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Genetic predispositions to rheumatoid arthritis in Malaysian population

AKADEMISK AVHANDLING

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av

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ABSTRACT

Genetic predisposition is a significant and fundamental determinant of susceptibility to rheumatoid arthritis (RA), a complex autoimmune disease with a painful and disabling condition. The vast majority of genetic studies in RA have been centered on populations of European descent with very few studies on East Asian populations.

In this thesis, we aimed to determine the genetic predisposition to RA in the Malaysian population residing in the South East Asian region. More specifically, we addressed the question of how far the identified RA risk loci in Europeans and East Asians can be translated across different populations. We undertook this investigation using the Malaysian Epidemiological Investigation of Rheumatoid Arthritis (MyEIRA) case control study involving mainly the early RA cases, which comprised of Malay, Chinese and Indian ethnic groups. We showed that different HLA-DRB1 shared epitope (SE) alleles, which are common in Asian (i.e. DRB1*0405), but not in European populations conferred significantly increased risk of developing anti-citrullinated protein antibody (ACPA)-positive, but not ACPA-negative RA. With the preponderance of the DRB1*12 alleles in our study population, we demonstrated a novel protective effect of DRB1*1202 associated with ACPA-positive RA in Malay and Chinese populations.

The combination between genetic and environment factors is widely believed to be the major trigger of RA development. Our analysis of gene-environment interaction between smoking and HLA-DRB1 shared epitope (SE) alleles revealed a strong association with ACPA-positive RA and this interaction seem to apply between smoking and DRB1*0405 allele, which is common in Asian populations.

Polymorphisms in the peptidylarginine deiminase type IV (PADI4) gene have been repeatedly shown to associate with RA susceptibility in individuals of Asian descent, but weak or no association was observed in the European populations, despite of comparable risk allele frequency between these populations. We scrutinized the entire PADI locus including PADI1, PADI2, PADI3, PADI4 and PADI6 genes with a set of 320 single nucleotide polymorphisms (SNPs) for association with RA. Our findings revealed an association between PADI4 in the diverse populations from Malaysia. In addition, we also suggest a novel association in a PADI2 gene.

Approximately 40% of RA patients are diagnosed as having ACPA-negative disease. As yet, few validated risk alleles were associated exclusively with ACPA-negative RA. We investigated the association between the previously reported ACPA-negative-associated dendritic cell immunoreceptor (DCIR) polymorphisms and RA in four independent Asian populations from China and Malaysia. Our results provide evidence for an association between the DCIR variant and RA in non-European populations. We also confirmed the genetic effect of DCIR polymorphisms on RA risk particularly in ACPA-negative RA.

Taken together, this thesis provides evidence that no single population is sufficient for fully uncovering the risk variants underlying RA in all populations. Therefore, studies in diverse population could provide a better understanding of genetic architecture of RA especially in the RA susceptibility risk loci.