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Is The Risk Of Revision After Arthroplasty Surgery Associated With Specific Gene Loci? A Genome-Wide Association Study Of Single Nucleotide Polymorphisms In 1,130 Arthroplasty-Treated Twins.

Orthopaedics / Pelvis, Hip & Femur / Joint Replacement - Secondary

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Background
The etiology of revision surgery following total joint replacement (TJR) is complex. A possible genetic component has been investigated in a few candidate-driven genetic studies, indicating that certain single nucleotide polymorphisms (SNPs) are associated with an increased risk of revision surgery following TJR. Yet, candidate-driven approaches are limited in that they only investigate a small part of the genome.

Objectives
We aimed to identify genetic determinants of an increased risk of revision surgery within the setting of a genome wide association study (GWAS).

Study Design & Methods
Genetic information on all 1,130 twins in the Swedish Twin Registry's TwinGene dataset treated with TJR in the hip or knee regardless concordance was extracted. Of these, 94 underwent any type of revision surgery – our primary outcome – during follow-up, and 75 of those 94 twins underwent revision due to aseptic loosening, our secondary outcome. Genetic information was collected using the Illumina OmniExpress and the Illumina Psych arrays. The Haplotype Reference Consortium served as the reference for gene imputation. Since some members within our cohort were siblings, Cox regression models with a robust sandwich estimator and adjusted for age, sex and principal components were fitted to calculate hazard ratios (HRs) with 95% confidence intervals (CI) at a significance level of $p<5e-8$.

Results
For the primary outcome, revision surgery for any reason, 6 SNPs reached statistical significance, with the leading four signals located on chromosome 3 in the gene region coding for the sodium-dependent taurine and beta-alanine transporter (SLC6A6). The leading SNP, rs62233562, was associated with an HR of undergoing revision surgery of 3.1

(95%CI 2.2-4.4, p=1.74e-10), and similar HR were attained for the subsequent SNPs 3:14506680 (p=1.8e-10), rs2289129 (p=1.8e-10), and rs17309567 (p=3.16*e-10) in the same gene region. The fifth SNP was located on chromosome 1 in the calmodulin-binding transcription activator 1 (CAMTA1) gene (rs11120968, HR 2.3; 95%CI 1.7-3.1, p=1.45e-8) and the sixth SNP, rs13081679, in an intron region on chromosome 3 (HR 2.9; 95%CI 2.0-4.1, p=2.63e-08). For the secondary outcome, revision surgery due to aseptic loosening, 3 SNP reached statistical significance: The previously identified rs17309567 remained statistically significant with a HR of 3.35 (95%CI: 2.31-4.86, p=1.69e-10), followed by 2 SNPs on chromosome 9 within the region coding for the ABO-system: rs7853989 (HR: 3.46; 95%CI 2.33-5.13, p=6.91e-10), and 9:136126631 (HR: 2.82; 95%CI 1.95-4.07, p=3.35e-08). Of the 30 SNP with the lowest p-values associated with the risk of revision due to aseptic loosening, 27 were located within the region coding for the ABO-system.

Conclusions

We identified several SNPs that seem to confer an increased risk of revision surgery performed for any reason or due to aseptic loosening. The previously established relationship of the SLC6A6 gene with trunk fat mass can guide future studies designed to elucidate pathogenic mechanisms. Given the known association of SNPs in the ABO-gene with variations in the inflammatory response, our finding that SNPs within gene regions encoding for the ABO-system are associated with an increased risk of revision surgery due to aseptic loosening merits further investigation, but they also warrant independent replication.