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R. Capstick
Nuffield Department of Surgical Sciences, University of Oxford, UK

T. Bragg
Department of Plastic and Reconstructive Surgery, West Wing, John Radcliffe Hospital, Oxford, UK

H. Giele and D. Furniss
Nuffield Department of Surgical Sciences, University of Oxford; Department of Plastic and Reconstructive Surgery, West Wing, John Radcliffe Hospital, Oxford, UK

Abstract
Dupuytren's disease is a complex condition, with both genetic and environmental factors contributing to its aetiology. We aimed to quantify the extent to which genetic factors predispose to the disease, through the calculation of sibling recurrence risk (λ_s), and to calculate the proportion of heritability accounted for by currently known genetic loci. From 174 siblings of patients with surgically confirmed disease, 100 were randomly selected. Controls were recruited from patients attending an ophthalmology outpatient clinic for eye conditions unrelated to diabetes. There were no statistically significant differences in baseline characteristics between the case and control groups. In siblings, 47% had Dupuytren's disease, compared with 10% of controls, giving a λ_s of 4.5. Currently known loci that predispose to Dupuytren's disease account for 12.1% of the total heritability of the disease. Dupuytren's disease was significantly more common in siblings than in controls. These results accurately quantify the magnitude of the genetic predisposition to Dupuytren's disease.

Keywords
Dupuytren's disease, genetics, sibling recurrence risk

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Introduction

Dupuytren's disease (DD) is the commonest inherited disease of connective tissue in humans (OMIM, 2011). It is a benign fibroproliferative disease of the palmar fascia, which causes flexion contractures in involved digits, leading to both physical and psychological morbidity (Townley et al., 2006; Zyluk and Jagielski, 2007). The UK incidence of DD in men is 34.3 per 100,000 per year (Khan et al., 2004). The prevalence of DD varies significantly depending on the age (Khan et al., 2004), gender (Hindocha et al., 2009), and ethnicity (Thurston, 2003) of the population examined, with Figures ranging from 0.2%–56% being reported (Hindocha et al., 2009). However, in the UK, it is believed that around 4% of the general population are affected by the disease (Hindocha et al., 2009). The aetiology of DD remains largely unknown (Townley et al., 2006). The mainstay of treatment for DD is surgery, though newer treatments are emerging (Hurst et al., 2009; van Rijssen et al., 2011). All are associated with significant complications, and recurrence rates are high.

DD is a typical complex genetic condition in which multiple predisposing genetic elements interact with environmental factors to result in disease expression, not an autosomal dominant condition as previously thought (Dolmans et al., 2011). Robust, replicated associations between environmental factors and DD have been reported for diabetes mellitus (Noble et al., 1984), alcohol use, and tobacco smoking (Thurston, 2003). Other potential associations and protective influences have been described, but results vary

The first two authors contributed equally to this study

Corresponding author:
D. Furniss, Department of Plastic Surgery, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK.
Email: dominic.furniss@doctors.org.uk

between studies, or have never been replicated (Arafa et al., 1984; Arafa et al., 1992; Sanderson et al., 1992).

In addition to these environmental and lifestyle exposures, the influence of genetic factors in the development of DD is supported by familial clustering (Burge, 1999; Ling, 1963), twin studies (Burge, 1999), population studies (Finsen et al., 2002), and molecular genetics (Dolmans et al., 2011). Genome-wide association studies (GWAS) are the current gold standard used to explore the multiple genetic influences that play a role in the development of complex diseases. A recent GWAS in DD found nine loci contributing to the development of DD (Dolmans et al., 2011).

Although the role of genetic factors in DD is well documented, the degree to which these factors contribute to disease development has never been adequately quantified. Sibling recurrence risk (I_s) is a measure that allows an estimation of the degree to which genetic factors contribute to the development of a disease (Olson and Cordell, 2000). It has been used for this purpose in many other conditions, including osteoarthritis (McDonnell et al., 2007) and rheumatoid arthritis (Wordsworth and Bell, 1991). This study aimed to calculate sibling recurrence risk using a previously validated strategy (McDonnell et al., 2007). The influences of other factors – age, gender and disease severity – upon sibling recurrence risk were also examined. Furthermore, we aimed to calculate the proportion of heritability accounted for by currently known genetic loci in DD (Orozco et al., 2010).

Methods

Participants in the British Society for Surgery of the Hand Genetics of DD (BSSH-GODD) study were used as index patients. Attempts were made to contact 703 of the index patients on the database. Index patients were selected for their proximity to the study centre, in order to match their geographical origin with that of the control group as closely as possible. Contact was successfully made with 562 index patients, of which 316 had at least one sibling available for inclusion in the study. Packages were sent to each of these index patients, with instructions for them to pass invitations along to all available siblings. Positive reply slips were received from siblings of 174 index patient family groups. One sibling of each index patient was selected using a random number generator to ensure that larger families were not overrepresented, thus controlling for ascertainment bias. Where only one sibling of an individual index patient was available, these participants were included as a matter of course. From this random selection, 100 siblings were enrolled in the study.

Once enrolled, participants were examined by a surgeon with at least 5 years' experience in diagnosing and treating DD. The presence of a nodule, cord, or contracture of the palmar fascia, or a past history of surgery for DD, was considered diagnostic. The examination took place either at our base hospital (48 participants), at the participants' home (48 participants), or at another hospital in the region (four participants). In addition to examining for the presence of DD, we recorded data on age, gender, ethnicity, and diabetes. A past history of surgery for DD was also recorded as a proxy marker for disease severity in order to allow separate statistical analysis of participants with greater severity of disease. Controls were recruited from patients attending an ophthalmology outpatient clinic for non-diabetic eye conditions at our hospital, and had the same examination and data collection as the sibling group. We chose this control group because, apart from diabetes mellitus, there are no known shared genetic or environmental risk factors for DD and ophthalmological disease.

Sibling recurrence risk (I_s) was calculated using the equation

$$\lambda_S = \frac{\%\ siblings\ with\ DD}{\%\ controls\ with\ DD}$$

This ratio, calculated with 95% confidence intervals (CIs), represents the risk of a sibling of an affected case also having the disease, when compared with an individual selected from the general population, as represented by the control group. $p \leq 0.05$ was defined as statistically significant.

We calculated the sibling recurrence risk accounted for by each individual locus discovered in the DD GWAS (Dolmans et al., 2011), and then calculated the proportion of heritability accounted for by all of the loci using the equation below (Orozco et al., 2010).

$$\%\ heritability\ explained = \frac{(\log \lambda_S\ locus\ 1 + \log \lambda_S\ locus\ 2 + \ldots + \log \lambda_S\ locus\ n) \times 100}{\log \lambda_S\ disease}$$

Results

Table 1 shows the measured variables in the sibling and control groups. Overall, sibling recurrence risk was found to be 4.5 (95% CI 2.6–7.8, $p < 0.0001$). Owing to the strong association between DD and male gender, sex-specific figures for sibling recurrence risk were also calculated. These were found to be 3.4 (2.0–7.5, $p < 0.0001$) for brothers of index patients compared with male controls, and 6.3 (2.3–17.1, $p < 0.0001$) for sisters of index patients compared with female controls (Figure 1).

Table 1. Group characteristics.

Characteristic	Sibling group *n* = 100	Control group *n* = 124	*p* value*
Age: mean (SD) years	68.1 (10.9)	69.0 (13.3)	0.573§ *t* = 0.564
Male gender: *n* (%)	40 (40)	61 (49.2)	0.179
Ethnicity:			1.000
White British: *n* (%)	98 (98)	122 (98.4)	
White Irish: *n* (%)	2 (2)	2 (1.6)	
History of diabetes: *n* (%)	10 (10)	8 (6.5)	0.452
DD present: *n* (%)	47 (47)	13 (10.5)	< 0.0001
History of surgery for DD: *n* (%)	17 (17)	3 (2.4)	< 0.0001

*: Two-tailed *p*-values calculated using Fisher's exact test.
§: Calculated using independent samples *t*-test.

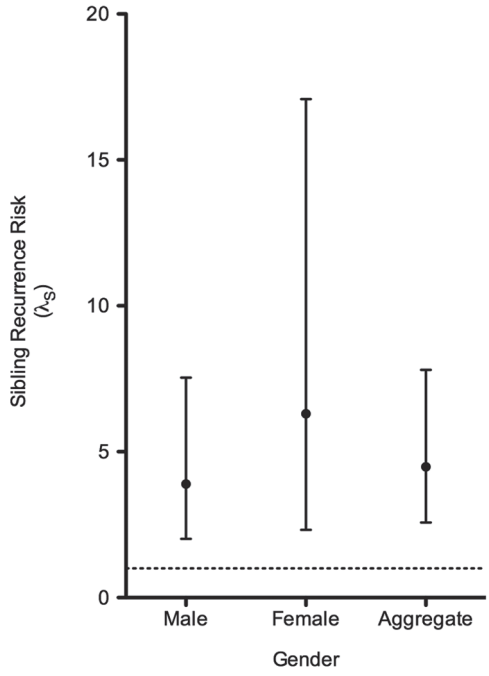

Figure 1. Sex-specific sibling recurrence risk. Filled circles represent the sibling recurrence risk, with error bars indicating 95% CIs. The dotted line represents a risk of 1; a value greater than this suggests a genetic predisposition to DD.

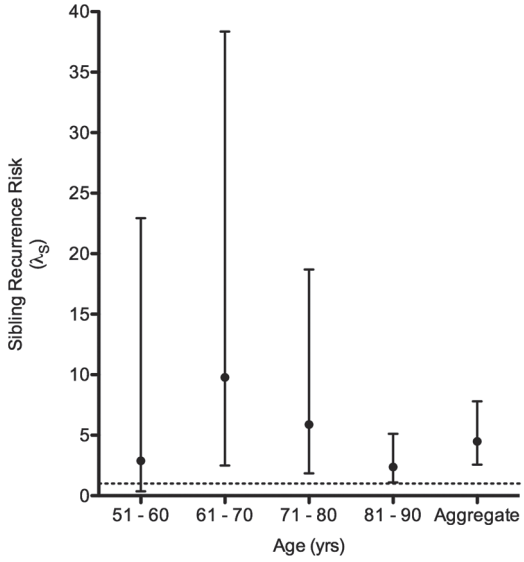

Figure 2. Age-specific sibling recurrence risk. Explanatory notes as for Figure 1.

Calculations of sibling recurrence risk for different age groups were also made (Figure 2). Sibling recurrence risk for the 61–70, 71–80, and 81–90 year age-groups reached statistical significance, but did not for the 51–60 year age group, probably because of small sample size (Table 2).

A past history of surgery for DD was found in 17/100 siblings and 3/124 controls. This allowed us to calculate the sibling recurrence risk for a past history of surgery for DD (I_sSurg) as 7.1 (95% CI 2.1–23.3; $p <$ 0.0001).

We calculated the per-locus I_s for the nine loci currently known to contribute to DD (Dolmans et al., 2011; Orozco et al., 2010), and then calculated the percentage of heritability of DD explained by these genetic loci. Currently known genetic loci that predispose to DD account for 12.1% of the total heritability of the disease.

Discussion

The case and control groups were well matched for baseline characteristics (Table 1). The only statistically significant differences between the two groups were the prevalence of DD, and the proportion of participants that had previously had surgery for the condition.

DD was significantly more common in the sibling group than in controls. Any increased prevalence of DD in the sibling group can be attributed to a common environmental exposure, a genetic cause, or a

Table 2. Sibling recurrence risk stratified by age group.

Age (years)	Sibling prevalence (%)	Control prevalence (%)	Sibling recurrence risk (95% CI)	*p*-value*
30–40	0/0 (0)	0/4 (0)		
41–50	0/4 (0)	0/10 (0)		
51–60	4/18 (22)	1/13 (8)	2.89 (0.4–22.9)	0.368
61–70	22/36 (61)	2/32 (6)	9.8 (2.5–38.4)	< 0.0001
71–80	13/28 (46)	3/38 (8)	5.9 (1.9–18.7)	< 0.0001
81–90	8/13 (62)	7/27 (26)	2.4 (1.1–5.1)	0.040

*: Two-tailed *p*-values calculated using Fisher's exact test.
CI: confidence interval.

combination of both. One favoured way to ensure that results reflect a genetic rather than environmental cause is to use spouses as controls (McDonnell et al., 2007), as they share the same environment as case group participants but are genetically different. However, owing to the skewed gender distribution of DD patients (Hindocha et al., 2009), this method would be inappropriate in a study examining the risk of DD. Despite this, when a clear causal environmental mechanism is not known, clustering of disease cases within a family is considered to be likely owing to genetic influences (Burge, 1999), and it seems likely that the significantly increased sibling recurrence risk found in this study reflects a genetic cause.

Ling (1963) examined the relatives of DD patients for signs of the condition, and found a much higher prevalence than that found in population controls taken from a different study in a different geographical region. He examined all available relatives of each DD patient, and included knuckle pads as a diagnostic criterion for DD. It is possible to recalculate the sibling recurrence risk from this article. He reported 25/107 siblings affected with DD, and comparing this to a contemporary population estimate (Early, 1962) of 3.9% gives an estimate of I_s of 5.99 – broadly in agreement with our calculation. Importantly, Ling showed that although only 16% of index patients reported a positive family history of DD, 68% of index patients actually had affected relatives, highlighting the importance of examining participants directly when calculating sibling recurrence risk.

An attempt to calculate sibling recurrence risk was also made by Hindocha et al. (2006), who found it to be 2.9 (95% CI 2.6–3.3). Ninety-two of 300 invited patients took part in the study, and were asked the DD status of their 699 relatives. The replies were then validated by postal questionnaire in 111 of these relatives, of whom 62 replied. In turn, the questionnaire was validated by clinical examination in just 12 relatives. In these 12 relatives, 7 self-reported having DD, whereas 10 actually had DD on clinical examination. The lack of direct clinical assessment of disease status of over 98% of relatives means that the result must be viewed with caution. Further, the authors included every sibling of each DD index patient, meaning larger families would also have a proportionally greater influence on the calculation of sibling recurrence risk. Single sibling-index patient pairs should be used to reduce this ascertainment bias (Burton et al., 2000; Olson and Cordell, 2000), the approach we have taken in this study. Finally, Hindocha et al. (2006) compared their sibling group with two control groups previously reported. The first was collected by Early (1962) from a comparable geographical area but with a statistically different age distribution to the study's case group, and the second was reported by Gudmundsson et al. (2002) from another country with different ethnicities present. These multiple limitations call into question the validity of the study of Hindocha et al. (2006).

The sex-specific calculations of sibling recurrence risk shown here suggest that genetic factors play a greater role in the development of DD in women than in men. However, large CIs owing to the small subgroup sizes reduce the certainty of this finding. To determine if a significant difference in the sibling recurrence risk for men and women exists, a study with larger sample sizes would need to be conducted.

The impact of age upon sibling recurrence risk was also examined. There was a trend that younger siblings were at a comparatively higher risk of having DD when compared with older participants in the sibling group. This implies that genetic factors play a greater role in disease development in younger patients. The fact that statistically significant group differences were not found in the 51–60 age-group is likely a reflection of the smaller sample sizes in this group.

The case and control groups used here were homogenous in terms of ethnicity. Furthermore, the groups were specifically selected to reside close to our city, to reduce the effects of any fine-scale population stratification on the results. This similarity in the groups is important if meaningful comparisons are to be made between them, owing to the association between ethnicity, geographical origin, and DD

prevalence. However, it also means that the sibling recurrence risk calculated here may be both geographically and race-specific.

A past history of surgery for DD was used as a proxy marker for disease severity. Not only was a past history of surgery significantly more common in the sibling group than in controls, the sibling recurrence risk specific to this variable was found to be higher than that calculated for DD as a whole. Though there are many factors that influence the decision on whether or not to operate in DD, this result suggests that a higher genetic burden may be associated with a greater severity of disease.

We took several steps in the design of this study to reduce both misclassification bias and ascertainment bias. First, since surgeons with at least 5 years' experience in diagnosing and treating DD made the diagnosis, we reduced the likelihood of both false-negative and false-positive classification of siblings and controls with regard to disease state. We used a clinically and academically relevant diagnostic strategy, where the diagnostic criteria and examining clinician were standardized. Sibling group participants were selected from the pool of available siblings in a random manner, and a single sibling was selected from each index patient family. This strengthens confidence in the case group as a representative sample of the available siblings, and limits ascertainment bias that could occur if some families were over represented.

This study recruited sibling group participants through the use of index patients who had previously undergone surgery for DD, a proxy marker for disease severity. Therefore it is possible that the sibling group participants were related to a skewed sample of DD patients. The sibling recurrence risk reported here may have been less pronounced if the index patients had less severe disease.

This study has provided a methodologically robust quantification of the sibling recurrence risk associated with DD. This quantification made it possible to determine that 12.1% of heritability has been accounted for to date. Further molecular studies are required to reveal the full genetic architecture of DD, which in turn may lead to the rational design of new therapies aimed at both treating the disease and preventing recurrence.

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Conflict of interest

None declared.

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Ethical approval

Approval was obtained from Oxfordshire Research Ethics Committee B (09/H0605/65).

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