J Shoulder Elbow Surg (2016) 25, 865–872

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Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

SHOULDER

Identification of a genetic variant associated with rotator cuff repair healing

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Background: A familial and genetic predisposition for the development of rotator cuff tearing has been identified. The purpose of this study was to determine if a familial predisposition exists for healing after rotator cuff repair and if the reported significant association with a single-nucleotide polymorphism (SNP) in the *ESRRB* gene is present in patients who fail to heal.

Materials and methods: The study recruited 72 patients undergoing arthroscopic rotator cuff repair for a full-thickness posterosuperior tear. Magnetic resonance imaging studies were performed at a minimum of 1 year postoperatively (average, 2.6 years). Healing failures were classified as lateral or medial. Self-reported family history of rotator cuff tearing data and genome-wide genotypes were available. Characteristics of cases with and without a family history of rotator cuff tearing were compared, and a comparison of the frequency of SNP 1758384 (in *ESRRB*) was performed between patients who healed and those who failed to heal.

Results: Of the rotator cuff repairs, 42% failed to heal; 42% of patients reported a family history of rotator cuff tear. Multivariate regression analysis showed a significant association between familiality and overall healing failure (medial and lateral failures) ($P = .036$) and lateral failures independently ($P = .006$). An increased risk for the presence of a rare allele for SNP rs17583842 was present in lateral failures compared with those that healed ($P = .005$).

Conclusions: Individuals with a family history of rotator cuff tearing were more likely to have repair failures. Significant association of a SNP variant in the *ESRRB* gene was also observed with lateral failure.

Level of evidence: Level I; Prospective Cohort Design; Prognosis Study

Keywords: Rotator cuff tear; genetic association; tendon healing; familiality; ESRRB; rotator cuff repair

Failure of healing after rotator cuff repair has been reported to occur from <10% to >90% of the time.[3,6,8,17] Identifying factors that are associated with healing after rotator cuff repair may allow surgeons to modify treatments to improve healing or to better counsel patients about outcomes based on risk factors. Various patient-related (nonmodifiable) and surgeon-related (modifiable) factors have

Institutional Review Board approval was obtained from the University of Utah School of Medicine before initiation of this study: No. 29048.

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1058-2746/$ - see front matter © 2016 Journal of Shoulder and Elbow Surgery Board of Trustees.
http://dx.doi.org/10.1016/j.jse.2016.02.019

been identified that influence rotator cuff tendon healing; these include age, tear size, muscle fatty infiltration and atrophy, muscle-tendon unit retraction, smoking, osteoporosis, diabetes, repair construct, rehabilitation, and biologics.[3-5,10,15,19,23,25,28,29,33] No prior studies have evaluated a familial or genetic predisposition for healing after rotator cuff repair.

Strong evidence exists supporting a genetic predisposition for the development of rotator cuff disease.[27,30] A significantly elevated risk has been shown to exist for family members of patients with rotator cuff disease to also have rotator cuff disease compared with population controls.[28] The relationship exists for close and distant (beyond third-degree) relatives, supporting both environmental and genetic influences. Several genetic variants have been identified as being associated with the risk for development of a rotator cuff tear, including variants in the estrogen-related receptor beta (*ESRRB*) gene.[24,32] ESRRB is a nuclear receptor that has been postulated to have roles in promoting cell survival in hypoxic environments.[1] Dysregulation of the function of ESRRB may promote cell death in a variety of tissues, including musculoskeletal tissue. It is unclear whether the same familial and genetic risk factors for the development of rotator cuff tearing are also risk factors for failure of healing after repair.

The purpose of this study was to evaluate evidence for association of healing after rotator cuff tear repair with family history of rotator cuff tearing and specifically to test the hypothesis of association of the *ESRRB* gene and healing after rotator cuff repair. We hypothesized that the familial and genetic factors recognized to increase the risk for rotator cuff tearing also predispose patients to failure to heal after repair. We also evaluated other risk factors associated with repair healing, including age, tear size, muscle quality, tendon retraction, and tear construct, to determine if a positive family history of rotator cuff tearing is an independent predictor of healing after surgery.

Methods

The primary surgeon (R.Z.T.) performed 72 complete arthroscopic rotator cuff repairs of the posterosuperior rotator cuff at the University of Utah. Patients previously recruited into our ongoing genetic study of patients with full-thickness rotator cuff tears who underwent an arthroscopic complete rotator cuff repair and were at least 1 year postoperative from the surgical repair were selected for this study. Genome-wide genotype data were available for all patients recruited into the genetic study. DNA was obtained by a blood draw. Exclusion criteria included revision repairs, partial repairs, repairs involving margin convergence, and any patient with <1-year follow-up after surgical repair.

Preoperative magnetic resonance imaging (MRI) studies were evaluated for coronal tear size, sagittal tear size, and supraspinatus fatty infiltration. Coronal tear size was measured on T2-weighted coronal sections, with retraction measured as the distance from the lateral edge of the greater tuberosity to the tendon end. Sagittal tear size was determined by measuring the anteroposterior length of the exposed rotator cuff footprint of the most lateral section of the greater tuberosity on the sagittal T2-weighted images. Tears were classified by size into small (<1 cm), medium (1-3 cm), large (3-5 cm), and massive (>5 cm) on the basis of sagittal tear size. Supraspinatus fatty infiltration was measured using the Fuchs classification as a modification of the Goutallier classification for computed tomography scans.[7,9] Grading was on the most lateral sagittal T1-weighted image on which the scapular spine was in contact with the scapular body. The stages were identified as follows: stage 0, normal; stage 1, some fatty streaks; stage 2, fatty infiltration throughout with less fat than muscle; stage 3, fatty infiltration with equal muscle and fat; and stage 4, fatty infiltration with more fat than muscle.

Surgical procedure

Intra-articular examination and a complete subacromial bursectomy were performed in all cases. Tissue on the undersurface of the acromion extending all the way posterior to the scapular spine was released. Arthroscopic single-row repairs using triple-loaded suture anchors and simple stitches as well as double-row repairs using a suture bridge construct (Arthrex, Naples, FL, USA) were performed. Construct was determined by preference of the surgeon. Typically, small tears (<1 cm) had a single-row repair performed with triple-loaded anchors. Easily mobilized tears >1 cm that could completely cover the footprint without significant tension had either a single-row repair with triple-loaded anchors or a double-row transosseous-equivalent repair based on the discretion of the surgeon. Large, retracted tears that could not completely cover the footprint without significant tension after mobilization had a single-row repair with triple-loaded anchors at a more medialized location on the footprint.

Single-row rotator cuff repairs were performed using several metal, 5.5-mm corkscrew suture anchors (Arthrex) loaded with 3 No. 2 FiberWire sutures (Arthrex). Suture anchors were placed at the most lateral aspect of the greater tuberosity to which the tear would mobilize. With larger retracted tears, anchors were placed more medial on the footprint. The number of suture anchors used depended primarily on the tear size, with separation of anchors by approximately 1 to 1.5 cm. Sutures were passed as simple stitches in an anterograde fashion, taking approximately a 1.5-cm bite of tissue with each stitch. All stitches were tied with 2 half-hitches on the same post, followed by another half-hitch in the alternate direction on the same post, followed by 3 half-hitches in alternating directions and alternating posts. If a double-row transosseous-equivalent repair was performed, several medial metal 5.5-mm corkscrew suture anchors (Arthrex) were placed at the anatomic neck separated by about 1.5 cm. Each anchor was double loaded, and 2 horizontal mattress stitches were placed