Genome-Wide Association Study of End-Stage Glenohumeral Osteoarthritis

Elizabeth L. Yanik,[1] Vy Pham,[1] Paul Jeffries,[1] Jay D. Keener,[1], Nancy L. Saccone[1]
[1]Washington University School of Medicine, St. Louis, MO
Email: yanike@wustl.edu

Disclosures: Elizabeth L. Yanik (N), Vy Pham (N), Paul Jeffries (N), Jay D. Keener (1- Stryker, Shoulder Innovations; 3b-Stryker; 4-Genesis, 8-J Shoulder Elbow Surg), Nancy L. Saccone (N)

INTRODUCTION: Many genetic variants are known to influence joint formation and cartilage degeneration in hip and knee osteoarthritis (OA), but little is known about the genetics of glenohumeral OA. Established OA variants at other joints may also influence glenohumeral OA development, but there could also be unique variants that influence glenohumeral OA (e.g., variants influencing glenohumeral joint shape). We used the UK Biobank cohort to conduct a comprehensive investigation of the genetics of OA-related shoulder arthroplasty, as a measure of end-stage glenohumeral OA.

METHODS: Among 478,725 genotyped UK Biobank participants, those with OA-related shoulder arthroplasty were identified based on diagnosis and procedure codes in linked hospital data. OA-related shoulder arthroplasty cases were compared to participants without shoulder arthroplasty as controls in a genome-wide association study to identify novel variants. Associations were estimated based on logistic regression models adjusted for age, sex, and the first ten principal components, with genome-wide significance determined based on a P-value$<5\times10^{-8}$. A targeted examination was conducted of associations for 17 candidate variants selected a priori based on associations with OA at other upper and lower extremity joints[1] with significance based on a Bonferroni-corrected p-value of <0.003 (=0.05/17). Finally, an assessment of the genetic correlation of OA-related shoulder arthroplasty with OA at other joints was conducted using cross-trait linkage disequilibrium score regression.

RESULTS: There were 792 OA-related shoulder arthroplasty cases identified, including 544 women and 248 men, and 477,933 controls, including 258,010 women and 219,923 men. A genome-wide significant signal was identified in *C8orf34* on chromosome 8, with rs7000878 as the lead variant (odds ratio=1.51, 95%CI=1.35-1.69, P-value$<2.16\times10^{-12}$, Figure 1). Among the candidate variants, three variants in the *TGFA* gene were significantly associated with OA-related shoulder arthroplasty after Bonferroni correction, rs3821269, rs1851610, and rs3755380 (all P-values<0.003). These *TGFA* variants were associated with 1.17-1.19 times higher odds of OA-related shoulder arthroplasty. In cross-trait linkage disequilibrium score regression, OA-related shoulder arthroplasty had the strongest correlation with hand OA (correlation coefficient=0.63, P-value=0.08), followed by knee OA (coefficient=0.60, P-value=0.06), and hip OA (coefficient=0.47, P-value=0.02), though only the correlations with knee and hip OA met statistical significance.

DISCUSSION: A novel association was identified in the *C8orf34* gene, which encodes a protein that plays a role in transcription regulation and cell cycle regulation. We additionally showed for the first time that OA-related variants in the *TGFA* gene are associated with OA-related shoulder arthroplasty risk. *TGFA* is a known effector gene for OA that influences joint degeneration and skeletal development. The associations identified with OA-related shoulder arthroplasty were stronger than those that have been previously documented for hand, knee, and hip OA (hand, knee, hip odds ratios range: 1.04-1.07).[1] Finally, the genetic associations of OA-related shoulder arthroplasty were moderately correlated with the genetics of hand, hip, and knee OA, indicting that there are likely numerous shared genetic mechanisms, as well as some distinct genetic mechanisms for glenohumeral OA and shoulder arthroplasty.

SIGNIFICANCE/CLINICAL RELEVANCE: For glenohumeral OA, knowledge of the key genetic markers can inform biological insights and enable identification of high-risk patients for whom preventive behavioral changes could be most impactful. Identification of these patients could also facilitate faster diagnosis after symptom onset.

REFERENCES: 1. Hatzikotoulas, et al. Translational genomics of osteoarthritis in 1,962,069 individuals. *Nature*. 2025.

ACKNOWLEDGEMENTS: This research has been conducted using the UK Biobank Resource (http://www.ukbiobank.ac.uk/) under Application 27034. This work was supported by NIH grant R01AR083937.

Figure 1. Manhattan plot of genome-wide association study results for OA-related shoulder arthroplasty in 478,725 UK Biobank participants.