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Genetic contribution to the etiology of Achilles tendon rupture. A Danish nationwide register study of twins

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ABSTRACT

Background: It is unknown if genetics contribute to the etiology of acute Achilles tendon rupture (ATR). The aims of the present study were, 1) To calculate the concordance rate for monozygotic (MZ) twins and same-sex dizygotic (SSDZ) twins and 2) to estimate the heritability of ATR.
Methods: The study was performed as a registry study using the Danish Twin Registry and the Danish National Patient Registry.
Results: The study sample consisted of 85,534 twins born from 1895 to 1995. Of these, 572 (0.67%) were registered with ATR in the period from 1994 to 2014. The concordance rate was 8.1% (95% CI 1.4–14.7%) for MZ twins and 4.3% (95% CI 0.7–7.9%) for SSDZ twins. The heritability of ATR was 47% (95% CI 31–62%).
Conclusion: This study found that genetics contribute substantially to the etiology of ATR with an estimated heritability of the liability to ATR of approximately 50%. The finding generates the hypothesis that genetics play a role in the pathological changes that occur in the Achilles tendon before a rupture. The risk of ATR for a twin within a 20 year period, if the co-twin has had an ATR, was 8% for MZ twins and 4% for SSDZ twins.

1. Introduction

A typical acute Achilles tendon rupture (ATR) is characterized by a sudden pain in the Achilles tendon accompanied with an inability to push off during walking [1]. The injury is primarily seen in adults in the fourth and fifth decade of life. ATR is relatively frequent with a yearly incidence of 31–35 per 100,000 in the general population. The incidence has shown an increasing trend in the past decades, particularly in the older population [2,3]. The injury causes sick leave and the majority of the patients are suffering from permanent functional deficits [4–6]. The increasing incidence and the severity of ATR underline the importance of developing preventive measures of the injury. New prevention strategies are dependent on an understanding of the etiology, pathogenesis, and risk factors.

The etiology and pathogenesis of ATR are still largely unknown. It is well-known that pathological changes such as chronic inflammation that weaken the Achilles tendons can occur and that they may result in a rupture during everyday activities and sports [7–10]. It is not clear why these changes develop in some Achilles tendons, but not all.

Many predisposing factors have been proposed to increase the risk of ATR. ATR is more frequent in men than women (male-to-female ratio 3–5:1) [3,11]. Systemic glucocorticoids, quinolone antibiotics, severe kidney disease, and diabetes type 2 have been found to increase the risk of ATR [12–15]. Additionally, genetics may play a role. One study found a non-statistically significantly higher rate of first- and second-degree relatives with Achilles tendon disorders in patients with ATR compared with patients without ATR [16]. Furthermore, several genes have been suggested to be linked to Achilles tendon injury [17–20]. To what extend genetics influence the risk of ATR is not clear. The relative contributions of genetic and environmental factors to the etiology can be quantified by conducting twin studies. To our knowledge, no twin studies have yet estimated the heritability of ATR.

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In this twin study, the aims were 1) to calculate the concordance rate for monozygotic (MZ, ~100% identical genetics) twins and same-sex dizygotic (SSDZ, ~50% identical genetics) twins and 2) to investigate how much genetics contribute to the etiology of ATR by estimating the heritability.

2. Materials and methods

2.1. Data sources

This registry study was based on a linkage of the following three nationwide registers in Denmark:

The Danish Twin Registry contains information about twins born in Denmark in the period 1870–2009, and currently includes more than 86,000 twin pairs [21]. Twin zygosity is available for birth cohorts born up to the year 2000 and includes the twin categories: monozygotic (MZ), same-sex dizygotic (SSDZ), opposite-sex dizygotic (OSDZ), and unknown zygosity (UZ). Determination of zygosity is questionnaire-based with four questions about the degree of similarity between the co-twins. Zygosity has been validated using either serological or genetic markers in a subgroup of the twins and the misclassification rate has been found to be less than 5% [22].

The Danish Civil Registration System was established in 1968, where all persons alive and living in Denmark were registered and assigned a unique personal identification number. Since then all persons with permanent residence in Denmark are registered. This unique personal identification number enables unambiguous linkage of all national registers in Denmark. The CRS includes, among other variables, information on the unique personal identification number, sex, date of birth, vital status, date of death, and date of emigration [23].

The Danish National Patient Register contains information on all patient contact to Danish hospitals since 1977. The register includes dates of admission and discharge, start and end dates of outpatient treatment, dates of emergency visits as well as all diagnoses codes From 1994 and onward, diagnoses were classified according to the 10th revision of the International Classification of Diseases (ICD-10).[24].

2.2. Study population

All twin pairs, in which both co-twins were alive and not emigrated from Denmark by the start of the study period (January 1994), were identified using the Danish Twin Registry. Vital status, and date of death or emigration from Denmark originate from the Danish Civil Registration System. Diagnoses of acute Achilles Tendon Rupture (ATR) before age 18 years were not included in the present study, and therefore we restricted the study sample to those twin pairs who had their 18th birthday before the end of the study period (February 2014) and in which both co-twins were alive and not emigrated from Denmark before their 18th birthday.

2.3. Diagnosis of acute Achilles tendon rupture

Using the Danish National Patient Register, we identified all twins with a diagnosis of ATR (ICD-10 codes DS860 and DS860A) in the period from January 1994 to February 2014. In the present study, we included primary and secondary diagnoses and all patient types (i.e. inpatient, outpatient, and emergency room patient). A study investigating the data quality of a clinical database for patients with ATR in Denmark found a combined validity for the diagnosis codes DS86.0 and DS86.0 A of 80% (210 correctly registered patients with ATR out of 263) [25]. Additionally, a study found a validity of the diagnosis code DS86.0 A of 98% (83 correctly registered patients with ATR out of 85) [26].

2.4. Statistical analyses

MZ twins have identical genotypes, whereas DZ twins on average share half of their genetic variants like biologic full siblings. A greater phenotypic similarity in MZ twins than in DZ twins is expected if there is a substantial genetic component in the etiology of the phenotype. We assessed the similarity of MZ and DZ twins using the probandwise concordance rate, which is defined as the conditional probability that a twin is affected given the cotwin is affected and corresponds to recurrence risk in siblings [27]. Higher concordance rates among MZ twins than among DZ twins were interpreted as being caused by genetic factors.

Concordant twin pairs were defined as twin pairs in which both twins were diagnosed with ATR in the study period and discordant twin pairs as twin pairs in which only one twin received an ATR diagnosis in the study period. The probandwise concordance rates were calculated as 2CP/(2CP+DP), where CP is the number of concordant twin pairs and DP is the number of discordant twin pairs. Confidence intervals for the probandwise concordance rates were approximated by asymptotic normality assumption.

The correlations for ATR, expressed as tetrachoric correlations owing to a dichotomous, outcome were estimated using the multifactorial threshold model, which assumes that there is an underlying normally distributed liability (susceptibility) to a disease due to genetic and environmental factors [28].

The heritability is the proportion of observed phenotypic differences in a population that can be explained by genetic variance. According to standard biometric practice, the total phenotypic variance (V) in the population can be separated into four different variance components V = A + D + C + E, where A represents the variance contribution from additive genetic components (average sum of effects of alleles across and within loci), D represents the variance contribution from dominant genetic components (interaction of alleles within loci), C represents the variance contribution of shared environmental effects, and E represents the variance contribution of non-shared environmental effects [29]. The shared environmental effects (all the environmental effects that twins raised together share, such as prenatal and early family environment) contribute to the twin's similarity, whereas non-shared environmental effects (i.e. environmental factors that are not shared by raised-together twins) contribute to their differences. The genetic and environmental variance components of liability for ATR and the likelihood-based confidence intervals were estimated using structural equation modeling assuming an equal prevalence of ATR for twin 1 and twin 2 as well as for MZ and DZ.

In the full standard biometric model D and C cannot be estimated simultaneously, and therefore ADE and ACE models were fitted separately. Simpler models might explain the data equally well, and therefore models AE, CE, and E were also tested. The models were each evaluated for how well they fitted the data using the Chi-square goodness of fit test for nested models (i.e. had non-significant Chi-square goodness-of-fit test statistic) and was parsimonious (i.e. no parameters could be removed without a significant increase in Chi-square). The Akaike Information Criterion (AIC), which provides a summary index of both fit and parsimony to compare non-nested models, was used to identify the best fitting non-nested model. The model with the lowest AIC value was preferred. The variance components were derived from the best-fitted model.

The level of statistical *significance was set to 0.05.* Concordance rates and 95% CI were retrieved using Stata version 16.1 and heritability analyses were performed using R version 3.5.2 with Mets package version 1.2.8.1 [30].

Table 1
Population characteristic by twin zygosity.

	All twins	Monozygotic twins	Same-sex dizygotic twins	Opposite-sex dizygotic twins	Unknown zygosity twins
Total, n	85,534	19,150	30,160	27,984	8240
Male, n (%)	43,194 (50.5)	9358 (48.9)	15,444 (51.2)	13,992 (50.0)	4400 (53.4)
Year of birth, median (25%–75%)	1963 (1947–1979)	1964 (1947–1977)	1959 (1944–1975)	1962 (1947–1979)	1984 (1960–1991)
ATR diagnosis, n (%)	572 (0.67)	124 (0.65)	233 (0.77)	182 (0.65)	33 (0.40)
Male with diagnose, n (%)	427 (74.7)	82 (66.1)	186 (79.8)	136 (74.7)	23 (69.7)
Age at first diagnosis, median (25%–75%)	43.5 (36.3–54.8)	44.2 (34.9–58.3)	44.2 (37.9–55.1)	43.0 (36.6–52.0)	46.0 (32.7–54.7)

ATR = Acute Achilles Tendon Rupture (DS860, DS860A).

2.5. Trial registration

Institutional review board (IRB) approval was given by the Ethical Review Board of the Capital Region of Denmark, registration number 21047471.

3. Results

The study sample consisted of 85,534 twins born from 1895 to 1995. Of these, 572 (0.67%) had at least one contact to a Danish hospital with a diagnosis of ATR in the period from 1994 to 2014 (Table 1). The majority of those diagnosed with ATR were males (74.7%), and the median age at the time of the first diagnosis was 43.5 years. Stratified by zygosity, the number of twins registered with ATR were 124 (0.65%) for MZ, 233 (0.77%) for SSDZ, 182 (0.65%) for OSDZ and 33 (0.40%) for UZ.

Table 2 describes the probandwise concordance rates for ATR for MZ and SSDZ twins and the heritability for ATR. Due to small numbers of concordant twin pairs, OSDZ and UZ are not included separately in the table. The total study sample included 42,767 complete twin pairs. There were 560 twin pairs, in which at least one twin received a diagnosis of ATR, and 12 of these were concordant twin pairs. By zygosity, among 119 MZ twin pairs, 5 were concordant and among 228 SSDZ twin pairs, 5 were concordant. The concordance rate for MZ twins was 0.081 (95% CI 0.014–0.147) and for SSDZ twins 0.043 (95% CI 0.007–0.079), whereas the tetrachoric correlations were 0.43 (95% CI 0.23–0.59) for MZ twins and 0.28 (95% CI 0.11–0.44) for SSDZ twins.

Structural equation analyses revealed that the best fitting model attributed variation in the liability to ATR entirely due to additive genetic and non-shared environmental factors (AE model). Thus, neither the genetic dominance (D) and the shared environment (C) factors were needed to account for the observed data. According to this AE model, 47% (95% CI 31–62%) of the variance could be attributed to additive genetic components (the heritability). The rest of the variance could be explained by non-shared environmental factors.

4. Discussion

This study found that genetics contribute substantially to the etiology of ATR with an estimated heritability of the liability to ATR of approximately 50%. The risk of ATR for a twin, if the co-twin has had an ATR, was 8% for MZ twins and 4% for SSDZ twins, whereas 0.67% of the twins in the overall population within the observation period had an ATR.

Interpretation of heritability for a binary trait such as ATR can be difficult. To understand the estimated heritability it is assumed 1) that everybody has an underlying liability (susceptibility) of having an ATR that is normally distributed due to genetic and environmental factors, and 2) that an ATR occurs when a certain threshold in the underlying liability is exceeded. The results from the study suggest that the underlying liability of ATR is based on approximately 50% of genetics and 50% of environmental factors. In comparison, rupture of the anterior cruciate ligament (ACL) has an estimated heritability of 69%, meniscal tears have an heritability of 39–43% (depending on sex), whereas stroke has a heritability of 17% [31–33]. As explained in the introduction, it is well-known that pathological changes weakening the Achilles tendons can occur before a rupture [7–9]. The finding of a substantial genetic contribution to the etiology of ATR implies that genetics may play a role in these pathological changes.

The calculated concordance rate for monozygotic twins of 8% was approximately double as high as for SSDZ twins. These results speak for additive genetic components. The concordance rate of 4% for SSDZ twins may currently be the best estimate of the familiar risk for first-degree relatives of having an ATR. Full-siblings share about the same amount of genetic material as SSDZ twins (~50%). They also, to some extent, share the same early life environment as twins do. In comparison, 0.67% of the twins in the overall population within the observation period had an ATR. This new knowledge will help health care professionals to inform the patient and the patient's relatives about the increased risk of ATR. Additionally, a better understanding of the risk factors and the pathophysiology might result in new prevention strategies in the future.

No other studies have yet estimated the heritability of ATR. Therefore, the results from the present study cannot be directly compared with results from other studies. One study investigated if patients with ATR had a higher rate of first- and second-degree relatives with Achilles tendon disorders. They found a non-statistically significant odds ratio of 4.0 compared with patients without ATR [16]. Several studies have investigated the association between specific gene variants and ATR. Blood type O has been proposed to be associated with ATR [19,20]. Other studies did not manage to confirm this finding [34,35]. El Khoury et al. found that a gene variant of the protein MMP-3 was overrepresented in patients with ATR compared with controls [18]. The specific gene variant results in an overproduction of the MMP-3 protein. The overproduction may increase the risk of tissue degeneration because the MMP-3 protein

Table 2
Probandwise concordance rates, tetrachoric correlation and heritability for acute achilles tendon rupture by twin zygosity.

	Number of concordant twin pairs	Number of discordant twin pairs	Crude probandwise concordance rates [95%CI]	Tetrachoric correlation [95%CI]	Heritability [95%CI]
Monozygotic twins	5	114	0.081 [0.014;0.147]	0.43 [0.23;0.59]	0.47 [0.31;0.62]
Same-sex dizygotic twins	5	223	0.043 [0.007;0.079]	0.28 [0.11;0.44]	

plays a role in the breakdown of the extracellular matrix. Furthermore, Mokone et al. found that specific numbers of repeated dinucleotides in the gene coding for Tenascin-C were associated with Achilles tendon injuries. This protein is involved in regulating cell-matrix interactions [17]. The exact genetic and biological mechanisms behind the finding of the present study remain to be discovered.

The study has several limitations. First, despite being based on a national sample of twins, the ATR sample size was limited which resulted in a relatively large confidence interval of the estimated heritability (31–62%). Second, the study was limited by the validity of the diagnosis codes (see Section 2.3) [25,26]. A PPV above 80% is often defined as satisfying, though it can result in biased estimates of the concordance rates and the heritability [36,37]. The patients incorrectly registered with ATR are probably non-differentiated between mono- and dizygotic twins. Therefore, the potential bias will most likely result in underestimation of the concordance rates in MZ and DZ. Third, it was not possible to differentiate between acute and chronic rupture. Fourth, differences in heritability between sex and different age groups were not investigated.

An important strength of the study was the use of one of the world's largest twin registries. The registry has shown completeness of registered twin pairs of approximately 90% for twins born in Denmark before 1968 and completeness of 100% for all twin pairs born in Denmark after 1968 [38]. Additionally, the method used in the registry to determine zygosity has been proven to assign correctly in 95% of all twin pairs compared with zygosity determined by genetic markers [38].

5. Conclusions

This study found that genetics contribute substantially to the etiology of ATR with an estimated heritability of the liability to ATR of approximately 50%. The finding generates the hypothesis that genetics play a role in the pathological changes that occur in the Achilles tendon before a rupture. The risk of ATR for a twin within a 20 year period, if the co-twin has had an ATR, was 8% for MZ twins and 4% for SSDZ twins, whereas 0.67% of the twins in the overall population within the observation period had an ATR. The new knowledge will help health care professionals to inform the patient and the patient's relatives about the increased familial risk of ATR.

Disclaimers

None.

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Competing interests

The authors declare that they have no competing interests.

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