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Genetic and familial predisposition to rotator cuff disease: a systematic review

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Background: Rotator cuff disease is a common disorder leading to shoulder pain and loss of function. Its etiology in atraumatic cases is uncertain and is likely to extend beyond repetitive microtrauma or overuse. Our objective was to determine whether there is a genetic or familial predisposition to rotator cuff disease.
Methods: A literature search of PubMed and Embase databases identified 251 citations. After review of the titles, abstracts, and full articles, 7 met our inclusion and exclusion criteria.
Results: Four studies assessed familial predisposition to rotator cuff disease. One of these demonstrated that siblings of an individual with a rotator cuff tear were more likely to develop a full-thickness tear and more likely to be symptomatic. A 5-year follow-up showed that the relative risks were increased for the siblings to have a full-thickness tear, for a tear to progress in size, and for being symptomatic. Another study demonstrated that a significantly higher number of individuals with tears had family members with a history of tears or surgery than those without tears did. The other 3 studies investigated whether a genetic predisposition to rotator cuff disease exists and found significant association of haplotypes in *DEFB1*, *FGFR1*, *FGF3*, *ESRRB*, and *FGF10* and 2 single-nucleotide polymorphisms within *SAP30BP* and *SASH1*.
Conclusion: Prior studies provide preliminary evidence for genetic and familial predisposition to rotator cuff disease. However, there is a lack of large genome-wide studies that can provide more definitive information and guide early detection of individuals at risk, prophylactic rehabilitation, and potential gene therapies and regenerative medicine interventions.
Level of evidence: Systematic Review

Keywords: Rotator cuff disease; rotator cuff tears; tendinopathy; genetic predisposition; familial predisposition; epidemiology

Tendon disorders account for >30% of all musculoskeletal office visits.[1] Rotator cuff disease is a common disorder and affects 30% to 50% of the population older than 50 years.[17] It includes a spectrum of pathologic changes ranging from tendinopathy to partial or complete tears.[19] Rotator cuff disease is associated with shoulder pain and loss of function.[28] There

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were an estimated 272,148 ambulatory surgeries performed for rotator cuff tears in the United States in 2006.[9]

The cause of atraumatic rotator cuff tears has been studied by only a limited number of investigators and remains unknown. The pathophysiologic mechanism of rotator cuff tearing is described as intrinsic defects of tendons, including increased tendon cell death, higher proportion of fat composition, aberrant microstructure of structural fibers, and abnormal nutrient vessels.[4,14] This suggests that atraumatic rotator cuff tears are not purely due to repetitive microtrauma or overuse. It is possible that the biologic changes are regulated by genes. Identifying genes associated with rotator cuff disease and rotator cuff tears can help early recognition of individuals at higher risk of development of this pathologic process. This could warrant application of primary or secondary prevention strategies for this specific population.

The purpose of this study was to perform a systematic review on the genetic and familial predisposition to rotator cuff disease.

Materials and methods

The term *rotator cuff disease* is used loosely in the literature. This term can encompass disorders ranging from impingement to tendinopathy to rotator cuff tearing. The transition from rotator cuff tendinopathy to rotator cuff tear was described as a continuum by Neer.[19] Hence, in our study, we used the umbrella term *rotator cuff disease* and included studies on impingement syndrome and rotator cuff tendinopathy or tear.

A systematic literature search on familial or genetic predisposition to rotator cuff disease of PubMed and Embase databases was performed from their years of inception through March 2016. The database search was performed with the help of a trained librarian, and the keywords used included "rotator cuff disease," "genetics," "polymorphism," and "family." The full search criteria can be found in Appendix S1. Initially, 251 citations were identified, and 2 of the authors (C.G. and N.B.J.) independently reviewed the titles and abstracts for relevance. The full texts of 17 of the citations were then reviewed, and 10 studies were found not to be relevant to our topic. Bibliographies of full-text articles that met our inclusion criteria were also reviewed for additional articles. No additional articles were gained from the bibliography search.

The studies included in this review were assessed with the Methodological Index for Non-Randomized Studies (MINORS) and were scored accordingly.[25] The maximum possible score was 24. When required, authors of included articles were contacted for additional information. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology for reporting our manuscript.[13]

Results

The initial literature search produced 251 articles that were assessed for relevance by their title and abstract. Of these, 234 were excluded because of lack of relevance to our topic. After the remaining 17 full texts were reviewed, 7 studies were found to meet the inclusion criteria and were thus included in our final analysis (Fig. 1).

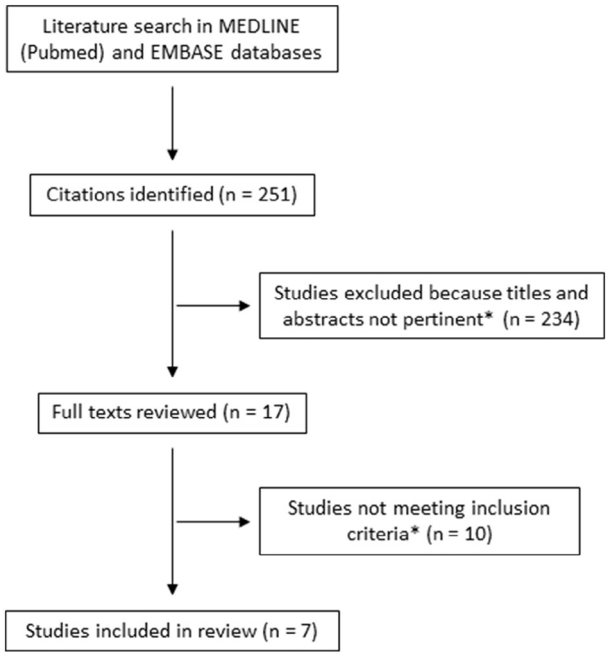

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the literature search and study selection. *Inclusion criteria: studies on familial predisposition or genetic epidemiology of rotator cuff disease.

Four studies investigated whether there is a familial predisposition to rotator cuff disease. One of these studies (n = 129) demonstrated that siblings of an individual with a rotator cuff tear were twice as likely to develop a full-thickness tear and nearly 5 times more likely to suffer symptoms compared with spouses of these individuals (Table I).[7] A 5-year follow-up (n = 62) showed that the relative risk for the siblings to have a full-thickness tear was 2.85 (95% confidence interval [CI], 1.75-4.64) compared with the control population, the relative risk for a tear to progress in size was 2.08 (95% CI, 1.58-2.7), and the relative risk of having a symptomatic tear was 1.44 (95% CI, 2.04-8.28) (Table I).[6] The 2009 study of Tashjian et al (n = 3091) used the Genealogical Index of Familiality to demonstrate a significant excess relatedness when all generations were used but not when looking only at more distant relationships (Table I).[29] When only individuals diagnosed before the age of 40 years (n = 652) were studied, significant excess relatedness was found when both all generations and only more distant relationships were used (Table I). Close relationships were defined as those between first- and second-degree relatives, whereas distant relationships were those with a genetic path length of at least 3. Excess relatedness was used interchangeably with excess familial clustering or heritable predisposition. The 2014 study of Tashjian et al (n = 92) demonstrated that a significantly higher number of individuals with rotator cuff tears (32.3%) also had family members with a history of rotator cuff tears or surgery compared with individuals without rotator cuff tears (18.3%) (Table I).[31]