14 GENETIC VARIANTS IN IL-15 ASSOCIATE WITH PROGRESSION OF JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS, A MULTI COHORT STUDY

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Background IL-15 levels are increased in serum, synovium and bone marrow of RA-patients. IL-15 influences both the innate and adaptive immune response; its major role is activation and proliferation of T cells. Data also emerge that IL-15 affects osteoclastogenesis. The authors investigated the association of genetic variants in IL-15 with rate of joint destruction in RA.

Method 1418 patients with 4885 x-ray sets of both hands and feet of four independent datasets were studied. First, explorative analyses were performed on 600 early RA patients enrolled in the Leiden Early Arthritis Clinic. Twenty-five SNPs tagging IL-15 were tested. Second, SNPs with significant associations in the explorative phase were genotyped in datasets from Groningen, Sheffield and Lund. In each dataset the relative increase of the progression rate per year in the presence of a genotype was assessed. Subsequently, data were summarised in an inverse weighting meta-analysis.

Results Five SNPs were significantly associated with rate of joint destruction in phase-1 and typed in the other datasets. Patients homozygous for rs7667746, rs7665842, rs2322182, rs6821171 and rs4371699 had respectively 0.94, 1.04, 1.09, 1.09 and 1.09 fold rate of joint destruction per year compared to other patients ($p=4.0 \times 10^{-6}$, $p=3.8 \times 10^{-4}$, $p=5.0 \times 10^{-3}$, $p=5.0 \times 10^{-3}$ and $p=9.4 \times 10^{-3}$).

Due to insufficient power of the cohorts of phase-2, independent replication was not obtained. Meta-analyses of all datasets combined resulted in significant results for four SNPs (rs7667746, $p < 0.001$; rs7665842, $p < 0.001$; rs4371699 $p = 0.01$; rs6821171, $p = 0.01$). These SNPs were also significant after correction for multiple testing.

Conclusion Genetic variants in IL-15 are associated with progression of joint destruction in RA.