Aggregated genetic information explains variations on hand radiographic scores in Rheumatoid Arthritis patient

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Background: Rheumatoid arthritis (RA) has an estimated heritability of approximately 60%. Joint destruction as a severity measure of RA is influenced by genetic factors, however the heritability of this trait remains unclear. Our objective was to determine the genetic heritability of joint destruction, quantified as Sharp/van der Heijde scores (SHS), and to conduct a genome wide association study (GWAS) to identify SNPs associated with quantitative joint damage in RA patients.

Method: We studied 422 anti-CCP+ RA subjects in a prospective observational RA cohort at an academic hospital with baseline bilateral hand radiographs and blood samples. Using the SHS method, 4 radiologists assigned an erosion score (0-5) for 16 joints, and a joint space narrowing score (0-4) for 15 joints in each hand (total SHS range 0-280). The inter-rater reliability for the SHS in our study was 0.93. SHS measures were normalized by taking the inverse normal of the rank. Samples were genotyped on the Affymetrix 6.0 platform. We applied standard quality control procedures, followed by imputation to 2.5M SNPs using IMPUTE with HapMap2 CEU. Clinical predictors of SHS such as age. gender, disease duration were studied using general linear regression. We applied mixed linear model analysis to estimate the proportion of variance explained by genotyped SNPs from the whole genome to determine heritability. We studied the association between each SNP and SHS using linear regression assuming a genetic additive model adjusting for the first three principal component values from Eigenvector analysis and RA disease duration.

Result: The 422 RA cases had mean age of 59 yrs, mean disease duration of 17 yrs, and 81% were female. The SHS range was 0-270 with median of 40. Clinical predictors including age and disease duration were significant in univariate analyses, and only disease duration was significant (P <0.0001) in multivariate analyses. Heritability analysis adjusted for disease duration and 3 principal components estimated 22% (p=0.39) of SHS variation was attributable to genetic variants using all genotyped SNP information. From the GWAS, we found 2 SNPs that exceeded the genome-wide significance threshold of 5E-8 (rs16925520 p=4E-9, rs2832760 p=3E-8) for association with SHS. The independent top 10 findings are shown in the table. The MHC region was not significantly associated with SHS. No known RA risk alleles (~50 loci) were associated with SHS.

Conclusion: Our study suggests that joint damage in RA (as measured by SHS) is a heritable trait where genetic factors explain ~22% of the phenotypic variance. These findings corroborate with a previous study where heritability was estimated to be higher at 45%-58%. Although several SNPs were associated with SHS at genome-wide significance, none were known RA risk alleles. These findings require confirmation in an independent sample.

Table. Top 10 SNPs associated with Sharp/van der Heijde Hand Score

chr	rs	gene	Base pair	Allele A	Minor allele frequency	beta	P-value

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9	rs16925520	*JMJD2C*	7162354	C	0.01	3.52	4.3E-09
21	rs2832760	*CLDN8*	30584023	G	0.30	0.31	3.3E-08
5	rs10079663	*VDAC1*	133384433	C	0.41	0.28	1.1E-07
8	rs13256240	-	83633555	A	0.01	-3.38	2.2E-07
9	rs10901313	*FUBP3*	132275229	C	0.02	-2.13	1.1E-06
4	rs1980037	*GYPB*	145136964	A	0.02	2.73	1.2E-06
19	rs4801371	*ZNF71*	61926872	A	0.04	-1.28	1.8E-06
4	rs10024454	*IGFBP7*	57942964	C	0.32	-0.27	2.2E-06
8	rs1471705	*ZFHX4*	77880207	A	0.01	-2.79	2.7E-06
1	rs6674099	*DISC2*	230033485	A	0.45	0.23	3.2E-06