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CONCISE REPORT

The genetic contribution to severe post-traumatic osteoarthritis

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ABSTRACT

Objective to compare the combined role of genetic variants loci associated with risk of knee or hip osteoarthritis (OA) in post-traumatic (PT) and non-traumatic (NT) cases of clinically severe OA leading to total joint replacement.

Methods A total of 1590 controls, 2168 total knee replacement (TKR) cases (33.2% PT) and 1567 total hip replacement (THR) cases (8.7% PT) from 2 UK cohorts were genotyped for 12 variants previously reported to be reproducibly associated with risk of knee or hip OA. A genetic risk score was generated and the association with PT and NT TKR and THR was assessed adjusting for covariates.

Results For THR, each additional genetic risk variant conferred lower risk among PT cases (OR=1.07, 95% CI 0.96 to 1.19; p=0.24) than NT cases (OR 1.11, 95% CI 1.06 to 1.17; $p=1.55\times10^{-5}$). In contrast, for TKR, each risk variant conferred slightly higher risk among PT cases (OR 1.12, 95% CI 1.07 to 1.19; $p=1.82\times10^{-5}$) than among NT cases (OR 1.08, 95% CI 1.03 to 1.1; p=0.00063).

Conclusions Based on the variants reported to date PT TKR cases have at least as high a genetic contribution as NT cases.

INTRODUCTION

Large joint osteoarthritis (OA) is a common complex disorder with multiple genetic, constitutional and environmental risk factors and marked variability in phenotype.[1 2]

OA is divided into 'primary' OA, considered to result mainly from genetic and constitutional factors, and 'secondary' OA when there is an obvious cause of joint insult.[3] A long-recognised risk factor for OA is direct joint injury, such as a subchondral fracture, meniscectomy, anterior cruciate tear or a deforming tibial or femoral fracture that results in poor alignment or leg length shortening.[4 5] An estimated 12% of symptomatic OA may be attributed to a post-traumatic (PT) cause[6] and differences in radiographic patterns have been reported between primary and PT knee OA cases.[7] However, two studies that examined the relationship between hand OA and the risk of developing knee OA following meniscectomy found that the presence of hand OA associated with a higher frequency and radiographic severity of post-meniscectomy OA,[8 9] demonstrating that development of OA following a meniscal tear and subsequent surgery are not necessarily of secondary origin.

Genetic factors are known to influence risk of hip OA, knee OA and generalised OA (see Valdes and Spector[10]). Recent genetic association studies have identified a number of genetic variants associated with knee or hip OA or with severe large joint OA leading to total joint arthroplasty.[11–15] To date, 12 independent variants have been reported to be associated with risk of hip or knee OA or related traits with a statistical significance level of $p<1\times10^{-7}$ with (table 1).

The aim of this study was to examine whether PT OA might have a lower genetic contribution than non-traumatic (NT) idiopathic large joint OA. We investigated the combined role of the published OA-risk genetic variants in two case control studies from the UK focusing on severe OA leading to total knee replacement (TKR) and total hip replacement (THR).

PATIENTS AND METHODS

Study cohorts

THR and TKR cases were recruited from two case-control studies in Nottingham, UK: the Nottingham OA Case-Control and the Genetics of Osteoarthritis and Lifestyle (GOAL) study. Controls were obtained from both these studies.

PT OA definition

PT THR was defined as THR in the presence of hip injury and PT TKR as TKR in the presence of knee injury as described in the online supplementary methods section.

Laboratory methods

Genomic DNA was extracted from peripheral blood leukocytes of affected individuals and controls using standard protocols. Genotyping was carried out by Kbioscience Ltd, Hertfordshire, UK. Single nucleotide polymorphisms (SNPs) were genotyped using the Kompetitive Allele Specific PCR (KASPar) chemistry.

Statistical analysis

Genetic score

The sum of risk alleles (which can take values 0, 1 or 2 for each variant) as defined in table 1 over all variants was computed for each study participant. Individuals with more than 1 missing genotype for all 12 variants were excluded, otherwise the genotype was imputed using the allele frequency in the population.

Logistic regressions using TKR or THR as outcomes and including age, gender, (BMI) and knee genetic risk score (for TKR) or hip genetic risk score (for THR) were performed. Analyses were

Table 1 Genetic variants used to generate the genetic risk score

Gene	SNP	DNA change	Reference	Trait associated	p Value in Caucasians	RAF controls (%)	Risk allele	Hip gene	Knee gene
GDF5	rs143383	T/C	Valdes *et al*[11]	Knee OA	8×10^{-9}	61.9	T	–	+
*COG5**	rs4730250	A/G	Evangelou *et al*[12]	Knee OA	9×10^{-9}	19.3	G	–	+
MCFL2	rs11842874	A/G	Day-Williams *et al*[13]	Hip or knee OA	9.2×10^{-9}	91.5	A	+	+
*PTHLH**	rs10492367	A/C	arcOGEN[14]	Hip OA	1.5×10^{-8}	21.0	A	+	–
SUPT3H	rs10948172	G/A	arcOGEN[14]	Hip or knee OA in men	7.9×10^{-8}	28.6	G	+	+
TP63	rs12107036	A/G	arcOGEN[14]	TKR in women	6.7×10^{-8}	53.6	G	–	+
*FILIP1**	rs9350591	C/T	arcOGEN[14]	THR	$2{\cdot}42\times10^{-9}$	10.9	T	+	–
*GLN3**	rs11177	A/G	arcOGEN[14]	Hip or knee OA	7.24×10^{-11}	39.0	A	+	+
DOT1L	rs12982744	C/G	Castaño-Betancourt *et al*[15]	Minimum joint space width†	1.1×10^{-11}	60.2	G	+	–
ASTN2	rs4836732	C/T	arcOGEN[14]	THR	6.1×10^{-10}	49.7	C	+	–
FTO	rs8044769	C/T	arcOGEN[14]	TKR in women	6.8×10^{-8}	51.3	C	+	+
CHST11	rs835487	A/G	arcOGEN[14]	THR	1.6×10^{-8}	34.0	G	+	–

*For conciseness only one of the genes in the region is shown. rs4730250 maps to a cluster of genes that comprises *COG5, HBP1, GPR22,PRKAR2B, DUS4L* and *BCAP29*. rs10492367 maps between *PTLHL* and *KLHDC5*. rs9350591 maps between *FILIP1* and *SENP6*. rs11177 maps to an amino-acid change within GLN3 but is in strong linkage disequilibrium (LD) with variants in the *GLT8D1* gene.
†Association with hip OA reported is $p<1.1\times10^{-4}$.
OA, osteoarthritis; RAF, risk allele frequency; SNP, single nucleotide polymorphism; THR, total hip replacement; TKR, total knee replacement.

carried out including all TKR (or THR) cases, only PT cases (PT-TKR or PT-THR) and only NT cases (NT-TKR or NT-THR). Results are reported as OR and corresponding 95% CI for the GOAL and Nottingham cohorts separately. ORs were also meta-analysed for both cohorts using a fixed effects analysis. Analyses were performed using R V.2.13.1 (http://www.r-project.org/).

RESULTS

The list of variants investigated in this study is shown in table 1 along with the best-reported p value in the literature. The role of injury as a risk factor was assessed in the GOAL study where history of trauma was recorded for cases and controls. After adjustment for age, sex and BMI the risk estimates found were OR=3.27, (95 % CI 2.51 to 4.25; p<1.1×10(−18)) for TKR and OR=5.08 (95 % CI 3.05 to 8.47; p<4.2×10(−10)) for THR. The combined genetic and descriptive statistics risks in each cohort are shown in table 2. These factors were analysed in each cohort to assess their role in defining risk of THR and TKR following trauma or in the absence of injury.

The mean of each of these risk factors stratified by injury status shows, as expected, a significantly younger age and a higher proportion of men in the post-trauma category (see online supplementary table S1).

The knee genetic risk score for TKR and the hip genetic risk score for THR are both significantly related to risk of total joint replacement (table 3). The average OR contributed by each additional variant carried is similar to those reported in the studies that identified these genetic variants (1.11 for hip OA risk variants and 1.09 for knee OA risk). Age and sex contribute differently to risk of PT-TKR and NT-TKR (see online supplementary table S1). We did not observe a significant difference in the risk conferred by knee genetic risk factors, but the OR is slightly higher for PT-TKR cases (OR=1.12) than for non-traumatic cases (OR=1.08). For THR only the gender composition is significantly different between NT and PT cases (see online supplementary table S1). The genetic risk conferred does not achieve statistical significance among PT-THR cases and is lower (OR=1.07) than among NT-THR cases (OR=1.11) where it is highly significant. Results were also computed excluding individuals with missing genotypes (see online supplementary table S2) and are very similar to those using imputed genotypes for missing data.

DISCUSSION

In this study we report for the first time the role of genetic factors in PT clinically severe OA requiring total joint replacement and compare it to the role that these same genetic factors play among 'primary' cases. Our hypothesis was that primary cases would carry a larger number of genetic risk variants than PT OA cases. However, the OR estimates for hip and knee risk scores are not significantly different between PT and NT subjects. Among TKR cases PT cases appear to carry a non-significantly larger proportion of risk variants. Among THR cases a lower contribution of genetic risk factors was seen in PT cases that did not achieve statistical significance.

Table 2 Descriptive statistics in the two study cohorts

Factor	Controls	TKR	THR
Nottingham case control, n:	711	1305	629
Female, %	57.0%	55.2%	57.9%
Age (SD)	66.29 (8.97)	69.75 (9.21)	70.39 (8.75)
BMI (SD)	26.57 (3.93)	30.15 (5.61)	28.83 (4.88)
Knee gene score (SD)	6.88 (1.62)	7.17 (1.68)	6.90 (1.74)
Hip gene score (SD)	6.14 (1.62)	6.10 (1.57)	6.41 (1.69)
Hip injury, %	NA	5.2%	10.8%
Knee injury, %	NA	33.6%	17.0%
GOAL study, n:	879	863	938
Female, %	48.2%	47.4%	52.6%
Age (SD)	62.90 (8.50)	69.05 (6.82)	67.83 (6.96)
BMI (SD)	27.23 (4.44)	31.37 (5.31)	29.31 (5.25)
Knee gene score (SD)	6.73 (1.67)	6.98 (1.70)	6.94 (1.73)
Hip gene score (SD)	5.93 (1.62)	6.10 (1.62)	6.24 (1.64)
Hip injury, %	1.8%	3.4%	7.4%
Knee injury, %	15.7%	32.7%	16.5%

BMI, body mass index; GOAL, Genetics of Osteoarthritis and Lifestyle; NA, not applicable; THR, total hip replacement; TKR, total knee replacement.

Table 3 Age, sex, BMI and genetic risk scores as risk factors for post-traumatic (PT) and non-traumatic (NT) total joint replacement in two study cohorts

Risk factor	Study cohort	All	p Value	PT	p Value	NT	p Value
TKR:							
Age	GOAL	1.13 (1.12 to 1.15)		1.10 (1.08 to 1.12)		1.16 (1.13 to 1.18)	
	Nottingham	1.07 (1.06 to 1.08)		1.04 (1.02 to 1.05)		1.09 (1.07 to 1.1)	
	Summary	1.09 (1.08 to 1.1)	4.88E-73	1.06 (1.05 to 1.07)	5.17E-20	1.11 (1.10 to 1.12)	7.05E-75
Sex	GOAL	0.99 (0.78 to 1.24)		0.61 (0.45 to 0.84)		1.41 (1.08 to 1.83)	
	Nottingham	0.76 (0.62 to 0.93)		0.49 (0.37 to 0.63)		1.00 (0.79 to 1.25)	
	Summary	0.85 (0.73 to 0.99)	0.039	0.53 (0.44 to 0.65)	1.39E-09	1.16 (0.97 to 1.37)	0.098
BMI	GOAL	1.24 (1.21 to 1.27)		1.20 (1.16 to 1.25)		1.26 (1.22 to 1.29)	
	Nottingham	1.21 (1.18 to 1.24)		1.20 (1.16 to 1.23)		1.22 (1.19 to 1.25)	
	Summary	1.22 (1.2 to 1.24)	9.8E-106	1.20 (1.17 to 1.23)	4.2E-55	1.24 (1.21 to 1.26)	1.35E-93
Knee OA	GOAL	1.08 (1.01 to 1.16)		1.14 (1.06 to 1.23)		1.07 (1.01 to 1.14)	
Risk	Nottingham	1.09 (1.03 to 1.16)		1.10 (1.02 to 1.2)		1.10 (1.03 to 1.17)	
Genes	Summary	1.09 (1.04 to 1.14)	0.00025	1.12 (1.07 to 1.19)*	1.82E-05	1.08 (1.03 to 1.13)*	0.00063
THR:							
Age	GOAL	1.1 (1.08 to 1.11)		1.06 (1.03 to 1.09)		1.10 (1.08 to 1.11)	
	Nottingham	1.07 (1.05 to 1.08)		1.08 (1.05 to 1.11)		1.06 (1.05 to 1.08)	
	Summary	1.08 (1.07 to 1.09)	3.87E-57	1.07 (1.05 to 1.09)	1.11E-09	1.08 (1.07 to 1.09)	1.02E-54
Sex	GOAL	1.38 (1.13 to 1.69)		1.04 (0.62 to 1.75)		1.45 (1.18 to 1.78)	
	Nottingham	1.03 (0.82 to 1.3)		1.33 (0.78 to 2.26)		0.99 (0.78 to 1.26)	
	Summary	1.22 (1.05 to 1.42)	0.011	1.17 (0.81 to 1.7)	0.40	1.23 (1.05 to 1.44)	0.0092
BMI	GOAL	1.11 (1.09 to 1.14)		1.13 (1.08 to 1.19)		1.11 (1.09 to 1.14)	
	Nottingham	1.15 (1.12 to 1.18)		1.15 (1.08 to 1.22)		1.15 (1.12 to 1.19)	
	Summary	1.13 (1.11 to 1.15)	2.78E-42	1.14 (1.1 to 1.18)	5.71E-11	1.13 (1.11 to 1.15)	4.83E-40
Hip OA	GOAL	1.13 (1.06 to 1.21)		1.06 (0.91 to 1.23)		1.14 (1.07 to 1.21)	
Risk	Nottingham	1.08 (1.01 to 1.16)		1.08 (0.92 to 1.27)		1.08 (1 to 1.16)	
Genes	Summary	1.11 (1.06 to 1.16)	1.2E-05	1.07 (0.96 to 1.19)*	0.24	1.11 (1.06 to 1.17)*	1.55E-05

*The difference between the PT and NT ORs did not reach statistical significance (p>0.05) for TKR and THR.
BMI, body mass index; GOAL, Genetics of Osteoarthritis and Lifestyle; OA, osteoarthritis; THR, total hip replacement; TKR, total knee replacement.

One possible explanation for the lack of differences between PT and primary cases is that the genome-wide association study (GWAS) analyses that identified these variants have not made a distinction between the two types of patients. Given that PT cases constitute a substantial proportion of all knee OA cases, any genetic risk factors identified are likely to be implicated in both types of patients. This is possible since in the case of hip OA the prevalence of hip injury is much lower and the hip genetic risk load among PT THR cases is lower than in primary cases. However the effect of knee risk variants is as strong or even stronger among PT TKR cases indicating that the genes so far identified to influence risk of knee OA play a role in the pathogenesis of severe PT knee OA. However, the OR for hip genes in the PT group is not significantly different from 1 and with the current sample size and the effect size observed the study is not powered to determine if PT THR has a modest genetic component.

Recent research supports the view that acute joint damage that occurs at the time of an injury initiates a sequence of events that can lead to progressive articular surface damage. Determination of the risk factors affecting joint tissues and their respective roles in disease progression is critical to advances in the treatment of PT OA.[4] Our data indicate that among the risk factors to take into account in PT knee OA are genetic influences.

There are some limitations to this study. Prior injuries were self-reported rather than based on medical records, and may be open to recall bias. Also some of the cases classified as PT OA may actually be 'primary' cases due to the type of injury experienced. Nevertheless, using the current definitions we found strong significant differences in age and gender between PT OA and NT cases, as reported in other studies.[3 4] Moreover, the questionnaire applied identified a very high risk due to injury for TKR (OR=3.27) and THR (OR=5.08) in the case control design. Such risks are much higher than all genetic factors combined. Thus, in spite of the caveats, the population classified as PT based on questionnaire data appears enriched for true PT OA cases. Another limitation is that the results apply to UK populations and may not generalise to other ethnic groups, but the genetic variants used are only those reported in Caucasians as having a role in risk of OA.

In conclusion, PT hip OA cases appear to have a lower genetic risk load than NT cases, whereas PT knee OA cases have at least as high a genetic contribution as NT cases. These data support the perspective of OA as common complex condition and further challenge a clear separation between 'primary' and 'secondary' forms of OA.

Contributors All authors contributed to the study design, data interpretation and the final manuscript. In addition, AMV analysed and interpreted the data and prepared manuscript. SAD and MD evaluated study subjects. AMV and MD supervised the study.

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Competing interests RAM is an employee of Astrazeneca plc.

Ethics approval the research ethics committees of Nottingham City Hospital and North Nottinghamshire.

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Supplementary Section

Study Cohorts

Nottingham OA and GOAL case-control studies. Hip and knee OA cases were recruited from hospital orthopaedic surgery lists (current and for the previous 5 years) in the Nottingham area. Some of the participants for this study were originally recruited as part of a sibling cohort study [16-17]. All participants gave written informed consent to take part. Approval for recruitment of knee and hip OA cases was obtained from the research ethics committees of Nottingham City Hospital and North Nottinghamshire. All cases had been referred to hospital with symptomatic, clinically severe hip or knee OA and the majority had undergone unilateral or bilateral THR or TKR within the previous 5 years. Pre-operative knee or pelvis radiographs of knee or hip OA cases were examined to confirm the diagnosis and to grade for changes of OA [16-18]. All pelvis and knee radiographs were scored for individual radiographic features of OA by a single observer and graded 0-3 according to a standard atlas using the Kellgren and Lawrence (K/L) grade for each knee of each hip joint [19]. Self-reported ethnicity was assessed by a nurse administered questionnaire and only individuals of European descent were included in the genetic study.

Subjects aged 45-85 who had undergone intravenous urography (IVU) in the same hospital were recruited as unrelated controls and underwent clinical examination and joint radiographs. Only individuals with no symptoms, and no clinical or radiographic evidence of large joint OA were included as controls. In addition unaffected siblings of joint replacement probands for some of the cases, free from radiographic OA and aged over 45 were considered as controls. A maximum of one unaffected sib per family was included among the controls. The allele frequencies between unaffected sibs and unrelated controls were compared and no differences were detected.

For the GOAL study, patients with clinically severe knee or hip OA were recruited in identical fashion from joint replacement lists to that described above for the Nottingham case-control study. Subjects aged 45-85 who had undergone IVU in the same hospital, and who had no hip or knee symptoms, were recruited as unrelated controls and underwent clinical examination and pelvis and knee radiographs. Only controls that had no clinical or radiographic signs of hip or knee OA were included in the present study.

History of knee and hip injury. The Nottingham study patients answered a detailed medical history questionnaire applied by a research nurse. Among the questions asked were: “have you ever had any injury to your hip which was severe enough for you to visit a doctor?” (yes/no, which side and at which age did this happen?); and “have you ever had any injury to your knee which was severe enough for you to visit a doctor?” (yes/no, which side and at which age did this happen?). Individuals who answered yes to the first question were classified as having suffered a hip injury and those who answered yes to the second question

were classified as having suffered a knee injury. For the GOAL study history of significant hip or knee injury was defined as: any self reported lower limb fracture; any significant injury/trauma due to occupation, sports or any leisure activity sufficient to require medical attention; any injury requiring immobilization or use of crutches for ≥2 weeks and in this study the questionnaire was also applied to controls.

Genotyping QC

The overall call rate was 98.2%. In control samples not affected with OA these polymorphisms were in Hardy-Weinberg equilibrium ($p>0.05$). 52 samples were genotyped in duplicate for each SNP (average concordance rate was 99.4%).

Supplementary Table 1. Differences in age, sex, BMI and genetic risk factors between post traumatic and non-traumatic study subjects. For controls either hip or knee injury has been considered.

	PT controls	n=149	NT controls	n=729	p-value
F %	33.56%		51.17%		**2.14E-06**
age (SD)	60.79	8.72	63.33	8.39	**1.24E-05**
BMI (SD)	27.67	4.61	27.14	4.40	n.s.
knee gene score (SD)	6.63	1.60	6.75	1.68	n.s.
hip gene score (SD)	5.77	1.56	5.97	1.63	n.s.

	PT TKR	n=720	NT TKR	n=1448	
F %	38.89%		58.63%		**1.74E-21**
age (SD)	67.90	8.34	70.25	8.24	**2.91E-06**
BMI (SD)	30.30	5.28	30.80	5.64	n.s.
knee gene score (SD)	7.14	1.65	7.08	1.71	n.s.
hip gene score (SD)	6.12	1.62	6.08	1.58	n.s.

	PT THR	n=223	NT THR	n=1344	
F %	44.8%		56.3%		**0.00142**
age (SD)	68.53	8.60	68.91	7.70	n.s.
BMI (SD)	29.17	4.98	29.11	5.13	n.s.
knee gene score (SD)	6.42	1.61	6.92	1.75	n.s.
hip gene score (SD)	6.97	1.67	6.29	1.66	n.s.

Supplementary Table 2. Association between genetic scores as risk factors for post-traumatic and no-traumatic total joint replacement meta-analysed in two study cohorts, excluding individuals with missing genotypes. All results are adjusted for age , sex and BMI. The total number of controls was 1540.

outcome	risk factor	O.R (95% CI)	p-value	num cases
TKR	knee OA risk genes	1.08 (1.03, 1.13)	0.0011	1870
PT TKR		1.11 (1.05, 1.19)	0.0006	631
NT TKR		1.07 (1.02, 1.13)	0.0082	1239
THR	hip OA risk genes	1.11 (1.05, 1.16)	2.76E-05	1519
PT THR		1.06 (0.95, 1.19)	0.31	129
NT THR		1.11 (1.06, 1.16)	3.11E-05	1390

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