

A49 **NON-HLA-DRB1 RA-ASSOCIATED RISK ALLELES
ASSOCIATE WITH ANTI-CCP AND SPECIFIC ACPA LEVELS**

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Background and objectives Anti-citrullinated protein antibodies (ACPA) with different fine specificities are exclusively found in sera and synovial fluid of rheumatoid arthritis (RA) patients. The presence and the levels of all known ACPA are predominantly associated with *HLA-DRB1*04* alleles. Although commonly controlled by HLA-DRB1 and uniquely identify post-translationally modified citrullinated (cit) epitopes, ACPAs have distinctive fine specificities and display low degree of cross-reactivity. Hence, different pathways may selectively regulate specific anti-citrulline immunity in RA. Here, the authors examined whether non-HLA-DRB1 risk alleles influence the levels of antibodies against cyclic citrullinated peptide (CCP) and four additional citrullinated RA-associated antigens in search for shared and distinctive pathways.

Material and methods Sera from 384 RA patients with an established disease were analysed for the presence of anti-CCP antibodies and reactivity towards cit-fibrinogen, cit- α -enolase, cit-type-II collagen and cit-vimentin. Genotyping for HLA-DRB1 and 64 additional RA-associated single-nucleotide polymorphisms (SNPs) was performed. Models of linear regression and contingency tables were used to calculate the association between genes and antibody presence and levels.

Results Two SNPs in HLA-DQ and HLA-DRA regions (rs6457617 and rs6457620, respectively) influenced both the CCP levels as well as the other ACPAs, whereas HLA-DPB2 (rs2064476) only influenced anti-CCP levels but not other fine specificities. Outside the HLA region, PTPN22 (rs2476601) and TRAF1 (rs3761847) were found to have an effect on anti-CCP levels as well as all other fine specificities. Several other genes selectively governed the titres of two or even one single fine specificity; for example, *CIITA* (rs4781003) for cit-fibrinogen, *CD40* for cit- α -enolase (rs4810485), *CLEC4A* (rs1133104) for cit-collagen and *OLIG3*, *TNFAIP3* (rs10499194) for cit-vimentin. These results will be replicated in a bigger cohort of approximately 2000 RA patients.

Conclusions Genes with close association to the immune system, yet outside the HLA-DRB1 region were found to influence the levels of ACPAs. Interestingly, several SNPs affected the overall antibody levels, that is, both against CCP and all four citrullinated antigens. In contrast, other SNPs specifically influenced the antibody levels towards one or two specificities. This data suggests that both common and unique pathways may control anticitrulline immunity in RA.