Factors Associated with Genetic Markers for Rotator Cuff Disease in Patients with Atraumatic Rotator Cuff Tears

Elizabeth L Yanik[1], Nancy Saccone, Alexander W Aleem[2], Aaron Mark Chamberlain, Benjamin Zmistowski[3], Julianne A Sefko[4], Jay D Keener[4]
[1]Orthopaedic Surgery, Washington University In St. Louis, [2]Washington University in St. Louis, [3]Washington University School of Medicine, [4]Washington University

INTRODUCTION: For degenerative rotator cuff tears, evidence continues to accumulate that genetics contributes to the risk of symptomatic tear development and may play a role in the ability of the rotator cuff to heal after surgical repair. To better understand the potential for genetic markers to serve as useful independent predictors of rotator cuff repair outcomes, we must understand the degree with which they correspond with patient characteristics. However, few studies have examined how genetic markers correspond with the characteristics of patients presenting with rotator cuff tears, such as the age at diagnosis and prevalence of bilateral tears.

METHODS: We prospectively enrolled patients with atraumatic rotator cuff tears presenting to five providers at a single institution. After providing informed consent, a saliva sample was collected from each enrolled patient for genotyping. Electronic medical records were reviewed to capture clinical characteristics. We examined eight single nucleotide polymorphisms (SNPs) that were directly measured in our genotyping array and have been associated with rotator cuff tears in the prior literature. For each SNP, we estimated associations of SNP dosage with 1) age at atraumatic rotator cuff tear diagnosis and 2) the presence of bilateral, atraumatic tears at the time of sample collection. We hypothesized that genetic markers for rotator cuff disease would be associated with a younger age at diagnosis and higher prevalence of bilateral tears. Linear regression was used to estimate associations with diagnosis age adjusted for sex and principal components to account for confounding by ancestry. Logistic regression was used to estimate associations with bilateral tear prevalence adjusting for age, sex, and principal components.

RESULTS: Of 355 patients enrolled in the study, 336 provided saliva specimens with sufficient DNA to produce high quality genotype data. Among this 336, the median age at rotator cuff tear diagnosis was 61 (interquartile range=54-66) and 74 (22%) had bilateral atraumatic tears (Table 1). The majority of patients were non-Hispanic White (91%), and likely of European ancestry. SNP rs11850957 in the STXBP6 gene was associated with a younger age at diagnosis. This association remained after limiting to non-Hispanic White patients and adjusting for principal components to account for potential confounding by ancestry (-2.65 years, 95%CI=-4.43, -0.87, P-value=0.0035, Table 2), and was statistically significant even after accounting for multiple comparisons (P-value<0.00625). No other significant associations with age at atraumatic cuff tear diagnosis were identified. No SNPs were associated with prevalent bilateral atraumatic cuff tears.

DISCUSSION AND CONCLUSION: Our study has shown that obtaining specimens for genetic testing is practical in the orthopaedic clinic setting. Most SNPs examined were not associated with either age at atraumatic rotator cuff tear diagnosis or prevalence of bilateral tears. The exception to this was a SNP in the STXBP6 gene, which was associated with age at diagnosis. The STXBP6 protein may play a role in immune response by altering phagocytosis and antigen presentation of monocytes and macrophages. Further research is needed to understand associations between genetic markers and healing after rotator cuff repair.

Table 1. Characteristics of atraumatic rotator cuff tear patients with high quality genotype data included in analyses.

Patient Characteristics	N(%)/Median(IQR)
Total	336
Age at Tear Diagnosis	61 (54, 66)
Sex	
Female	158 (47.0%)
Male	178 (53.0%)
Race	
White	306 (91.1%)
Black	28 (8.3%)
American Indian/Alaskan Native	1 (0.3%)
Asian	1 (0.3%)
Ethnicity	
Hispanic	1 (0.3%)
Non-Hispanic	344 (99.4%)
Unknown	1 (0.3%)
Bilateral Tears	
Yes, atraumatic	74 (22.0%)
Yes, traumatic	34 (10.1%)
No	228 (67.9%)

Table 2. Associations of a priori selected SNPs with age at atraumatic rotator cuff tear diagnosis and prevalent bilateral atraumatic tears.

SNP	Chromosome	Gene	Association with Age at Diagnosis*		Association with Bilateral Atraumatic Tears†	
			Mean Difference (95%CI)	P-value	Odds Ratio (95%CI)	P-value
rs3045	5	ANKH	-1.21 (-3.67, 1.25)	0.3358	0.65 (0.36, 1.15)	0.1378
rs1011814	5	FGF10	0.55 (-0.95, 2.05)	0.4706	0.90 (0.62, 1.29)	0.5584
rs12527089	6	SASH1	2.79 (-0.33, 5.91)	0.0801	0.79 (0.35, 1.79)	0.5698
rs4722846	7	CREB5	-0.91 (-2.48, 0.66)	0.2564	0.91 (0.62, 1.34)	0.6289
rs4903399	14	LOC105370575	-1.31 (-3.04, 0.42)	0.1376	0.99 (0.64, 1.51)	0.9484
rs2761884	14	BMP4	-0.78 (-2.31, 0.76)	0.3218	0.89 (0.61, 1.30)	0.5518
rs11850957	14	STXBP6	**-2.65 (-4.43, -0.87)**	**0.0035**	0.82 (0.52, 1.29)	0.3883
rs1800469	19	TGFB1	0.44 (-1.16, 2.05)	0.5879	1.02 (0.69, 1.50)	0.9244

*Estimates based on linear regression adjusted for sex and first four principal components
†Estimates based on logistic regression adjusted for sex, age, and first four principal components