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

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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 Spector[2] for review).

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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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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 $p=9.7\times10^{-7}$ and achieved $p=9\times10^{-5}$ (OR 1.13, 95% CI 1.06 to 1.20) when Asian subjects were excluded.[5]

The genome-wide statistical significance level of $p<5\times10^{-8}$ 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-analysis[5] 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* rs143833 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 $p=6.2\times10^{-11}$ in all samples and with $p=8.3\times10^{-9}$ 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[5] was excluded (OR 1.18, 95% CI 1.12 to 1.23, $p=4.1\times10^{-11}$). Stratification according to gender did not reveal differences in the effect size (OR 1.14, 95% CI 1.05 to 1.23, $p=1.6\times10^{-3}$ in men vs OR 1.19, 95% CI 1.10 to 1.27, $p=3.7\times10^{-6}$ 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.

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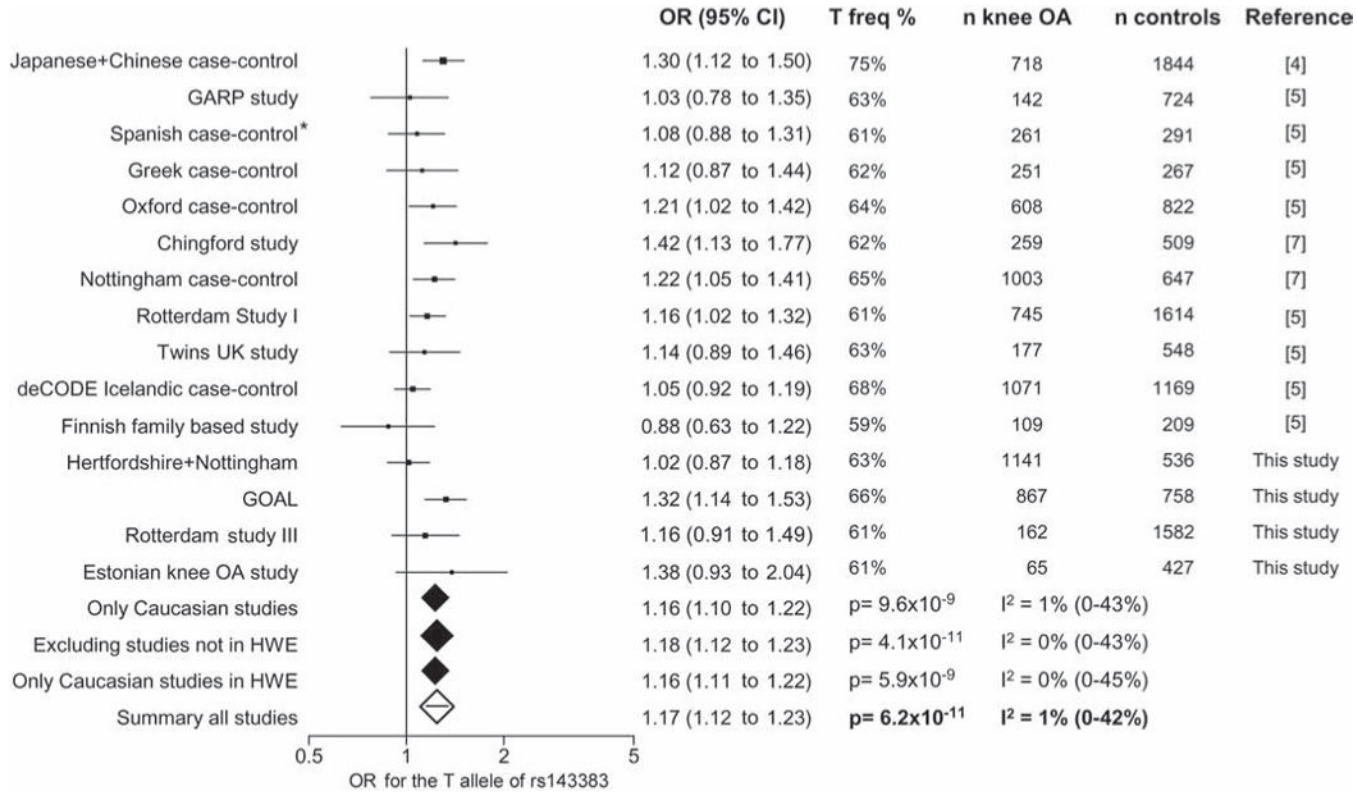

Figure 1.

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.

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				Published data	
	Rotterdam study III	**Estonian knee osteoarthritis study**	**Hertfordshire cohort plus Nottingham cases**	**Genetics of osteoarthritis and lifestyle**	**Chingford study**	**Ten studies from large-scale meta-analysis (*)**
GDF5 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.