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

References – supplementary section:

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