Karolinska Institutet

Institutionen för Medicin

Genetic Studies of non-HLA loci in Rheumatoid Arthritis: Expression and Interaction of Candidate Genes

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SUMMARY

Genetic predisposition is an important contributor in development of human complex diseases, like rheumatoid arthritis (RA). In this thesis work, we present advances for involvement of non-HLA genetic risk factors for RA. In the same study, by using methods of genetic epidemiology and molecular genetics, we demonstrate how even moderate contribution from candidate genes could be found, interpreted and how this may affect important biological functions.

The majority of the study has been performed in a large population based cohort of Swedish RA patients with matched controls and with additional cohorts from Norway, UK and the Netherlands. Data has been generated with both TaqMan allelic discrimination and DNA array-based genotyping. A subset of the cohort has been used for studying mRNA expression with quantitative PCR. Three risk loci have been investigated in this thesis: the MHC class II Transactivator (CIITA), the Dendritic Cell Immunoreceptor (DCIR) and Protein Tyrosine Phosphatase Non receptor 22 (PTPN22). For CIITA we aimed to produce further evidence for association with disease by replication and fine mapping of the locus. For DCIR and PTPN22 our aim was to examine the gene expression for finding potential regulatory differences.

We present data that CIITA is a valid risk factor for RA and that this risk seems to be population specific. The risk for disease was higher in the subgroup defined by shared epitope (SE) positivity. We extensively analyzed a possible interaction effect for the risk of developing disease in four independent populations. However, no significant interaction between the CIITA and the HLA-DRB1 locus was found. When measuring expression of promoter isoforms of CIITA in cells from peripheral blood, we found that both CIITA_pIII and CIITA_pIV expression are associated with genetic variation in the locus.

For DCIR we could establish that five splice forms were present in blood mononuclear cells, including a novel variant, which were down regulated upon immunostimulation. Transcript DCIR_v4 was associated with genetic variation in the locus. This correlation was similar for both RA patients and controls.

Finally, we present a novel finding that the expression of PTPN22 splice forms is different for RA patients and healthy controls with more of the full-length, putatively more active, splice forms for patients and less of the alternative variant. This mixed effect was replicated in three independent cohorts.

In conclusion, we present a framework for delineating genetic risk association signals by fine-mapping loci and combining with expression analysis of existing splice forms. More specifically, we give further insights for three genetic risk factors for RA that may lead to less expression of HLA class II (CIITA) and stronger inhibition of immune cell signaling (DCIR and PTPN22).

A combined orchestrated effect of all this risk variants together with other risk factors known for RA may be what predisposes certain individuals for rheumatoid arthritis.

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