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*[1] 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.[1] We aimed to replicate these findings in the ESPOIR cohort which is a prospective, multicentre French cohort of patients with early arthritis.[2] 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.[3] 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,

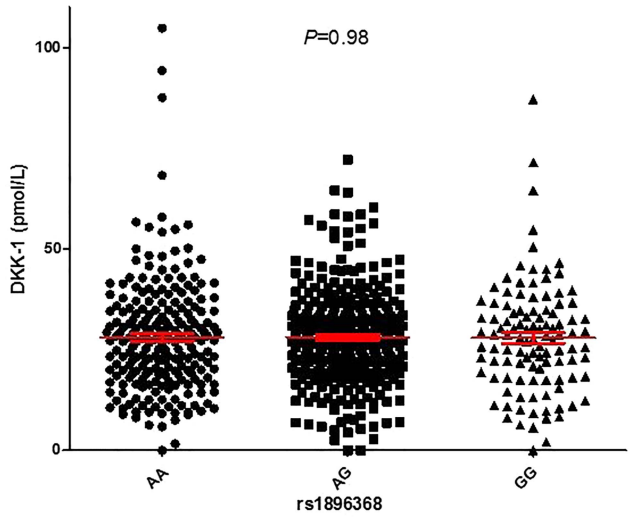

Figure 1 DKK-1 levels of expression according to rs1896368 genotypes. DKK-1 serum levels at baseline among are represented for 641 RA patients according to their rs1896368 genotype.

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[4] to impact serum DKK-1 (baseline C-reactive protein and monocyte chemoattractant 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.[1] 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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Acknowledgements We thank the French rheumatologists in the following rheumatology departments for referring patients to the ESPOIR cohort: Amiens (P. Fardellone, P. Boumier), Bordeaux (T. Schaeverbecke), Brest (A. Saraux), Lille (R. M. Flipo), Paris-Bicêtre (X. Mariette), Paris-Bichat (O. Meyer), Paris-Cochin (M. Dougados), Paris-St. Antoine (F. Berenbaum), Rouen (O. Vittecoq), Strasbourg (J. Sibilia), Toulouse (A. Cantagrel) and Tours (P. Goupille). We are grateful to S. Martin for all the centralised assays of CRP level, IgA and IgM RFs, and anti-CCP antibodies. We also thank Dr Yassine Taoufik, Dr Pascale Chrétien, Bruno Oualid and Emilie Rouyer for technical assistance and unrestricted access to the Evolis microplate system (Department of Immunology, Hôpitaux Universitaires Paris Sud, France).

Contributors CM-R and LAC: study conception and design. CM-R, GN, SB, PD, AC, VD-P, GJT and XM: acquisition of data. CMR, KT, JN, RSand LAC: data analysis. All authors were involved in drafting the manuscript or revising it critically for important intellectual content. All authors approved the final version to be published. CM-R had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Funding An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years of the ESPOIR cohort study. Two additional grants from INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Pfizer, Abbvie and Roche-Chugai also supported the ESPOIR cohort study. A research grant from Pfizer 'Passerelle' was obtained for DKK-1 and SOST quantification for the whole cohort. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests None.

Patient consent Obtained.

Ethics approval French ethic committee board.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Miceli-Richard C, Taylor KE, Nititham J, *et al*. *Ann Rheum Dis* 2015;**74**:1480–1481.

Received 25 August 2014
Revised 2 March 2015
Accepted 8 March 2015
Published Online First 24 March 2015

Ann Rheum Dis 2015;**74**:1480–1481. doi:10.1136/annrheumdis-2014-206530

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Ann Rheum Dis 2015 74: 1480-1481 originally published online March 24, 2015
doi: 10.1136/annrheumdis-2014-206530

Notes