15 SMOKING INTERACTS WITH HLA-DRB1 SHARED EPITOPE IN THE DEVELOPMENT OF ACPA-POSITIVE RHEUMATOID ARTHRITIS: A CASE-CONTROL STUDY FROM MALAYSIAN EPIDEMIOLOGICAL INVESTIGATION OF RHEUMATOID ARTHRITIS (MYEIRA)

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10.1136/annrheumdis-2011-201236.15

Background and objectives To investigate whether smoking and HLA-DRB1 shared epitope (SE) alleles may interact differently in the development of the two major subgroups of rheumatoid arthritis (RA), anti-citrullinated proteins antibody (ACPA)-positive and ACPA-negative disease, in a multiethnic population of Asian descent.

Methods A case-control study with early diagnosed RA cases was performed in Malaysia between 2005 and 2009. In total, 1056 cases and 1416 matched controls participated in the study. High resolution HLA-DRB1 genotyping was performed for shared epitope (SE) alleles. All participants answered a questionnaire on a broad range of issues, including smoking habits. Possible interaction between smoking habits (defined as 'ever' and 'never' smoking) and DRB1-SE alleles was calculated.

Results In our multiethnic study, both the SE alleles and smoking were associated with an increased risk of developing ACPA-positive RA (OR SE alleles=5.2 (95% CI 4.3 to 6.4); OR smoking=2.2 (95% CI 1.6 to 3.2)). Smokers carrying SE alleles had an odds ratio of ACPA-positive RA of 24 (95% CI 9.9 to 56.2), compared with never-smokers without SE alleles. The interaction between smoking and SE alleles was significant, as measured by the attributable proportion due to interaction, which was 0.7 (95% CI 0.5 to 0.9).The combination of smoking and DRB1*0405 SE allele was significantly associated with ACPA-positive RA (OR=10.0 (95% CI 3.9 to 25.9); AP=0.3 (95% CI −0.3 to 0.9)). A very strong interaction between smoking and SE alleles was however, observed for all other non-DRB1*0405 SE alleles taken as a group in coffering risk of ACPA-positive (OR=63.0 (95% CI 8.1 to 491.3); AP=0.9 (0.8 to 1.1)). The combination of smoking and SE alleles was not associated with an increased risk in ACPA-negative RA.

Conclusion The risk of developing ACPA-positive RA is associated with a strong gene-environment interaction between smoking and HLA-DRB1 SE alleles in a multiethnic population of Asian descent from Malaysia.