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Genetic and Familial Predisposition to Rotator Cuff Disease: A Systematic Review

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Abstract

Background—Rotator cuff disease is a common disorder leading to shoulder pain and loss of function. Its etiology in atraumatic cases is uncertain and likely extends beyond repetitive micro-trauma 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 reviewing the titles, abstracts, and full articles, seven met our inclusion/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 five-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. The other three studies investigated whether a genetic predisposition to rotator cuff disease exists and found significant association of haplotypes in *DEFB1, FGFR1, FGFR3, ESRRB*, and *FGF10*, and two 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

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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 over 30% of all musculoskeletal office visits[1]. Rotator cuff disease is a common disorder and affects 30–50% of the population older than 50 years of age[17]. It includes a spectrum of pathology ranging from tendinopathy to partial or complete tears[19]. Rotator cuff disease is associated with shoulder pain and loss of function[28]. There 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 only been studied by a limited number of investigators and remains unknown. The pathophysiology of rotator cuff tearing is described as intrinsic defects of tendons, including increased tendon cell death, a 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 micro-trauma or overuse. It is possible that the biological 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 developing this pathology. 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/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 the appendix (Appendix A). Initially, 251 citations were identified, and two 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 which were assessed for relevance by their title and abstract. Of these, 234 were excluded due to lack of relevance to our topic. After the remaining 17 full texts were reviewed, seven studies were found to meet the inclusion criteria and were thus included in our final analysis (Figure 1).

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 five times more likely to suffer symptoms, when compared to spouses of these individuals (Table I)[7]. A five-year follow-up (n = 62) showed that the relative risk for the siblings to have a full-thickness tear was 2.85 (95% CI 1.75–4.64) compared to 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]. Tashjian et al's 2009 study (n = 3,091) used the Genealogical Index of Familiality to demonstrate a significant excess relatedness when all generations were used but not when only looking at more distant relationships (Table I)[29]. When only individuals diagnosed before age 40 (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, while distant relationships were those with a genetic path length of at least three. Excess relatedness was used interchangeably with excess familial clustering or heritable predisposition. Tashjian et al's 2014 study (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 when compared to individuals without rotator cuff tears (18.3%) (Table I)[31].

Three studies investigated the genes associated with rotator cuff disease by using association analyses to map genes to rotator cuff disease. One of these studies (n = 203) found a significant association of certain haplotypes in *DEFB1*, *FGFR1*, *FGFR3*, and *ESRRB* with rotator cuff disease (Table II)[17]. After adjusting for ethnic group and sex, another association was found for *FGF10* (Table II). A second study (n = 175) discovered two haplotypes in *ESRRB* that significantly increased the risk of tears (Table II)[32]. The third study (n = 311) found two single nucleotide polymorphisms (SNPs) within genes *SAP30BP* and *SASH1* associated with rotator cuff tears (Table II)[30]. The specific SNPs and haplotypes associated with rotator cuff disease from these three prior studies are presented in Table III. The accompanying forest plots are in Figures 2 and 3.

The results of bias assessment according to the MINORS criteria are in Table IV[25]. All of the studies had a clearly stated aim, prospective collection of data, end points appropriate to

the aim of the study, loss to follow-up <5%, and contemporary groups. Six studies included consecutive patients[6, 7, 17, 29, 30, 32], two stated they had unbiased assessments of study end points[6, 7], one had a prospective calculation of the study size[17], three had adequate control groups[6, 7, 29], five had baseline equivalence of groups[6, 7, 17, 29, 31], and five had adequate statistical analyses[7, 17, 29, 30, 32]. The lowest score was 16[31], and the highest was 22[7].

Discussion

Rotator cuff disease is a common tendon disorder that is associated with shoulder pain and functional disability. The pathogenesis of rotator cuff disease is not completely understood. Identifying a possible genetic association could help our understanding of the disease process that leads to rotator cuff pathology. This systematic review summarized studies on familial and genetic predisposition to rotator cuff disease. Although there were only a limited number of studies on this topic, they do in general constitute a consensus that rotator cuff disease is a heritable trait.

Rotator cuff disease is a generic term that can be used to describe impingement syndrome, subacromial/subdeltoid bursal pathology, rotator cuff tendinopathy, and rotator cuff tear. An issue with prior literature is the absence of a uniform definition and diagnostic criteria for rotator cuff disease. Even in studies limited to rotator cuff tears, the case definition is variable. One study used clinical diagnosis[29] by a physician as their criterion, whereas other studies used ultrasound[6, 7] and MRI[17, 30–32] for diagnosis. One of the studies used a criterion of whether the patient underwent a surgical rotator cuff repair[29]. Rotator cuff pathology is a clinical syndrome since structural defects found on imaging have been demonstrated in asymptomatic individuals.[16, 24] Hence the case definition of rotator cuff pathology needs to account for both clinical presentation and structural deficit.

Harvie et al compared the rates of symptomatic and asymptomatic tears in siblings and spouses of individuals with rotator cuff tears, and determined that both were higher in siblings[7]. A follow-up study demonstrated that rotator cuff tears in siblings also had a higher risk of progressing[6]. Another study reported differing results when analyzing all of their subjects versus analyzing only those diagnosed before the age of 40[29]. The entire cohort did not demonstrate excess relatedness when only distant relationships were studied, implying that perhaps environmental factors were playing a confounding role. In contrast, the subgroup of younger patients showed excess relatedness in both close and distant relationships.

The genetic association studies observed associations between rotator cuff disease and SNPs in seven candidate genes (Table III, Figure 2, Figure 3)[17, 30, 32]. *DEFB1* (Defensin, Beta 1) encodes the protein antimicrobial peptide defensin β-1, which aids in preventing epithelial surfaces from being colonized by microbes. The rs1800972 C>G variant was significantly more frequent in individuals with rotator cuff disease[17]. This base change is thought to lead to a decreased production of defensin β-1 production and higher expression levels.[20, 21] The G allele is also more common in individuals with severe acute pancreatitis and less predominant in individuals with diabetes and *S. aureus* nasal colonization[8, 20, 21].

ESRRB (estrogen-related receptor beta) encodes a protein similar to the estrogen receptor and is believed to have an inhibitory effect on estrogen signaling[27]. Mutations in this gene have also been associated with hearing impairment and dental decay[35]. In addition, upregulation of *ESRRB* has been linked with the progression of endometriosis[3]. In vitro studies have demonstrated a correlation between estrogen deficiency and poor tendon healing[34], implying a possible role *ESRRB* may have in rotator cuff disease.

FGF3 (fibroblast growth factor 3) and *FGF10* (fibroblast growth factor 10) encode fibroblast growth factor proteins and are involved in a number of processes such as cell growth and tissue repair, including tendons, and could thus be associated with the pathogenesis of rotator cuff disease. Mutations in *FGF3* have been linked with improper embryonic development of the inner ear[33]. Mutations in *FGF10* can lead to aplasia of lacrimal and salivary glands[5]. *FGFR1* encodes one of the receptors also associated with fibroblast growth factor; however, this gene is more specific to limb development. Mutations have been associated with cleft lip and cleft palate, Pfeiffer syndrome, and osteoglophonic dysplasia[18, 22, 36].

SAP30BP is implicated in cell death. *SASH1* is a tumor suppressor gene implicated in a number of cancers[23, 37]. Thus, many of the SNPs associated with rotator cuff disease have a potential biologic mechanism for their association with rotator cuff disease, but further research is needed in this area.

A few studies on familial and genetic predisposition to rotator cuff disease have used controls from the general population, and have used cases and controls genotyped on different platforms in different experiments[30–32]. This is problematic since these studies assume that the prevalence of rotator cuff disease in the general population is low. This can also cause bias if the cases and the controls vary in other characteristics related to risk of rotator cuff disease, or if there are systematic differences in genotyping error between platforms. However, asymptomatic rotator cuff tears are demonstrated in 40% of persons over the age of 50 years, 54% in those over 60 years, and 65% in persons over 70[16, 24]. Many of these patients will progress to a symptomatic rotator cuff tear in the future[15]. Hence, true controls are individuals from the general population that are asymptomatic and do not have structural evidence for a rotator cuff tear.

The findings of previous studies provide evidence that there may be an important relationship between genes and rotator cuff disease. However, data on this issue is still limited. To our knowledge, only one study performed a genome wide association analysis (GWAS), which found two SNPs within genes *SAP30BP* and *SASH1* associated with rotator cuff tears[30]. Both gene products, SAM and SH3 domain-containing protein 1 (SASH1) and SAP30-binding protein (SAP30BP), were reported in the process of cell apoptosis[30]. The effort to identify susceptibility genes of common multifactorial traits could lead to some insight into the pathogenesis mechanism that would, in turn, facilitate the development of better therapeutic and prophylactic approaches. However, many significant GWAS signals associated with multifactorial traits, e.g. type 2 diabetes, were mapped outside the coding gene sequence, which imposes a barrier to understanding their identities and function as well as limits their usefulness in experimental studies[2, 10]. It is equally important to assess the

reproducibility of reported genotype-phenotype association, as more of them failed to replicate. This was attributed to several issues, including inappropriate reliance on standard significant thresholds, small samples, and genotype and phenotype heterogeneity[11, 12]. At the advent of GWAS, it appeared a promising proposal to estimate disease-risk by capturing the profile of common genetic variants. Nevertheless, the majority of common variants identified by GWAS only possess a very moderate effect size, and even the sum of these genetic effects only accounts for a minor portion of estimated trait heritability[26]. To address this issue, the effort has been made to identify the variants with lower frequency but higher penetrance by using imputed variants as well as to explore gene-gene and gene-environment interactions[26]. Further such studies would be beneficial, with the awareness that GWAS studies are designed to find common SNPs associated with complex traits and thus may not reveal conclusive information. Even if multiple SNPs are identified, they may still not fully explain the relationship between genes and rotator cuff disease. GWAS studies that identify SNPs would also need to be replicable and use a consistent definition of the clinical phenotype of rotator cuff tears.

Conclusions

There is data suggesting a genetic predisposition to rotator cuff disease. A large GWAS study with adequate controls could discover SNPs associated with symptomatic rotator cuff tears. The results from such a study could assist with early detection of individuals at risk of developing non-traumatic tears or suggest mechanisms of idiopathic rotator cuff disease. This may lead to medical treatments or prophylactic rehabilitation therapies to avoid development of symptomatic rotator cuff tears.

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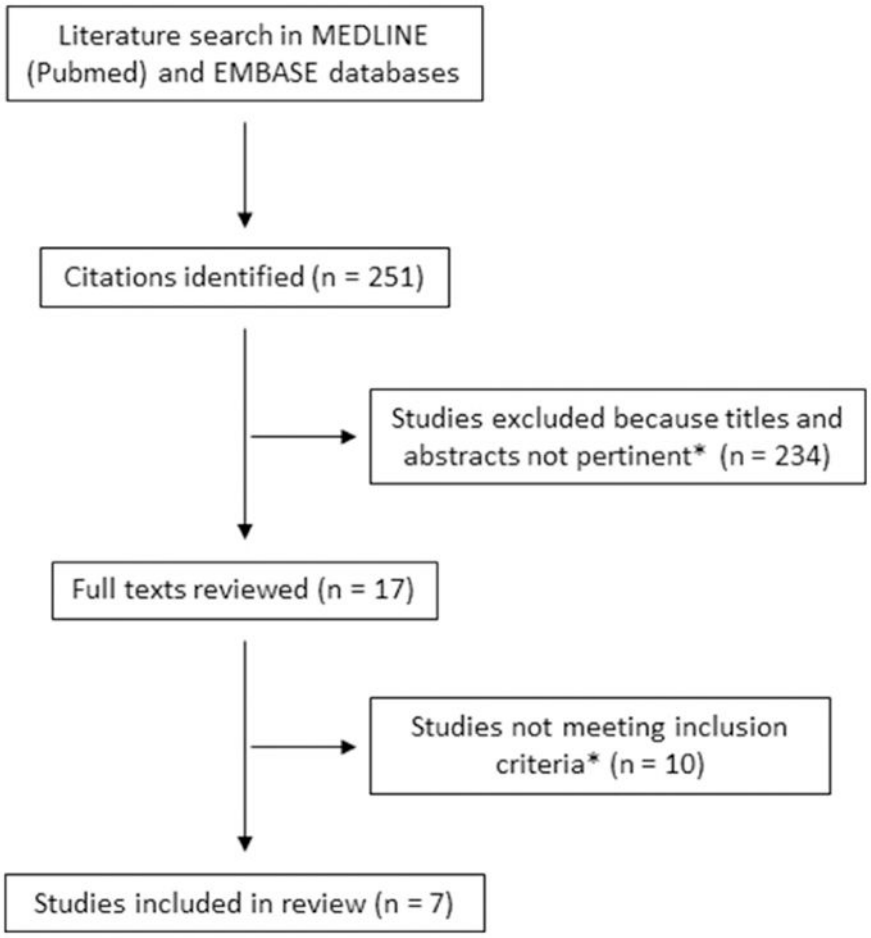

Figure 1.

PRISMA diagram of the literature search and study selection

*Inclusion criteria: studies on familial predisposition or genetic epidemiology of rotator cuff disease

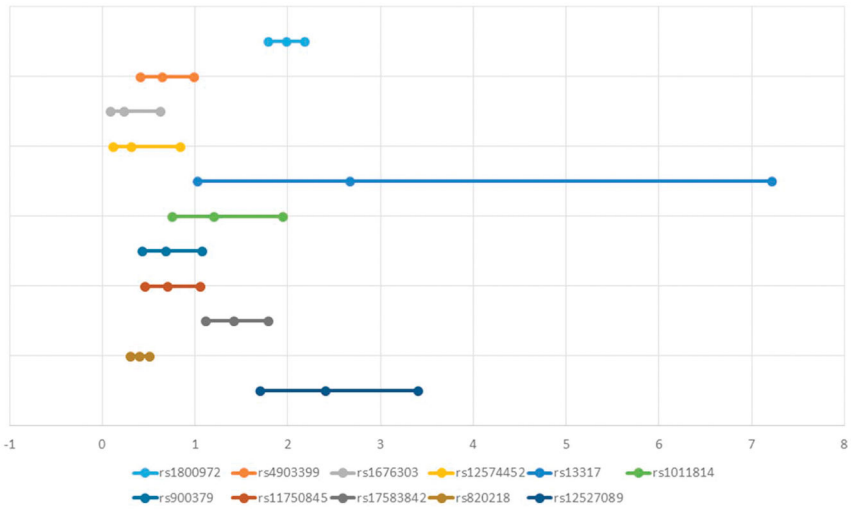

Figure 2.
Forest plot depicting the odds ratios and confidence intervals of specific SNPs

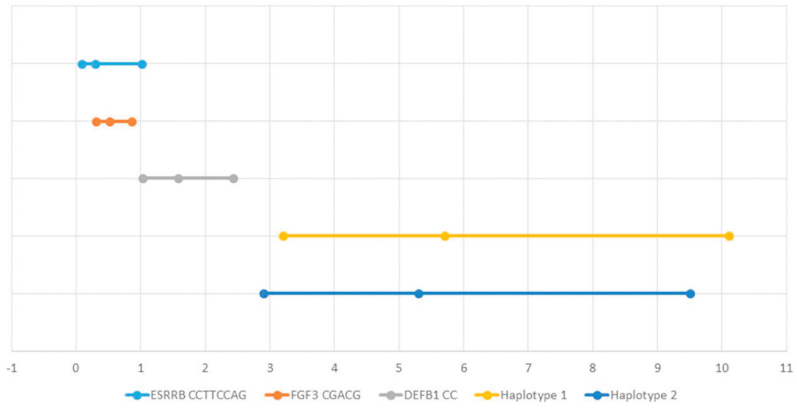

Figure 3.
Forest plot depicting the odds ratios and confidence intervals of specific haplotypes

Table I

Studies on familial predisposition to rotator cuff disease

Study	Methods	Participants	Group Definitions	Results	Source of Funding	Notes
Harvie et al.[6] (2004)	Case-control	Cases: n = 129; mean age 63.1 (41 to 85) Controls: n = 150; mean age 62.4 (43 to 85)	Case: Included siblings of individuals diagnosed with a rotator cuff tear by ultrasound. Excluded those who were not available for review, were not full first-degree relatives of individuals with rotator cuff tears, or had concomitant systemic disease affecting the function of the shoulder. Control: Included spouses of individuals diagnosed with a rotator cuff tear by ultrasound.	Relative to Controls, Cases participants had more than twice the risk of developing full-thickness tears ($p < 0.0001$), and nearly five times the risk of suffering symptoms ($p < 0.0001$). No significant differences were found in other measures between Cases and Controls.	Girdlestone Memorial Scholarship in Orthopaedic Surgery from The Lord Nuffield Orthopaedic Centre Trust	
Gwilym et al.[5] (2009)	Case-control	Cases: n = 62; mean age 66.6 (46 to 88) Controls: n = 68; mean age 66.1 (52 to 82)	Case: Included siblings of individuals diagnosed with a rotator cuff tear by ultrasound. Excluded individuals who had shoulder surgery or had a systemic disease affecting shoulder function. Control: Included spouses of individuals diagnosed with a rotator cuff tear by ultrasound. Excluded individuals who had shoulder surgery or had a systemic disease affecting shoulder function.	69.2% of Cases had full-thickness tears compared to 22.1% of Controls ($p = 0.0001$). The relative risk estimate for Cases to have a full-thickness tear was 2.85 (95% CI 1.75–4.64, $p = 0.0001$). The relative risk progression in Cases compared to Controls was 2.08 (95% CI 1.58–2.7) ($p = 0.007$). The relative risk of pain associated with a full-thickness tear in Cases compared to Controls was 1.44 (95% CI 2.04–8.28)	None stated.	5-year follow-up to Harvie et al.[6] (2004) with a loss of follow up of about half the original cohort
Tashjian et al.[24] (2009)	Population-based case-control	Cases: n = 3,091 Case Subgroup: n = 652 Controls: n = 15,455	Case: Included individuals who went to the University of Utah Hospital and Clinics, had an ICD-9 diagnosis code or CPT-4 procedure code, and had at least three generations of genealogical data. Case Subgroup: Included individuals in Case group who were diagnosed before age 40. Control: Included individuals who were in the Utah Population Database and had genealogical data.	The overall Genealogical Index of Familiality shows a significant excess relatedness for Cases ($p < 0.001$), but the distance tests shows that excess relatedness observed is not significant when close relationships are ignored ($p = 0.848$). First degree relatives of Cases had $p < 0.0001$, relative risk of 2.44, and 95% CI 2.06–2.89. Second degree relatives had $p = 0.0177$, relative risk of 1.24, and 95% CI 1.04–1.48. Third degree relatives had $p = 0.2866$, relative risk of 1.08, and 95% CI 0.94–1.24. For Case Subgroup participants, both the overall ($p = 0.001$) and distance Genealogical Index of Familiality ($p = 0.004$) tests show significant excess relatedness. First degree relatives of Case Subgroup participants had $p = 0.2614$, relative risk of 1.73, and 95% CI 0.69–4.37. Second degree relatives had $p = 0.0076$, relative risk of 3.66, and 95% CI 1.47–9.11. Third degree relatives had $p = 0.0479$, relative risk of 1.81, and 95% CI 1.05–3.11.	National Institutes of Health-National Library of Medicine University of Utah Huntsman Cancer Institute	

Study	Methods	Participants	Group Definitions	Results	Source of Funding	Notes
Tashjian et al.[26] (2014)	Case-control	Cases: n = 92; mean age 58.24 +/− 7.4 Controls: n = 92; mean age 58.42 +/− 8.5	Case: Included individuals who had magnetic resonance imaging (MRI)-confirmed, symptomatic, full-thickness rotator cuff tears. Control: Included individuals who were over age 18 and had no shoulder pain or prior shoulder injury or surgery.	32.3% of Cases reported having family members with a history of rotator cuff tears or surgery, compared with 18.3% of Controls (p = 0.035). 22.8% of Cases reported having family members with tendon problems or surgery, compared with 17.5% of Controls (p = 0.407). 38.7% of Cases reported having a history of other tendon problems, compared with 19.3% of Controls (p = 0.005). 18.3% of Cases reported having other prior tendon surgeries, compared with 13.6% of Controls (p = 0.605).	None stated.	Control matching between group participants was based on age to within five years

Table II

Studies on genetic predisposition to rotator cuff disease

Study	Methods	Participants	Group Definitions	Results	Source of Funding	Notes
Motta et al.[13] (2014)	Case-control	Cases: n = 203; mean age 51.8 +/− 5.1 Controls: n = 207; mean age 53.5 +/− 5	Case: Included individuals diagnosed with rotator cuff disease by clinical examination, radiography, and MRI. Excluded individuals who were older than 60 or younger than 45; or had a history of trauma, bursitis, rheumatoid arthritis, autoimmune diseases, pregnancy, chronic systemic corticoid use, or hyperlaxity. Control: Included individuals who had no history of shoulder pain, a negative specific test result for impingement syndrome, and absence of tendinopathy in other joints.	Whites ($p = 0.002$) and women ($p = 0.001$) had a higher prevalence of rotator cuff disease. Based on odds ratio calculation, the risk in women (OR 2.07, 95% CI 1.30–3.30) and whites (OR 1.88, 95% CI 1.21–2.90) was two times higher than in group 2. Cases had a higher incidence of high blood pressure ($p < 0.001$). Controls had a higher prevalence of systemic diseases ($p < 0.0001$), medication use ($p = 0.01$), and calcium supplementation ($p = 0.01$). A significant association of certain haplotypes in *DEFB1*, *FGFR1*, *FGFR3*, and *ESRRB* was observed with RCD. Adjusted by ethnic group and sex revealed another association in *FGF10*	None stated.	
Teerlink et al.[27] (2015)	Case-control	Cases: n = 175 Controls: n = 2,595	Case: Included individuals who had a full-thickness supraspinatus or infraspinatus rotator cuff tear documented on MRI after age 30 and before age 80. Excluded individuals who had a partial-thickness rotator cuff tear, tendinopathy only, or significant glenohumeral arthritis; or had prior surgery on the involved shoulder.	There was a significant association between *ESRRB* genetic variants and rotator cuff disease. Two haplotypes constructed from 22 SNPs spanning *ESRRB* both significantly increased the risk of rotator cuff tearing	Veterans Administration Merit Review Grant (Number 1157449) U.S. Department of Veterans Affairs	
Tashjian et al.[25] (2016)	GWAS	Cases: n = 311 Controls: n = 2,641	Case: Included individuals who had a full-thickness supraspinatus or infraspinatus rotator cuff tear documented on MRI, and who were older than 30 and younger than 80. Excluded individuals who had a partial-thickness rotator cuff tear, tendinopathy only, or significant glenohumeral arthritis; or had prior surgery on the involved shoulder.	Two SNPs within genes *SAP30BP* (rs820218) and *SASH1* (rs12527089) were significantly associated with rotator cuff tears	Veterans Administration Merit Review Grant (No. 1157449), U.S. Department of Veterans Affairs	Teerlink et al.[27] (2015) found an associated SNP in *ESRRB*, which was further confirmed in this study

Table III

Associations between rotator cuff disease and specific SNPs

Study	Gene	SNP	Chromosome	Base Pair Position	P value	Odds Ratio (95% CI)	Haplotypes	P value	Odds Ratio (95% CI)
Motta et al.[13] (2014)	DEFB1	rs1800972	8	6735423	$3.4x10^{-40}$	1.98 (1.79–2.18)	DEFB1 CC	$3.7x10^{-2}$	1.58 (1.03–2.43)
	ESRRB	rs4903399	14	76775202	$4.9x10^{-2}$	0.64 (0.41–0.98)	ESRRB CCTTCCAG	$5.4x10^{-2}$	0.30 (0.09–1.02)
		rs1676303	14	76992164	$6.4x10^{-3}$	0.23 (0.08–0.62)			
	FGF3	rs12574452	11	69631731	$2.7x10^{-2}$	0.31 (0.11–0.84)	FGF3 CGACG	$1.3x10^{-2}$	0.52 (0.31–0.86)
	FGFR1	rs13317	8	38269514	$5.3x10^{-2}$	2.67 (1.02–7.21)			
	FGF10	rs1011814	5	44335820	$4.6x10^{-1}$	1.20 (0.75–1.94)			
		rs900379	5	44369656	$9.9x10^{-2}$	0.68 (0.43–1.07)			
		rs11750845	5	44373060	$9.6x10^{-2}$	0.70 (0.46–1.05)			
Teerlink et al.[27] (2015)	ESRRB	rs17583842	14	76050858	$4.9x10^{-3}$	1.41 (1.11–1.79)	Haplotype 1	$3.4x10^{-9}$	5.7 (3.2–10.1)
		rs7157192	14	75936713	NA	NA	Haplotype 2	$5.9x10^{-8}$	5.3 (2.9–9.5)
Tashjian et al.[25] (2016)	SAP30BP	rs820218	17	73687545	$4.3x10^{-10}$	0.4 (0.3–0.5)			
	SASH1	rs12527089	6	148787159	$8.4x10^{-7}$	2.4 (1.7–3.4)			
	ESRRB	NA	NA	NA	$1.9x10^{-2}$	NA			

SNP = Single Nucleotide Polymorphism

NA = not available

Table IV

MINORS scores

Criteria	Score						
	Harvie et al.[6] (2004)	Gwilym et al.[5] (2009)	Tashjian et al.[24] (2009)	Tashjian et al.[26] (2014)	Motta et al.[13] (2014)	Teerlink et al.[27] (2015)	Tashjian et al.[25] (2016)
A clearly stated aim	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	0	2	2	2
Prospective collection of data	2	2	2	2	2	2	2
End points appropriate to the aim of study	2	2	2	2	2	2	2
Unbiased assessment of the study end point	2	2	0	0	0	0	0
Follow-up period appropriate to the aim of study	2	2	2	2	2	2	2
Loss to follow-up <5%	2	2	2	2	2	2	2
Prospective calculation of the study size	0	0	0	0	2	0	0
Adequate control group	2	2	2	1	2	1	1
Contemporary group	2	2	2	2	2	2	2
Baseline equivalence of groups	2	2	2	2	2	1	1
Adequate statistical analysis	2	1	2	1	2	2	2
Total	**22**	**21**	**20**	**16**	**22**	**18**	**18**

MINORS = Methodological Index for Non-Randomized Studies