ARD Online First, published on March 16, 2013 as 10.1136/annrheumdis-2012-203182

LETTER

The *DOT1L* rs12982744 polymorphism is associated with osteoarthritis of the hip with genome-wide statistical significance in males

Evangelos Evangelou,[1,2] Ana M Valdes,[2,3] Martha C Castano-Betancourt,[4,5] M Doherty,[3] Sally Doherty,[3] Tonu Esko,[6] Thorvaldur Ingvarsson,[7,8,9] John P A Ioannidis,[1,10] Margreet Kloppenburg,[11] Andres Metspalu,[6] Evangelia E Ntzani,[1] Kalliope Panoutsopoulou,[12] P Eline Slagboom,[5,13] Lorraine Southam,[12] Tim D Spector,[2] Unnur Styrkarsdottir,[14] Kari Stefanson,[9,13] André G Uitterlinden,[4,5] Margaret Wheeler,[3] Eleftheria Zeggini,[12] Ingrid Meulenbelt,[5,13] Joyce B van Meurs,[4,5] arcOGEN consortium, the TREAT-OA consortium

[1]Department of Hygiene and Epidemiology, University of Ioannina Medical School, University Campus, Ioannina, Greece
[2]Department of Twin Research and Genetic Epidemiology, St. Thomas' Hospital, King's College, Lambeth Palace Road, London, UK
[3]Academic Rheumatology, University of Nottingham, City Hospital Nottingham, Nottingham, UK
[4]Department of Internal Medicine, ErasmusMC, Rotterdam, The Netherlands
[5]The Netherlands Genomics Initiative-sponsored Netherlands Consortium for Healthy Aging (NGI-NCHA), Rotterdam/Leiden, The Netherlands
[6]Estonian Genome Center, University of Tartu, Tartu, Estonia
[7]Department of Orthopedic Surgery, Akureyri Hospital, Akureyri, Iceland
[8]Institution of Health Science, University of Akureyri, Akureyri, Iceland
[9]Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[10]Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, USA
[11]Department of Rheumatology and Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

Osteoarthritis (OA) of the hip is a major cause of pain, disability and use of healthcare resources.[1] Although OA is multifactorial, it is known to have significant genetic contribution and a number of studies have attempted to dissect such contribution (see[2] for review).

The *DOT1L* gene encodes the DOT1-like histone H3 methyltransferaseis, a potentially dedicated enzyme for Wnt target gene activation in leukaemia recently shown to be associated with endochondral bone formation.[3]

A polymorphism (rs12982744) in *DOT1L* has been found to be strongly associated with minimum joint space width (minJSW) at the hip. This exact same single nucleotide polymorphism (SNP) was previously identified to be associated with increased height.[4 5] The C allele associated with lower minJSW and lower height was associated with hip OA, although this association did not reach genome-wide significance (GWS) (OR 1.14, CI 1.06 to 1.22; $p=1.5\times10^{-4}$).[3]

The GWS level of $p<5\times10^{-8}$ is the threshold at which genetic associations are considered credible.[6] The aim of our study was to prove that common genetic variation in the *DOT1L* gene is important in hip OA at this level of confidence.

Genetic association data for rs12982744 and hip OA were derived from the Translational Research in Europe Applied Technologies for OsteoArthritis (TREAT-OA) consortium and combined with data from the UK (arcOGEN consortium), Estonia (Estonian Genome Center of the University of Tartu) and other studies (Nottingham, GOAL).[3] The total sample size was 9789 hip OA cases and 31 873 controls of which there were 4155 cases and 15 213 controls in male subjects and 5634 cases and 16 660 controls in female subjects. Summary OR was calculated using a fixed effects model. The individual study estimates and sample sizes are shown in figure 1. A full detailed description of each study cohort on recruitment, radiographic and clinical assessment is found in.[7 8] Studies were approved by the relevant Ethics Committee and informed consent was obtained from all study participants.

The results of the meta-analysis show that in male subjects the C allele of *DOT1L* rs12982744 is GWS with a 17% increased risk of hip OA (OR 1.17, 95% CI 1.11 to 1.23, $p=7.8\times10^{-9}$) with no observed heterogeneity ($I^2=0$). In female subjects, the OR is 1.05 (95% CI 1.00 to 1.10, $p=0.04$) with $I^2=31\%$. The effect size estimate is significantly different between both sexes ($p=0.003$) with non-overlapping CIs. For both genders combined, the p value was 8.1×10^{-8} ($I^2=35\%$) (figure 1). The difference in effect size between genders is not surprising considering the sexual dimorphism of this trait: men have a larger mJSW and prevalence of hip OA rises specifically in women after menopause, suggesting a role of sex hormones in the disease process.

In this large-scale meta-analysis we show that the association between a *DOT1L* SNP and hip OA achieves GWS in male subjects strengthening the robustness of *DOT1L* as a risk factor for hip OA.

This makes *DOT1L* a potential therapeutic target for modulation and intervention in hip OA. This is relevant since small molecular inhibitors have been developed and a phase I trial has been started (http://epizyme.com/programs/dot1l.asp).

This result also highlights the greater statistical power of quantitative endophenotypes for genetic studies.

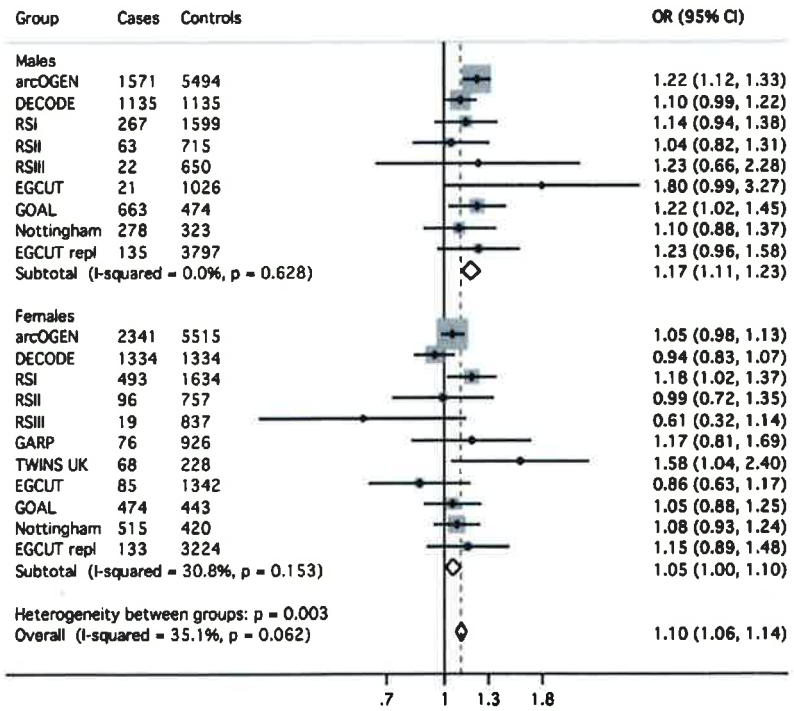

Figure 1 Forest plot of study-specific estimates and fixed effects summary OR estimates and 95% CIs for the association between the C allele and the rs12982744 polymorphism of the *DOT1L* gene and hip osteoarthritis. Analyses were carried out using Stata V.12 (College Station, Texas, USA).

[12]Wellcome Trust Sanger Institute, Hinxton, UK
[13]Department of Molecular Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands
[14]deCODE Genetics, Reykjavik, Iceland

EE and AMV contributed equally.

Correspondence to Dr Ana M Valdes, Academic Rheumatology, University of Nottingham, Clinical Sciences Bld, Nottingham City Hospital, Nottingham NG5 1PE, UK; ana.valdes@nottingham.ac.uk

Contributors All authors contributed to the study design, data interpretation and the final manuscript. In addition, EE analysed the data; JvM, EE and AMV interpreted the data and prepared the manuscript; and JvM supervised the study.

Funding This work was supported by EC framework 7 programme grant 200800 TREAT-OA. EZ, KP and LS are funded by the Wellcome Trust (098051). KP is funded by Arthritis Research UK (19542). arcOGEN was funded by a special purpose grant from Arthritis Research UK (18030). The Leiden University Medical Centre, the Dutch Arthritis Association and Pfizer Inc., Groton, CT, USA support the GARP study, while genotypic work was supported by the Netherlands Organization of Scientific Research (MW 904-61-095, 911-03-016, 917 66344 and 911-03-012), Leiden University Medical Centre, and by the 'Centre of Medical System Biology' and the 'Netherlands Consortium of Healthy Aging' in the framework of the Netherlands Genomics Initiative (NGI). Furthermore, the research leading to these results has received funding from the Dutch Arthritis Association (DAA 2010_017) and the European Union's Seventh Framework Programme (FP7/2007-2011) under grant agreement n° 259679. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), and by The Netherlands Society for Scientific Research (NWO) VIDI Grant 917103521.

Competing interests None.

Ethics approval Each participating study obtained approval from the appropriate ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Evangelou E , Valdes AM, Castano-Betancourt M C, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2012-203182

Accepted 24 February 2013

Ann Rheum Dis 2013;**0**:1–2.
doi:10.1136/annrheumdis-2012-203182

REFERENCES

1 Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005;365:965–73.
2 Valdes AM, Spector TD. Genetic epidemiology of hip and knee osteoarthritis. *Nat Rev Rheumatol* 2011;7:23–32.
3 Castaño Betancourt MC, Cailotto F, Kerkhof HJ, *et al*. Genome-wide association and functional studies identify the DOT1L gene to be involved in cartilage thickness and hip osteoarthritis. *Proc Natl Acad Sci USA*. 2012;109:8218–23.
4 Allen H Lango, Estrada K, Lettre G, *et al*. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 2010;467:832–8.
5 Sovio U, Bennett AJ, Millwood IY, *et al*. Genetic determinants of height growth assessed longitudinally from infancy to adulthood in the northern Finland birth cohort 1966. *PLoS Genet* 2009;5:e1000409.
6 Johnson AD, O'Donnell CJ. An open access database of genome-wide association results. *BMC Med Genet* 2009;10:6.
7 arcOGEN Consortium and arcOGEN Collaborators. Identification of new susceptibility loci for osteoarthritis—the arcOGEN study. *Lancet* 2012;380:815–23.
8 Kerkhof HJ, Meulenbelt I, Akune T, *et al*. Recommendations for standardization and phenotype definitions in genetic studies of osteoarthritis: the TREAT-OA consortium. *Osteoarthritis Cartilage* 2011;19:254–64.

The *DOT1L* rs12982744 polymorphism is associated with osteoarthritis of the hip with genome-wide statistical significance in males

Evangelos Evangelou, Ana M Valdes, Martha C Castano-Betancourt, et al.

Ann Rheum Dis published online March 16, 2013
doi: 10.1136/annrheumdis-2012-203182