

## Supplementary Section

### Study cohorts:

Genetics of Osteoarthritis and Lifestyle (GOAL) study. Cases with clinically severe knee OA were recruited from hospital orthopaedic surgery TKR lists in the Nottingham area as previously described [1]. Approval for recruitment was obtained from the research ethics committees of Nottingham City Hospital and North Nottinghamshire. Anteroposterior weight bearing and skyline knee radiographs were examined to confirm the diagnosis and to grade for changes of OA and scored for individual radiographic features of OA by a single observer and graded 0-4 according to a standard atlas using the Kellgren and Lawrence (K/L) grade for each knee joint for both the tibiofemoral and patellofemoral compartments [2]. Only individuals of European descent were included in the genetic study.

The Nottingham case-control study: Individuals affected by knee OA were recruited in Nottingham both from families with a history of OA and from clinic populations [3,4]. Approval for recruitment of index knee OA cases was obtained from the research ethics committees of Nottingham City Hospital and North Nottinghamshire. All had been referred to the hospital with symptomatic, clinically severe knee OA and the majority had undergone unilateral or bilateral TKR within the previous 5 years. Pre-operative knee radiographs were examined to confirm the diagnosis. Grading of X-rays of the tibiofemoral and patellofemoral compartment of the index knee was undertaken by the same observer as in GOAL and was available for all subjects included. Controls were age-matched individuals from the same catchment area free from radiographic OA as for controls in the GOAL cohort. Further details on this cohort can be found in [5].

*Hertfordshire Cohort Study* (HCS) is a large population-based study. Details of the study design have been published previously [6]. Ethical approval was obtained from East and North Hertfordshire ethical committees. Men and women were recruited and attended a clinic for further investigation; a subgroup underwent knee X-rays. Both anteroposterior weight bearing and sky line X-rays were taken for both knees and a K/L grade was assigned for each compartment using an atlas [2].

### Genotyping QC

The overall call rate was 97.3%. In control samples not affected with OA from the same three study cohorts these polymorphisms were in Hardy-Weinberg equilibrium ( $p > 0.05$ ) as follows

cohort	rs143383	rs4730250	rs11842874
HCS	0.472	0.2712	0.997
GOAL	0.883	0.6828	0.6201
Nottingham	0.298	0.1501	0.7661

52 samples were genotyped in duplicate for each SNP ( average concordance rate was 99.4%).

### References:

- 1- Zhang W, Robertson J, Doherty S, Liu JJ, Maciewicz RA, Muir KR, Doherty M. Index to ring finger length ratio and the risk of osteoarthritis. *Arthritis Rheum.* 2008;58(1):137-44.
- 2- Altman RD, Hochberg MC, Murphy WA, Wolfe F. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage* 1995;3(suppl A):3-70
- 3- Neame RL, Muir K, Doherty S, Doherty M Genetic risk of knee osteoarthritis: a sibling study. *Ann Rheum Dis.* 2004;63(9):1022-7.

- 4- Valdes AM, Spector TD, Tamm A, Kisand K, Doherty SA, Dennison EM, et al. Genetic variation in the SMAD3 gene is associated with hip and knee osteoarthritis. *Arthritis Rheum.* 2010;62(8):2347-52.
- 5- Aihie Sayer A, Syddall H, Dennison E M, Gilbody H J, Duggleby S L, Cooper C. *et al* Birth weight, weight at 1 year and body composition in older men: findings from the Hertfordshire Cohort Study. *Am J Clin Nutr* 2004. 80:199–203.
- 6- Zhang W, Robertson J, Doherty S, Liu JJ, Maciewicz RA, Muir KR, Doherty M. Index to ring finger length ratio and the risk of osteoarthritis. *Arthritis Rheum.* 2008;58(1):137-44.