A Genome-Wide SNP Association Study Identifies Novel Risk Loci for Rheumatoid Arthritis in Swedish EIRA Study

Rheumatoid arthritis (RA) affects ~1% of Western populations. The presence (~60% of cases) or absence (~40%) of anti citrullinated protein autoantibodies (ACPA) is a biomarker of disease defining two RA subtypes. Previous genetic studies have identified risk haplotypes for ACPA-positive cases in the human leukocyte antigen (HLA) region. This has resulted in the definition of a family of "shared-epitope" (SE) alleles at the HLA-DRB1 locus that together comprise the greatest single genetic risk factor for this subgroup of RA. A second locus (PTPN22) conferring risk in ACPA-positive but not anti-CCP negative cases has recently been identified and validated in multiple populations.

The objective of this study, presented by L. Padyukov MD, PhD, of the Karolinska Institut, Stockholm, was to identify novel variations predisposing individuals for RA in both ACPA-positive RA (n=658) and the less well studied ACPA-negative RA (n=642) cases, matched with 658 controls from the EIRA (Epidemiological Investigation of RA) cohort of Swedish cases and controls. A genome wide single nucleotide polymorphisms (SNP) association test for two major subgroups of RA was used.

The 317,503 SNPs of Illumina's Human Hap300 array were typed, and case-control analysis of the resulting data was performed using allelic and genotype models in HelixTree and Exemplar.

For ACPA-positive cases, 115 SNPs (all from the HLA region) passed Bonferroni correction, while no SNPs met this stringent threshold in the ACPA-negative cases. SNP rs2476601, the previously reported non-synonymous variation in PTPN22 was significantly associated (p=1.9x10-4) in ACPA-positive cases, but showed no evidence of association in ACPA-negative cases (p=0.44). With the detection of these two loci (HLA & PTPN22) as reassuring "positive controls", additional follow-up and validation was performed for several novel autosomal genes and genomic regions, beyond the HLA, that have emerged with robust evidence of association from this study. In an independent set of 768 cases and 527 controls from the EIRA cohort ~150 non-HLA SNPs were genotyped and association in the combined group was assessed.

Data show relatively moderate, but distinct effects from non-HLA loci on ACPA-positive RA risk with major new susceptibility locus in TRAF1-C5 locus at chromosome 9q33. This association was most convincing in a combined analysis of our data together with North American RA Consortium (NARAC) genome-wide scan data. We found in our study that ACPA-positive and ACPA-negative RA association patterns behave as two genetically distinct diseases. There was no association with major histocompatibility (MHC) locus for ACPA-negative disease. A significant difference in genetic risk for the disease between these two well-established RA subsets (ACPA-positive and ACPA-negative RA) illuminates the importance of studying the clinical divergence between these two subsets. Weaker signals could be discovered in combined materials, thus there is a need to study a greater number of individuals (eg, >10,000) for each RA subtype.

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