latter reported with imputation of genome-wide association study (GWAS) data of European ancestry where the imputation conditions were established in largely Canadian patients (which may differ from the heterogeneous US population reported in the earlier study), and no association of imputed MICA alleles and actual MICA typing has been established in Chinese patients and controls. Considering the expense and expertise required to sequence and genotype HLA region genes, imputation of HLA region genotypes may be a more plausible approach as such imputation conditions are established in other populations. However, it is not accurate enough for replacement of sequencing genotyping in critical conditions, such as clinical practice.[3 4] It is also worth mentioning that the imputation provided only 3-digit (MICA*007), but 5-digit genotype (MICA*007:01) by the sequencing. In this case, the discordant report warrants further confirmation with a sequencing genotyping approach. It is important to emphasise that MICA is a critical ligand for NKG2D that is expressed on the surface of NK, NKT, CD8+ and TCRγδ+ T cells. Significantly increased frequencies of specific MICA alleles as well as aberrant MICA and NKG2D signalling have been reported in various rheumatic diseases. Allelic variants of MICA at position 129 and genotype MICA*007 may result in variable affinities to NKG2D[5] and imbalance between membrane-bound and soluble MICA,[6] respectively, which determine the activity of NKG2D and subsequently immune activation. Therefore, the common finding of significantly increased MICA*007 in AS should not be neglected for its functional importance in pathogenesis of AS, a chronic inflammatory disease.

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