Genetic influences in the progression of tears of the rotator cuff

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The aim of this study was to investigate genetic influences on the development and progression of tears of the rotator cuff. From a group of siblings of patients with a tear of the rotator cuff and of controls studied five years earlier, we determined the prevalence of tears of the rotator cuff with and without associated symptoms using ultrasound and the Oxford Shoulder Score.

In the five years since the previous assessment, three of 62 (4.8%) of the sibling group and one of the 68 (1.5%) controls had undergone shoulder surgery. These subjects were excluded from the follow-up.

Full-thickness tears were found in 39 of 62 (62.9%) siblings and in 15 of 68 (22.1%) controls ($p = 0.0001$). The relative risk of full-thickness tears in siblings as opposed to controls was 2.85 (95% confidence interval (CI) 1.75 to 4.64), compared to 2.42 (95% CI 1.77 to 3.31) five years earlier. Full-thickness tears associated with pain were found in 30 of 39 (76.9%) tears in the siblings and in eight of 15 (53.3%) tears in the controls ($p = 0.045$). The relative risk of pain associated with a full-thickness tear in the siblings as opposed to the controls was 1.44 (95% CI 2.04 to 8.28) ($p = 0.045$).

In the siblings group ten of 62 (16.1%) had progressed in terms of tear size or development compared to one of 68 (1.5%) in the control group which had increased in size.

Full-thickness rotator cuff tears in siblings are significantly more likely to progress over a period of five years than in a control population. This implies that genetic factors have a role, not only in the development but also in the progression of full-thickness tears of the rotator cuff.

The lifetime risk of experiencing pain in the shoulder is 30%, with an annual risk of suffering at least one episode of up to 50%. The impingement syndrome and tears of the rotator cuff cause this pain in over three-quarters of affected patients.¹

The overall incidence of full-thickness tears in the general population is between 7% and 27%, and of partial-thickness tears between 13% and 37%.²⁻⁴ Not all of these tears are symptomatic. Theories on the cause of these tears range from purely mechanical or attritional damage⁵ to intrinsic age-related degeneration.^{6,7} Whether intrinsic or extrinsic factors contribute to the occurrence of tears, there is a common pathway of alteration of the cellular and extracellular matrix, with evidence of an apoptotic process⁸⁻¹¹ within the tendon. The underlying genetic susceptibility to pathology of the rotator cuff has been previously highlighted.¹² We hypothesise that the genetic influences that produce the increased incidence of tears of the rotator cuff in siblings

of patients with known tears compared to controls, will also influence the progression and size of the tear in the medium term.

Patients and Methods

In 2002 we recruited siblings from a register of patients undergoing operative repair of the rotator cuff at our institution between 1996 and 2002.¹² We recruited spouses of patients with tears of the rotator cuff because they are likely to have some shared environmental risks. The siblings and controls were contacted again in 2007 and asked to participate in a follow-up study. Local ethics committee permission was given for this investigation.

The number of siblings available for study five years after the original investigation was 62 of the original cohort of 129 (48.1%). The number of controls available for study was 68 of the original 150 (45.3%). The proportions of the original participants who were not available were not significantly different between the two groups ($p > 0.05$). The

Table I. Distribution of sizes of tear in all the lesions found in 62 siblings and 68 spouses

Size of tear	Siblings (%)	Controls (%)
Small (< 1 cm)	19 (35)	11 (20)
Medium (1 cm to 3 cm)	7 (13)	2 (1)
Large (3 cm to 5 cm)	5 (10)	2 (1)
Massive (> 5 cm)	8 (15)	0 (0)
Overall	39 (63)	15 (22)

numbers and reasons for loss to follow-up were failure to respond to the invitation (siblings 25, controls 24); death (siblings 10, controls 16); refusal to participate (siblings 12, controls 22); unfit to travel (siblings 8; controls 15); had since undergone surgery to the shoulder (siblings 3, controls 1); and onset of systemic disease affecting function of the shoulder (siblings 3, controls 4).

All participants independently completed the Oxford Shoulder Score^{13,14} for each shoulder. Ultrasound examination was then carried out by an experienced shoulder ultrasonographer who was unaware of the findings at the initial visit. A Sonosite Micromaxx portable scanner (Sono Site Inc., Bothell, Washington) with a 13 MHz variable frequency linear-array probe was used and results were recorded on a standard proforma. Full-thickness tears, when detected, were classified according to the criteria of Post, Silver and Singh¹⁵ using the size of largest measurement of the tear. Partial-thickness tears were excluded. For the risk calculations uni- and bilateral tears carried equal weight. All calculations are stated per participant with or without a full-thickness tear.

Painful tears were defined according to a positive response to one or more of the four pain-related questions in the 12-item Oxford Shoulder Score. The relative risk estimates were based on detection of full-thickness tears and calculated by dividing the percentage of siblings with such tears by the percentage of controls. Significance tests were performed using the chi-squared, with Yates' correction for the small sample size. A p-value < 0.05 was considered significant.

Results

The gender ratio for the siblings was 30:32 male-to-female, and for the controls was 33:35. The mean age of the siblings was 66.6 years (46 to 88) and for the controls was 66.1 years (52 to 82). The ratio of uni- to bilateral tears was 19:20 in the siblings compared to 7:8 in the controls. None of these parameters were significantly different between the groups ($p > 0.05$ for all parameters).

Prevalence of tears. Full-thickness tears were identified in 39 of 62 siblings (62.9%) and in 15 of 68 controls (22.1%). This difference was significant ($p = 0.0001$). In the siblings the number of bilateral tears was 20 and 19 were unilateral. In the controls the number of bilateral tears was eight, with

seven unilateral. Using the occurrence of either a uni- or a bilateral tear the relative risk estimate for the sibling group to have a full-thickness tear was 2.85 (95% CI 1.75 to 4.64, $p = 0.0001$). The distribution of sizes of tear in both siblings and controls is shown in Table I.

Progression of tears. Of the siblings, ten of the 62 (16.1%) had tears which had progressed. Six had increased in size and four were fresh. In the control group of 68 only one tear (1.5%) had progressed, and this had increased in size; there were no fresh tears. Comparing the presence and size of the tears to five years previously, the relative risk progression in the sibling group compared to the control group was 2.08 (95% CI 1.58 to 2.7) ($p = 0.007$).

Relationship between tears and pain. Full-thickness tears associated with pain were found in 30 of the 39 (76.9%) tears in the siblings and in eight of the 15 (53.3%) in the control group ($p = 0.045$). The relative risk of pain associated with a full-thickness tear in the siblings compared to the controls was 1.44 (95% CI 2.04 to 8.28).

In the siblings 12 of the 62 (19.4%) had pain and no tear, compared to 15 of 68 (22.1%) in the controls ($p = 0.7$). Thus, only 11 of the siblings (17.7%) had neither pain nor a tear, whereas 38 (55.9%) of the controls had neither ($p = 0.0001$). Pain-free tears were found in nine of 62 siblings (14.5%) and seven of 68 controls (10.3%) ($p = 0.09$). A summary of the relation between cuff tears and pain is shown in Table II.

Treatment in the five-year period. Since the last review of these patients three of 62 (4.8%) of the siblings had undergone shoulder surgery, two with cuff repairs and one with a subacromial decompression for impingement without a tear, whereas only one of the 68 controls (1.5%) had undergone a cuff repair ($p = 0.27$). Of the siblings, eight (12.9%) had received treatment with glucocorticoid injection, as had five of the controls (7.4%) ($p = 0.29$). Of the siblings, ten (16.1%) had received one or more treatments by physiotherapy, chiropractic, osteopathy, acupuncture or massage, all without glucocorticoid injection, as opposed to four (5.9%) of the controls ($p = 0.06$).

Discussion

The aetiology of tears of the rotator cuff is unknown and descriptions include 'normal' degenerative attrition associated with age,³ secondary to occupation,¹⁶ or consequent

Table II. Association of cuff tears with pain in the sibling and the control groups. Percentages shown relate to the total size of the cohort

	Siblings (%)	Controls (%)
Pain & cuff tear	30 (48.4)*	8 (11.8)*
Pain & no tear	12 (19.4)	15 (22.1)
No pain & cuff tear	9 (14.5)	7 (10.3)
No pain & no tear	11 (17.7)*	38 (55.9)*
Total	62	68

* chi-squared p-value < 0.001

upon the mechanical effects of acromion morphology. Recent investigations have focused on the basic science behind both the proposed aetiological factors in respect of the vascularity and morphology, and the changes in the cellular/extracellular composition of the tendon.¹⁷

We have previously highlighted the influence of genetic factors on the development of rotator cuff tears.¹² These factors may predispose the tendon to degeneration through influences on apoptosis or regenerative capacity. As such, age-related degeneration may only affect those individuals with a genetic predisposition. Age itself should not be considered the most important risk factor, as illustrated by our patients who have been shown to have significant differences in their prevalence of cuff tears when stratified by family history but matched for age, gender and environmental conditions.

We considered that progression of a rotator cuff tear, in terms of its size, will be influenced by the same genetic factors that predisposed the individual to develop a tear in the first instance. This hypothesis was upheld, with a tear in a sibling of a patient with known rotator cuff disease being significantly more likely to progress in size than one in a control subject without a first-degree family history of rotator cuff disease.

In our study we found that 16.1% of the sibling group had progressed in terms of tear size, as opposed to 1.5% of the control group. This rate of progression is lower than that reported by other authors.¹⁸

The association of pain with a tear of the rotator cuff also appears to be influenced by genetic factors. A tear in the sibling of a patient with a painful tear has a relative risk of being painful of 1.44, compared to one in a control subject. This finding adds support to the growing evidence that pain perception itself has a heritable component^{19,20} and potentially offers pathology of the shoulder as a model for research into the genetics of pain.

The potential for methodological errors in this study were highlighted in the description of our previous study.¹² We acknowledge the loss of follow-up of around half the original cohort. We consider this level of attrition to be high but acceptable, given that the trial was prospective, investigated an older cohort, and required additional clinic attendance for assessment.

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References

1. Lewis JS. Rotator cuff tendinopathy/subacromial impingement syndrome: is it time for a new method of assessment? *Br J Sports Med* 2008;Epub.
2. Lehman C, Cuomo F, Kummer FJ, Zuckerman JD. The incidence of full thickness rotator cuff tears in a large cadaveric population. *Bull Hosp Jt Dis* 1995;54:30-1.
3. Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. *J Shoulder Elbow Surg* 1999;8:296-9.
4. Moosmayer S, Smith HJ, Tang R, Larmo A. Prevalence and characteristics of asymptomatic tears of the rotator cuff: an ultrasonographic and clinical study. *J Bone Joint Surg [Br]* 2009;91-B:196-200.
5. Neer CS 2nd. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. *J Bone Joint Surg [Am]* 1972;54-A:41-50.
6. Codman EA, Akerson IB. The pathology associated with rupture of the supraspinatus tendon. *Ann Surg* 1931;93:348-59.
7. Milgrom C, Schaffler M, Gilbert S, van Holsbeck M. Rotator-cuff changes in asymptomatic adults: the effect of age, hand dominance and gender. *J Bone Joint Surg [Br]* 1995;77-B:296-8.
8. Matthews TJ, Hand GC, Rees JL, Athanasou NA, Carr AJ. Pathology of the torn rotator cuff tendon: reduction in potential for repair as tear size increases. *J Bone Joint Surg [Br]* 2006;88-B:489-95.
9. Matthews TJ, Smith SR, Peach CA, et al. In vivo measurement of tissue metabolism in tendons of the rotator cuff: implications for surgical management. *J Bone Joint Surg [Br]* 2007;89-B:633-8.
10. Hashimoto T, Nobuhara K, Hamada T. Pathologic evidence of degeneration as a primary cause of rotator cuff tear. *Clin Orthop* 2003;415:111-20.
11. Fukuda H, Hamada K, Yamanaka K. Pathology and pathogenesis of bursal-side rotator cuff tears viewed from en block histologic sections. *Clin Orthop* 1990;254:75-80.
12. Harvie P, Ostlere SJ, Teh J, et al. Genetic influences in the aetiology of tears of the rotator cuff: sibling risk of a full-thickness tear. *J Bone Joint Surg [Br]* 2004;86-B:696-700.
13. Dawson J, Fitzpatrick R, Carr A. Self-administered questionnaire for assessment of symptoms and function of the shoulder. *J Bone Joint Surg [Am]* 1998;80-A:766-7.
14. Dawson J, Legers K, Fitzpatrick R, Carr A. The Oxford shoulder score revisited. *Arch Orthop Trauma Surg* 2009;129:119-23.
15. Post M, Silver R, Singh M. Rotator cuff tear: diagnosis and treatment. *Clin Orthop* 1983;173:78-91.
16. Herberts P, Kadefors R, Hogfors C, Sigholm G. Shoulder pain and heavy manual labor. *Clin Orthop* 1984;191:166-78.
17. Rees JL. The pathogenesis and surgical treatment of tears of the rotator cuff. *J Bone Joint Surg [Br]* 2008;90-B:827-32.
18. Yamaguchi K, Tetro AM, Blam O, et al. Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. *J Shoulder Elbow Surg* 2001;10:199-203.
19. Foulkes T, Wood JN. Pain genes. *PLoS Genet*. 2008;4:e1000086.
20. Buskila D. Genetics of chronic pain states. *Best Pract Res Clin Rheumatol* 2007;21:535-47.