Identification of Rare Candidate Genetic Variants Associated with Rotator Cuff Tearing

Robert Zaray Tashjian[1], Michael Jurynec, Craig C Teerlink, Lisa Cannon-Albright, Kristina Lisa Allen-Brady
[1]University of Utah

INTRODUCTION:

Rotator cuff tearing has been shown to have a genetic predisposition. Multiple common genetic variants have been identified to be associated with rotator cuff tearing. Rare, highly penetrant variants associated with a large risk have not been previously identified. Analysis of related affected cousins who belong to high-risk pedigrees is a powerful approach for identification of strong candidate rare variants for predisposition to rotator cuff tearing.

METHODS:

We analyzed genetic sequence data for 9 affected cousin pairs (first or second cousins) (25 total patients) where all cousins had undergone arthroscopic surgery for repair of a full thickness rotator cuff tear and who are members of pedigrees exhibiting a significant excess of individuals undergoing full thickness rotator cuff tear surgery. **(Figures 1 and 2)** Validation of association of the candidate variants identified with risk for rotator cuff injury defined by ICD9/10 diagnostic codes was accomplished utilizing case and control genetic data from the UK Biobank.

RESULTS:

A total of 121 rare (minor allele frequency <0.005) genetic variants were identified as shared in at least one cousin pair affected with rotator cuff tearing (mean age at diagnosis 68 years). Of the rare variants identified, one variant was identified in an Amyloid Precursor Protein-Binding Protein (*APBB1*), three separate rare coding variants were identified in the gene for Tenascin W (*TNN*) as well as three separate genes in the mitogen activated protein kinase (MAPK) pathway (*MAP3K4*, *MAP3K1*, *MAP3K9*). Of the 121 rare candidate variants, 65 were observed in UK Biobank data. Analysis of these variants in 3,899 cases with rotator cuff injury and 11,697 matched controls (mean case age 59.9 years) identified one significant association in the *APBB1* gene (OR=2.38, p=0.007, uncorrected). The three candidate variants in *TNN* gene had OR of 1.89, 1.78, and 1.70 and p=0.05, 0.08, and 0.09 (uncorrected), respectively. Variants in the MAPK pathway (*MAP3K4*, *MAP3K1*, *MAP3K9*) were identified as candidates, although UK Biobank data was not available for them (likely due to low frequency).

DISCUSSION AND CONCLUSION:

This unique analysis of closely related individuals with confirmed rotator cuff tears from high-risk pedigrees has identified a strong set of 121 rare candidate genetic predisposition variants which should be pursued in independent studies. Although no variants were found to be significantly associated with rotator cuff tearing risk after Bonferroni correction, their presence in affected cousins in high-risk pedigrees makes them all strong candidate predisposition variants. Among these rare variants, variants in Amyloid Precursor Protein-Binding Protein, Tenascin W, as well as several MAPK pathway genes were identified. *APBB1* is an adaptor protein in the nucleus and variants have been identified as being associated with nicotine dependence. Rotator cuff tearing is strongly linked to nicotine usage. Tenascin W is an extracellular matrix molecule critical for cell adhesion and motility and response to injury. A common genetic variant in Tenascin C has already been identified as being associated with rotator cuff tearing and failure of healing after repair. We have now identified another member of the Tenascin family as being associated with rotator cuff tearing. The MAPK genes are enzymes critical to the MAPK pathway which is responsive to environmental stress including wounds and inflammation therefore dysregulation of these genes may impair local wound healing leading to chronic injury including rotator cuff tearing. Alteration of the MAPK pathway has already been shown to regulate fatty degeneration of the rotator cuff musculature in the setting of rotator cuff tearing, therefore rare variants in these genes further supports a role for the MAPK pathway in rotator cuff injury. Further clinical and animal testing and extension of the high-risk pedigrees identified is required to confirm the role of these genes in rotator cuff tearing.