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*Ann Rheum Dis* published online September 24, 2010
doi: 10.1136/ard.2010.134155

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The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genome-wide statistical significance

Osteoarthritis of the knee is a major cause of pain, disability and the use of healthcare resources among middle-aged and older people. Although osteoarthritis is multifactorial, it is known to have a significant genetic contribution and a number of studies have attempted to dissect such a contribution (see Valdes and Spector for review).

The GDF5 gene encodes the growth differentiation factor 5, a bone morphogenetic protein involved in joint formation, expressed in different joint structures, which has been shown to ameliorate tendon, ligament and bone healing after trauma in mice. A promoter polymorphism (rs143383) in GDF5 has been found to be strongly associated with both hip and knee osteoarthritis in Asian individuals, and is the most widely replicated genetic association with knee osteoarthritis, although much less so for hip and hand osteoarthritis. This variant is functional, with the lower gene expression variant having increased genetic risk. A large-scale meta-analysis reported the association of the major (T) allele with knee osteoarthritis achieved OR 1.15 to 1.18 when Asian subjects were excluded. This variant is functional, and the use of healthcare resources among middle-aged and older people.

We genotyped 3303 controls and 2235 knee osteoarthritis cases from the UK, Estonia and The Netherlands, added published data from the Chingford Study (259 cases and 509 controls), and combined with published effect size estimates from the recent large-scale meta-analysis using both fixed and random effects models as described in Evangelou et al. A full detailed description of each study cohort on recruitment, radiographic and clinical assessment is found in Hofman et al. and Valdes et al. The studies were approved by the relevant ethics committees and informed consent was obtained from all study participants. Genotypes were subtracted from the genome-wide association dataset of the Rotterdam Study III with methods described previously. DNA from UK and Estonian study participants was genotyped by Kbioscience (Hertfordshire UK) using methods described elsewhere. The total, including previously reported data, is 10 103 controls and 6861 knee osteoarthritis cases of European descent and 1844 controls and 718 cases of Asian descent, which has 86% statistical power to detect the association as genome-wide significant with an OR of 1.15 or higher for the T allele. The descriptive characteristics of new samples studied are shown in Table 1 along with the OR for the T allele and CI. The individual study effect sizes are shown in figure 1.

The results of the combined meta-analysis show that the T allele of GDF5 rs143383 is associated with a 17% increased risk of knee osteoarthritis (OR 1.17, 95% CI 1.12 to 1.23). When all data were analysed the genetic association reached genome-wide significance with p=6.2×10^{-11} in all samples and with p=8.3×10^{-9} in European descent samples alone (figure 1). There was no significant between-study heterogeneity. The p value was even smaller when one study violating Hardy–Weinberg equilibrium was excluded (OR 1.18, 95% CI 1.12 to 1.23, p=4.1×10^{-11}). Stratification according to gender did not reveal differences in the effect size (OR 1.14, 95% CI 1.05 to 1.23, p=1.6×10^{-3} in men vs OR 1.19, 95% CI 1.10 to 1.27, p=5.7×10^{-6} in women by random effects).

We have shown that the association between a functional promoter single nucleotide polymorphism in the GDF5 gene and knee osteoarthritis achieves genome-wide statistical significance. The association is consistently replicated and no significant heterogeneity is detected between studies, further strengthening the robustness of GDF5 as a risk factor for knee osteoarthritis.

### Table 1 Descriptive statistics of study samples included, number of cases and controls for new and published studies and OR for the GDF5 rs143383 T allele

<table>
<thead>
<tr>
<th>Country of origin</th>
<th>Rotterdam study III</th>
<th>Estonian knee osteoarthritis study</th>
<th>Hertfordshire cohort plus Nottingham cases</th>
<th>Genetics of osteoarthritis and lifestyle</th>
<th>Chingford study</th>
<th>Ten studies from large-scale meta-analysis (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDF5 association data from</td>
<td>This study</td>
<td>This study</td>
<td>This study</td>
<td>This study</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Country of origin</td>
<td>Netherlands</td>
<td>Estonia</td>
<td>UK</td>
<td>Caucasian</td>
<td>UK</td>
<td>Europe, China, Japan</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Asian and Caucasian</td>
</tr>
<tr>
<td>No of knee osteoarthritis cases</td>
<td>151/1582</td>
<td>65/427</td>
<td>1141/536</td>
<td>861/759</td>
<td>259/509</td>
<td>5095/8135</td>
</tr>
<tr>
<td>BMI mean (SD)</td>
<td>27.7 (4.7)</td>
<td>28.1 (5.4)</td>
<td>27.2 (5.1)</td>
<td>28.3 (5.3)</td>
<td>26.7 (4.7)</td>
<td>64.1 (6.0)</td>
</tr>
<tr>
<td>Age mean (SD)</td>
<td>56.0 (5.5)</td>
<td>56.0 (5.5)</td>
<td>56.0 (5.5)</td>
<td>56.0 (5.5)</td>
<td>56.0 (5.5)</td>
<td>56.0 (5.5)</td>
</tr>
<tr>
<td>rs143383 T allele % in knee osteoarthritis/controls</td>
<td>64.6/61.0%</td>
<td>67.7/60.3%</td>
<td>63.6/62.9%</td>
<td>68.5/62.1%</td>
<td>67.6/69.5%</td>
<td>NA</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.16 (0.91 to 1.49)</td>
<td>1.38 (0.93 to 2.04)</td>
<td>1.02 (0.87 to 1.18)</td>
<td>1.32 (1.14 to 1.53)</td>
<td>1.42 (1.13 to 1.77)</td>
<td>1.15 (1.09 to 1.22)</td>
</tr>
</tbody>
</table>

*Data for all studies, the summary statistics reported for each of the individual studies were used separately and are shown in figure 1. BMI, body mass index; K/L, Kellgren–Lawrence radiographic grade; PF, patellofemoral; TF, tibiofemoral; TKR, total knee replacement; NA, not applicable because it refers to 10 different studies.

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Acknowledgements The authors thank Marijn Verkerk and Karol Estrada for their help creating the genome-wide association database for RS III and Dieuwke Schiphof for scoring the knee radiographs of RSIII. The authors thank all the study participants and the participating general practitioners and pharmacists contributing to all the study cohorts.

Funding This work was supported by EC framework 7 programme grant 200800 TREAT-osteoarthritis, Arthritis Research UK (ARUK), the Medical Research Council (UK), the Oxford NIHR Musculoskeletal Biomedical Research Unit, the Estonian Science Foundation grant no 5308, the Estonian Ministry of Social Affairs grants no 9.6-4/2035 and 12.1-5/597 and by AstraZeneca, Macclesfield, UK. The generation and management of genome-wide association genotype data for the Rotterdam Study is supported by The Netherlands Organisation of Scientific Research NWO Investments (no 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014–93–015; RIDE2) and The Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) (project no 050-060–810).

Competing interests RM is an Astra Zeneca plc employee and owns Astra Zeneca stock. All other authors declare no competing interests.

Ethics approval This study was conducted with the approval of the the Nottingham case–control and the GOAL study protocols were approved by the Nottingham City Hospital and North Nottinghamshire ethical committees. The Hertfordshire Cohort Study was approved by the East and North Hertfordshire ethical committees. The medical ethics committee of Erasmus University Medical School approved the Rotterdam study III. The Ethics Committee of the University of Tartu approved the Estonian knee osteoarthritis study.

Provenance and peer review Not commissioned; externally peer reviewed.

Accepted 9 August 2010
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