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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.¹ 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 Spector² 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.^{3 4}

A promoter polymorphism (rs143383) in *GDF5* has been found to be strongly associated with both hip and knee osteoarthritis in Asian individuals,⁴ and is the most widely replicated genetic association with knee osteoarthritis, although much less so for hip and hand osteoarthritis.⁵ This variant is functional, with the lower gene expression variant having increased genetic risk.⁴

A large-scale meta-analysis reported the association of the major (T) allele with knee osteoarthritis achieved OR 1.15 $p=9.7 \times 10^{-7}$ and achieved $p=9 \times 10^{-5}$ (OR 1.13, 95% CI 1.06 to 1.20) when Asian subjects were excluded.⁵

The genome-wide statistical significance level of $p < 5 \times 10^{-8}$ is increasingly seen as the threshold at which genetic associations are considered credible.⁶ The aim of our study was to prove that common genetic variation in the *GDF5* gene is important in knee osteoarthritis beyond reasonable doubt.

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),⁷ and combined with published effect size

estimates from the recent large-scale meta-analysis⁵ using both fixed and random effects models as described in Evangelou *et al.*⁵ A full detailed description of each study cohort on recruitment, radiographic and clinical assessment is found in Hofman *et al.*⁸ and Valdes *et al.*⁹ 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.¹⁰ DNA from UK and Estonian study participants was genotyped by Kbioscience (Hertfordshire UK) using methods described elsewhere.⁷ 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 $p=6.2 \times 10^{-11}$ in all samples and with $p=8.3 \times 10^{-9}$ 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 equilibrium⁵ was excluded (OR 1.18, 95% CI 1.12 to 1.23, $p=4.1 \times 10^{-11}$). Stratification according to gender did not reveal differences in the effect size (OR 1.14, 95% CI 1.05 to 1.23, $p=1.6 \times 10^{-3}$ in men vs OR 1.19, 95% CI 1.10 to 1.27, $p=3.7 \times 10^{-6}$ 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

	New data			Genetics of osteoarthritis and lifestyle	Published data	
	Rotterdam study III	Estonian knee osteoarthritis study	Hertfordshire cohort plus Nottingham cases		Chingford study	Ten studies from large-scale meta-analysis (*)
<i>GDF5</i> association data from	This study	This study	This study	This study	7	5
Country of origin	Netherlands	Estonia	UK	UK	UK	Europe, China, Japan
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Asian and Caucasian
No of knee osteoarthritis cases/controls	151/1582	65/427	1141/536	867/758	259/509	5085/8135
Knee osteoarthritis definition	TF K/L ≥ 2	TF K/L ≥ 2	TF or PF K/L ≥ 2 or TKR	TKR	TF K/L ≥ 2	Mixed
Women %	56	69	52	49	100	NA
BMI mean (SD)	27.7 (4.7)	28.1 (5.4)	28.2 (5.1)	29.3 (5.3)	26.7 (4.7)	NA
Age mean (SD)	56.0 (5.5)	47.1 (6.4)	67.2 (7.4)	66.5 (7.9)	64.1 (6.0)	NA
rs143383 T allele % in knee osteoarthritis/controls	64.6/61.0%	67.7/60.3%	63.3/62.9%	68.5/62.1%	67.6/59.5%	NA
OR (95% CI)	1.16 (0.91 to 1.49)	1.38 (0.93 to 2.04)	1.02 (0.87 to 1.1.8)	1.32 (1.14 to 1.53)	1.42 (1.13 to 1.77)	1.15 (1.09 to 1.22)

*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.

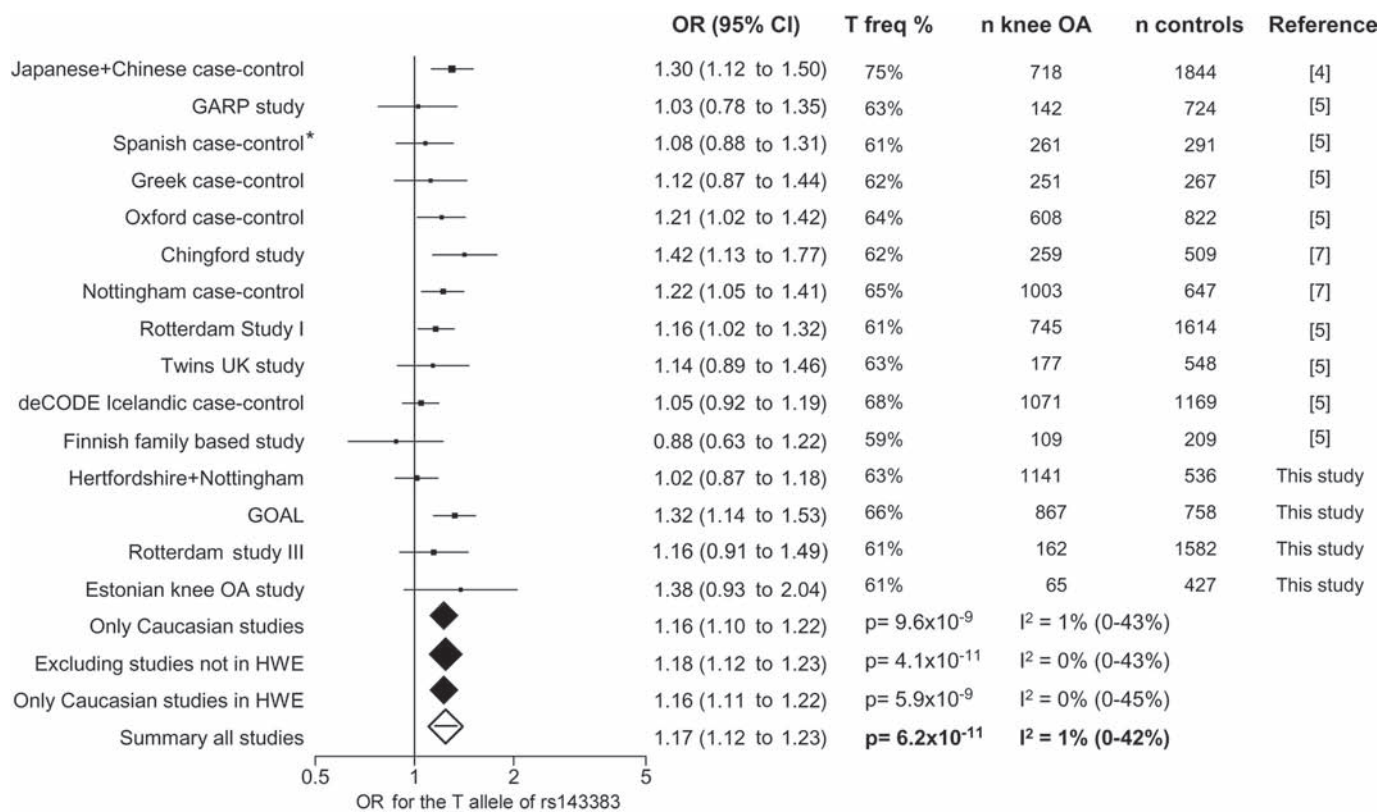


Figure 1 Forest plot of study-specific estimates and fixed-effects summary OR estimates and 95% CI for the association between the rs143383 polymorphism of the *GDF5* gene and knee osteoarthritis (OA) in current and previously published studies. The summary statistics and corresponding p values for all studies and for sensitivity analyses excluding studies out of Hardy–Weinberg equilibrium (HWE; indicated by *) and/or Asian studies are shown. The between-study heterogeneity I^2 and the respective 95% CI are also included.

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

Patient consent Obtained.

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.

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REFERENCES

1. **Dieppe PA**, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005;**365**:965–73.
2. **Valdes AM**, Spector TD. The clinical relevance of genetic susceptibility to osteoarthritis. *Best Pract Res Clin Rheumatol* 2010;**24**:3–14.
3. **Mikic B**. Multiple effects of GDF-5 deficiency on skeletal tissues: implications for therapeutic bioengineering. *Ann Biomed Eng* 2004;**32**:466–76.
4. **Miyamoto Y**, Mabuchi A, Shi D, *et al*. A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis. *Nat Genet* 2007;**39**:529–33.
5. **Evangelou E**, Chapman K, Meulenbelt I, *et al*. Large-scale analysis of association between GDF5 and FRZB variants and osteoarthritis of the hip, knee, and hand. *Arthritis Rheum* 2009;**60**:1710–21.
6. **Evangelou E**, Maraganore DM, Annesi G, *et al*. Non-replication of association for six polymorphisms from meta-analysis of genome-wide association studies of Parkinson's disease: large-scale collaborative study. *Am J Med Genet B Neuropsychiatr Genet* 2010;**153B**:220–8.
7. **Valdes AM**, Spector TD, Doherty S, *et al*. Association of the DVWA and GDF5 polymorphisms with osteoarthritis in UK populations. *Ann Rheum Dis* 2009;**68**:1916–20.
8. **Hofman A**, Breteler MM, van Duijn CM, *et al*. The Rotterdam Study: 2010 objectives and design update. *Eur J Epidemiol* 2009;**24**:553–72.
9. **Valdes AM**, Arden NK, Tamm A, *et al*. A meta-analysis of interleukin-6 promoter polymorphisms on risk of hip and knee osteoarthritis. *Osteoarthr Cartil* 2010;**18**:699–704.
10. **Kerkhof HJ**, Lories RJ, Meulenbelt I, *et al*. A genome-wide association study identifies an osteoarthritis susceptibility locus on chromosome 7q22. *Arthritis Rheum* 2010;**62**:499–510.