Genomics, genetic basis of disease and functional genomics.

THU0001

GENOME-WIDE ASSOCIATION STUDY ON JOINT EROSIONS IN RHEUMATOID ARTHRITIS SUPPORTS DIFFERENTIAL PATHOLOGICAL MECHANISMS ACCORDING TO ANTI-CCP STATUS


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Background: Joint damage is the pathological hallmark of rheumatoid arthritis (RA). To identify the genetic variation associated with a higher level of erosions has proven elusive.

Objectives: The objective of the present study was to perform a genome-wide association study on joint damage in a cohort of RA patients of the Spanish population. Our aims were to provide independent validation of previously reported variants and to identify new candidate risk loci. A stratified analysis was performed based on positivity to ACPA status.

Methods: A total of 1,135 patients diagnosed with RA using the ACR-EULAR criteria recruited by the IMID Consortium were genotyped using a 550,000 single-nucleotide polymorphism array. Additional SNPs were imputed using the 1KG genome data. Joint damage was performed using the S-score, a simplified radiographic erosion score that has a high correlation with the Sharp-van der Heijde score (1). Association testing of SNPs with joint damage was performed via linear regression with the addition of the years of evolution as covariate. The two main components of genetic variation were also added to adjust for potential population stratification. A total of 50 SNPs representing previously reported loci associated with joint damage were selected. Genetic association was also performed at the pathway level using Pascal.

Results: 45 out of 50 SNPs representing 31 previously reported loci for joint damage could be satisfactorily imputed. Association testing of the whole patient cohort replicated the association with IL2RA and TRAF1. Of relevance, after stratifying for anti-CCP five new loci were replicated: KIF5A and SOX in ACAP-positive RA and CD40, DKK1 and TNF in ACAP-negative RA. IL2RA was only significant in the ACAP-positive group and TRAF1 was not significant in either strata. GWAS on the ACAP-positive cohort and on the ACAP-negative group identified n=7 and n=18 loci with P-values <1 x 10^-5, respectively. From these, however, only 1 SNP showed nominal association in the other patient group. Based on this evidence, we performed a pathway-based analysis to understand the biological mechanisms underlying this difference. Pathway analysis showed 52 biological processes associated with joint damage in ACAP-negative RA and 32 pathways in the ACAP-positive group, with only two shared biological processes between the two groups. Pc Gamma receptor mediated phagocytosis was the topmost biological process associated with erosions specifically in ACAP-negative RA and Signalling by Fibroblast Growth Factor mutants was the top process specific for ACAP-positive patients.

Conclusion: The results from our study provide suggestive evidence that the genetic basis for joint damage is different according to the presence of ACPA. Replication of the new candidate loci in an independent patient cohort is underway.

References:

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THU0002

SOLVING THE COMPLEX MHC ASSOCIATIONS IN SLE IDENTIFIES SEX-RELATED GENE EFFECTS

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Background: Genome-wide association analyses reveal that the Major Histocompatibility Complex (MHC) is the site of the strongest association signals in SLE and Sjögren's syndrome. This associations in lupus and Sjögren's syndrome are linked to HLA alleles: HLA-DRB1*03:01 and HLA-DRB1*15:01 (in Europeans). The DRB1*03:01 allele resides on an extended MHC haplotype which includes loss of the complement C4A gene. Whether C4 makes a genetic contribution to SLE/Sjögren's risk has been a long standing issue of contention. In comparison, it has been shown that elevated copy number of C4 is a genetic risk factor for schizophrenia.

Objectives: To define the causal MHC genes in SLE/Sjögren's accommodating both structural and highly polymorphic variation.

Methods: Use NG sequencing data from across the MHC to generate a panel of variants that inform class III structural variation involving the candidate genes coding complement C4A and C4B as described. To further improve the resolution of the association using transancestral mapping approach in SLE: examining cohorts of European ancestry (from ImmunoChip) and data from the MHC region of an African-American GWAS in SLE.

Results: Comparing European and African data, we have shown that the association signals in SLE can be best explained by signals arising from 1) copy number variation of the complement component 4 (C4) genes in the MHC locus (Fig. 1 and 2) by a shared region in the class II region on the HLA-DRB1*15:01 (in Europeans) and HLA-DRB1*15:03 (in Africans) that likely operates to elevated HLA class II gene expression (Fig. 2). The C4 locus generates a 7-fold variation in risk for lupus (95% CI: 5.88-8.61; p<10^-17 in total) and 16-fold variation in risk for Sjögren’s syndrome (95% CI: 8.59-30.89; p<10^-23 in total), with C4A

Figure 1. Loss of C4 is risk in African and European ancestry cohorts. A = C4A, B = C4B, A-B = C4A + C4B(L) = Long form (with HERV), (S) = short form