Genetic contribution of DKK-1 polymorphisms to RA structural severity and DKK-1 level of expression

There is growing interest in the role of Dickkopf-1 (DKK-1), an inhibitor of the Wnt signalling pathway, in subchondral bone erosions in rheumatoid arthritis (RA). de Rooy et al have previously reported that polymorphisms within the DKK-1 locus might contribute to RA structural severity. In fact, rs1896368 was significantly associated with an increased rate of joint destruction with a 1.02-fold (95% CI 1.01 to 1.04) progression rate per year per minor allele (additive model). Patients carrying the rs1896368 at-risk allele also had significantly higher serum levels of DKK-1. Several other polymorphisms located within the DKK-1 locus were associated with a faster structural progression. We aimed to replicate these findings in the ESPOIR cohort which is a prospective, multicentre French cohort of patients with early arthritis. We took advantage of the large number of patients assessed within the ESPOIR cohort, with iterative and centralised radiological evaluation, which allowed for studying the role of DKK-1 polymorphisms as predictive markers of structural damage and/or as genetic modulators of DKK-1 expression. Patients had to be free of disease-modifying antirheumatic drugs and biologics to be included in the cohort, thus avoiding a bias due to alteration of DKK-1 serum levels.

In total, 646 patients fulfilling the American College of Rheumatology/European League Against Rheumatism criteria for RA after 2 years of follow-up were assessed in the present study. None of the 10 studied DKK-1 single nucleotide polymorphisms (SNPs) were significantly associated with the total van der Heijde-modified Sharp score (mSHS) at baseline, or after 1 or 2 years of follow-up. Furthermore, none of these SNPs were associated with structural progression during the first 2 years of follow-up (absolute variation in total mSHS between baseline and year 2) in cross-sectional analyses. The effect of each SNP on longitudinal structural progression was assessed in a linear mixed model with random effects in which the yearly assessment of total Sharp score was the outcome variable and time and each SNP’s genotypes the interacting variables. Again,
DKK-1 was observed (p=0.04) but multivariate analysis including none of the studied SNPs were associated with structural outcome during the first 2 years of follow-up.

Among the 641 patients with RA quantified for DKK-1 at baseline, a significant association between rs12354645 and serum DKK-1 was observed (p=0.04) but multivariate analysis including parameters previously demonstrated to impact serum DKK-1 (baseline C-reactive protein and monocyte chemotactic protein-1 serum levels) failed to retain this SNP (as well as any of the nine other genotyped SNPs) as significantly associated with DKK-1 serum levels. Haplotype analyses did not yield additional information. Therefore, the association of DKK-1 polymorphisms with structural progression and/or DKK-1 serum levels was not replicated in our cohort of early RA. These discrepancies could be due to the short follow-up time of radiographic assessment (2 years) compared with de Rooy’s study. Nevertheless, in their cohorts, differences according to rs1528873 were already observable at this time point. Even if clearly underpowered to replicate the low ORs associated with structural progression reported by de Rooy et al, our study had 30%–83% power to demonstrate a 1.5-fold increased risk of progression for carriers of the minor allele of DKK-1 SNPs (with MAF ranging from 0.06 to 0.48). Moreover, the role of rs1896368 (figure 1) (and any of the other DKK-1 studied SNPs) in the regulation of DKK-1 serum levels was clearly excluded in our study assessing a large number of RA patients. Taken together, these results suggest that DKK-1 polymorphisms are unlikely to regulate DKK-1 serum levels or to be main contributors to structural severity in RA. However, the contribution of rare variants within DKK-1 gene region to structural progression in RA cannot be ruled out on the basis of the current study. Further sequencing studies of the DKK-1 locus among patients with RA with well-defined phenotypes will be required to fully define the contribution of genetic variation to structural progression in RA.

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