Epidemiology of Dupuytren's disease: The importance of genetic susceptibility

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Complete List of Authors:	Becker, Kerstin; University of Cologne, Cologne Center for Genomics; University of Cologne, Cluster of Excellence on Cellular Stress Responses in Aging-associated Diseases Tinschert, Sigrid; Innsbruck Medical University, Div. of Human Genetics; Dresden University of Technology, Inst. of Clinical Genetics Lienert, Andrea; Praxis Dr. Peter E. Bleuler, - Bleuler, Peter; Praxis Dr. Peter E. Bleuler, - Staub, Frank; Center for Peripheral Neurosurgery, - Meinel, Albrecht; Center for Peripheral Neurosurgery, - Rößler, Jörg; Marcolini-Praxisklinik, Praxis Dr. Jörg Rößler Wach, Wolfgang; International Dupuytren Society, - Hoffmann, Reimer; Inst. for Hand and Plastic Surgery, - Kühnel, Florian; Carl-Thiem-Klinikum Cottbus, Dept. for Trauma, Hand, and Reconstructive Surgery Damert, Hans-Georg; University Hospital of Magdeburg, Dept. for Plastic, Aesthetic, and Hand Surgery Nick, Hans-Elmar; St.-Antonius-Hospital, Dept. for Plastic Surgery Spicher, Rüdiger; Roland-Klinik Bremen, Center for Hand and Reconstructive Surgery Lenze, Wolfgang; Praxis Drs. Frank/Lenze, - Hennies, Hans; University of Cologne, Cologne Center for Genomics; Innsbruck Medical University, Div. of Human Genetics; University of Cologne, Cluster of Excellence on Cellular Stress Responses in Aging-associated Diseases
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Epidemiology of Dupuytren's disease: The importance of genetic susceptibility

Kerstin Becker[1,2], Sigrid Tinschert[3,4], Andrea Lienert[5], Peter E. Bleuler[5], Frank Staub[6], Albrecht Meinel[6], Jörg Rößler[7], Wolfgang Wach[8], Reimer Hoffmann[9], Florian Kühnel[10], Hans-Georg Damert[11], Hans-Elmar Nick[12], Rüdiger Spicher[13], Wolfgang Lenze[14], Martin Langer[15], Peter Nürnberg[1,2], Hans Christian Hennies[1,2,3]

1. Cologne Center for Genomics, University of Cologne, Cologne, Germany

2. Cluster of Excellence on Cellular Stress Responses in Aging-associated Diseases, University of Cologne, Cologne, Germany

3. Div. of Human Genetics, Innsbruck Medical University, Innsbruck, Austria

4. Inst. of Clinical Genetics, Dresden University of Technology, Dresden, Germany

5. Praxis Dr. Peter E. Bleuler, Rüti, Switzerland

6. Center for Peripheral Neurosurgery, Dossenheim, Germany

7. Praxis Dr. Jörg Rößler, Marcolini-Praxisklinik, Dresden, Germany

8. International Dupuytren Society, Übersee, Germany

9. Inst. for Hand and Plastic Surgery, Oldenburg, Germany

10. Dept. for Trauma, Hand, and Reconstructive Surgery, Carl-Thiem-Klinikum Cottbus, Cottbus, Germany

11. Dept. for Plastic, Aesthetic, and Hand Surgery, University Hospital of Magdeburg, Magdeburg, Germany

12. Dept. for Plastic Surgery, St.-Antonius-Hospital, Eschweiler, Germany

13. Center for Hand and Reconstructive Surgery, Roland-Klinik Bremen, Bremen, Germany

14. Praxis Drs. Frank/Lenze, Bielefeld, Germany

15. Dept. for Trauma, Hand, and Reconstructive Surgery, University Hospital of Münster, Münster, Germany

Corresponding author:

Hans Christian Hennies, Cologne Center for Genomics, University of Cologne, Weyertal 115b, 50931 Köln, Germany.

Phone 49-221-47896802, fax 49-221-47896866, e-mail: h.hennies@uni-koeln.de.

Conflict of Interest

The authors declare they have no conflict of interest.

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Abstract

Dupuytren's disease (DD) is a progressive fibromatosis that causes the formation of nodules and cords in the palmar aponeurosis leading to flexion contracture of affected fingers. The etiopathogenesis is multifactorial with a strong genetic predisposition. It is the most frequent genetic disorder of connective tissues with a prevalence of about 2.5% in Germany and up to 40% in parts of Scandinavia. We have collected clinical data from 801 unrelated individuals with DD from Germany and Switzerland using a standardized questionnaire and evaluated the importance of different risk factors. We found that a genetic predisposition clearly had the strongest influence on the severity of the disease compared to environmental factors, followed by male sex. Patients with a positive family history were on average 55.9 years of age at the first surgical contracture treatment, 5.2 years younger than patients without known family history ($P = 6.7 \times 10^{-8}$). The percentage of familial cases was found to decrease with age of onset from 55% in the 40-49 year olds to 17% at age 80 years or older. Further risk factors analysed were cigarettes, alcohol, diabetes, hypertension, and epilepsy. Our data pinpoint the importance of genetic susceptibility for DD, which has long been underestimated.

Key words

Dupuytren's disease, Dupuytren's contracture, Dupuytren's diathesis, complex genetics, connective tissue, myofibroblast, risk factors, epidemiology

Introduction

Dupuytren's disease (DD) is one of the most common genetic disorders of connective tissues. It is characterised by a progressive fibrous proliferation of the palmar aponeurosis und the cutaneous retinacula of the hand. Typically, the formation of subcutaneous nodules is followed by fibrotic cords, which may subsequently lead to flexion contractures of single affected fingers. Histopathologically, an increased proliferation of fibroblasts and differentiation into myofibroblasts can be seen associated with a massive deposition of extracellular matrix. The disease shows a progressive clinical behaviour. The prevalence of DD is around 4% in England[1] and 2.5% in Germany[2], and it increases drastically with age;[3,4] it was 22% in a recent cross-sectional study of the population aged over 50 years in the northern part of the Netherlands[5] and 30% in the Norwegian population over 60 years of age[6]. Women are less frequently affected and develop the disease later in life. In men the time of first surgical treatment peaks around the fifth decade of life while women present for surgery approximately one decade later.[2] Moreover, it has been reported that patients with contractures had an increased risk for cancer and cancer associated death.[4,7]

The etiopathogenesis for DD is multifactorial. Several environmental factors have been proposed to contribute to DD development. Smoking and alcohol consumption, elevated blood glucose levels, low body weight, heavy manual labour, and exposure to vibrations have been reported to predispose to DD.[8-12] Reports also said that DD was common among diabetes mellitus type 2 patients but they may be in general less severely affected.[13] In a study with epilepsy patients 56% had DD.[14] The authors proposed that this association is probably due to epileptic drug intake and subsequent stimulation of tissue growth factors. DD is common in patients with frozen shoulder, another fibrotic disorder.[15] Incidence of DD has been described

as reduced among patients with rheumatoid arthritis[16], and DD patients had less frequently stiff joints and rheumatic disorders[17].

Frequent familial occurrence of DD indicates a genetic basis for the disease. Studies have determined a family predisposition in 12.5%[2] and 27%[18] of cases, respectively. The sibling recurrence risk λ_s has been determined as 2.9 based on a prevalence of 3.5 in Northwest England[19], and a recent whole genome association study identified nine genetic susceptibility loci for DD[20]. DD most likely has a complex genetic basis, where different genetic risk loci contribute to disease susceptibility[21]. However, the impact of a genetic predisposition and other risk factors on the progression of the disease is not conclusive in epidemiological studies. Here we have therefore investigated the influence of risk factors on the mean age of first surgical treatment in our study population.

Materials and Methods

Study population

In this case/control study individuals undergoing surgery for DD were recruited through the hand surgery departments of nine hospitals in Germany and one in Switzerland. Some probands were recruited through the collaboration with a patient support group. Participants provided written informed consent, with institutional review board approval.

Each participant completed a standardized, one-page questionnaire to collect data of clinical features including age, family history, hand involvement, and the presence of ectopic manifestations (knuckle pads or plantar fibromatosis (Ledderhose disease).

Patients were treated surgically either through needle fasciotomy or, in most cases, limited fasciectomy. No further distinction was made between the methods of treatment, the course of the disease was therefore not considered in our analyses except for the impact of family

history for the overall recurrence rate. Some probands participated in the study but did not undergo surgery.

Statistical methods

The age at first surgery is likely to reflect a combination of the age of onset and progression of disease. Both individuals with an early age of onset or an aggressive course of disease will potentially present earlier for surgery than those who are affected late in life or are mildly affected. Therefore we selected age at first surgery as a variable to compare different subgroups of probands.

The non-parametric Mann-Whitney-U test was performed to test whether groups differed in their ages at first surgery. Frequencies (nominal variables) were compared using χ^2 test or Fisher´s exact test (for small values). Frequencies were adjusted for age based on binary logistic regression. Statistical analyses were done with Microsoft Excel®. Associations in single tests were considered significant if the p-value was <0.05.

Results

The questionnaire was completed between 2007 and 2012 by 801 unrelated individuals with DD (639 from Germany, 162 (20.2%) from Switzerland). One hundred thirty-two (19.1%) were women, giving an overall male/female ratio of 4.6:1. For each proband the age at intake and the age at first surgery were recorded. The mean age at intake was 63.5 ± 10.5 years (N = 801). The mean age at first surgery was 59.0 ± 12.2 years for all individuals who underwent surgery (N = 736) (table 1). Women were on average 61.1 ± 11.4 years old when they first underwent surgery (N = 121, 16.4%) while men were on average 2.5 years younger (58.6 ± 12.3 years, N = 615). Sixty-five probands did not require surgery. They were on average 61.2 ± 11.7 years old. Twenty-two (33.8%) of these were women. In all age groups more men than

women underwent surgery for DD (table 1). The age at first surgery ranged from 22 to 87 years of age in men and from 27 to 84 years of age in women.

Family predisposition

Three hundred and six (38.2%) probands reported a family predisposition for DD (table 2). In 89 (29.1%) cases family members from the maternal line were affected: In 70 (78.6%) of these the mother was affected while in the remaining 19 cases other family members were affected, i.e. a grandparent, aunt or uncle. One hundred and forty-one probands had affected family members in their paternal line. The father was affected in 134 (95.7%) of these, in three of the remaining seven cases the paternal grandfather was affected while the father was not affected. Ten individuals had affected family members in both parental lines. Nine of these had both parents affected. For 66 cases the parental line was unknown (siblings or children affected) or not specified (6.2%). Ninety-eight (32.0%) probands had more than one affected family member. In 18 cases a grandparent but not the parent was affected by DD. For a number of additional individuals a family predisposition was suggestive but not confirmed e.g. because of the death of relatives (not included).

Individuals with positive family history are thought to be more severely affected by DD than those without positive family history. We therefore compared the two groups for the presence of ectopic lesions, bilateral affection status and recurrence of disease (table 2). Probands with positive family history had significantly more often ectopic lesions (knuckle pads and plantar fibromatosis). Probands in this group were also significantly more often bilaterally affected and more probands in this group had been treated after recurrence of disease (table 2). In addition, we collected a severity score for all probands based on the disease staging of Tubiana[22]. According to these data, no difference was observed between the two groups (mean (95% confidence interval): positive family history 2.17 (2.03-2.30), no known family history 2.17 (2.07-2.30); however, these data are supposed to be biased because of the

hospital-based mode of patient recruitment and were not further taken into account for the study of risk factors.

Probands with a family predisposition for DD were significantly younger when they first underwent surgery compared to those without known family predisposition (table 3). Ten individuals had affected family members in both parental lines. These probands were even younger at the age of first surgery. The age difference was also evident for men and women separately (table 3). Women who had affected family members in their paternal line had a lower mean age at first surgery than women with affected family members in their maternal line (difference not significant).

Behavioural risk factors

Alcohol abuse and heavy smoking have been suggested as behavioural risk factors for DD. Probands were therefore asked about smoking behaviour and alcohol consumption. Three hundred sixty-one probands (45.2%) were current or former smokers. Smokers (N = 331, 10.3% women) had a mean age of 58.1 ± 12.3 years at the time of first surgery. Non-smokers (N = 405, 21.5% women) were on average 59.7 ± 12.3 years old (p= 0.05). Heavy smokers (N = 81, 4.9% women) who consumed more than twenty cigarettes per day had a mean age of 57.1 ± 11.8 years when they underwent first surgery. When cases were divided into probands with and without familial predisposition (table 4) the age difference between smokers and non-smokers was more pronounced in probands without familial predisposition and not seen in the group with familial predisposition.

When smokers were further subdivided according to the number of cigarettes consumed per day, the age difference increased with the amount of consumed cigarettes for probands with family predisposition (table 4). Probands with family predisposition who consumed less than five cigarettes per day were 2.6 years older than non-smokers with family predisposition. In contrast, probands with family predisposition who consumed more than 20 cigarettes per day

were on average 2.7 years younger than non-smokers and 6.2 years younger than heavy smokers without family predisposition (table 4).

Six hundred sixty-three (82.8%) DD probands consumed alcohol. They were divided into occasional (60.8%) and regular (22.0%) alcohol consumers. The dosage of regular consumers comprised e.g. 1-3 bottles of beer or 1-3 glasses of wine per day. Alcoholism was recorded for two probands . There were only marginal differences in the mean ages of first surgery between probands who consumed alcohol regularly, occasionally or never. Probands who regularly consumed alcohol (N = 169) were 58.6 ± 11.6 years old at the time of first surgery while probands who did not consume alcohol (N = 117) were 59.7 ± 12.6 years old (p = 0.37). The largest difference in this context was seen in the group of probands with positive familial history. Here, probands who regularly consumed alcohol (N = 57) were 53.7 ± 12.1 years old compared to occasional alcohol consumers (N = 175, mean age ± SD = 56.1 ± 12.4) but the difference was not significant (p = 0.18).

Discussion

DD is a common genetic disorder with a strong increase of prevalence in the persons over 50 years of age. Although several epidemiological studies of DD have been conducted, prevalence data are not always conclusive. This is in part because of the clear regional differences in the prevalence of DD, with a peak in Northern Europe. Moreover, the contribution of genetic predisposition and environmental risk factors remains mostly unclear. We have therefore studied risk factors in individuals with DD referred to us for further treatment. 801 unrelated persons from Germany and Switzerland completed the standardized questionnaire and were included into the study. All these probands were particularly informed about the importance of family history, and pedigrees were recorded thoroughly. In our study

38.2% of probands reported a positive family history for DD, with one or more affected family members. In other studies the observed family predisposition rates varied between 12.5% and 44%.[1,2,5,18,19,23-25] It is to be noted that we have not selected any probands on the basis of their family predisposition. It is likely, however, that the overall rate of family predisposition observed here still underestimates the actual rate since some probands may not be aware of affected family members especially if they are other than first degree relatives and/or have died earlier. Ling showed in 1963 that the rate of patients with a positive family history for DD increased from 16% reported by themselves to 68% when relatives were examined by the author.[26] In our study the rate of a family predisposition was highest in the younger probands and clearly declined with age. This supports the observation that individuals with a family predisposition are affected earlier by the disease. On the other hand, older persons are more likely to overlook possibly affected family members because of the death of older relatives (e.g. parents and grandparents). We did not observe significantly more familial cases among women as was noted in previous studies[25].

Notably, within all investigated risk factors a family predisposition for DD had the largest impact on the mean age at first surgery. Probands who had affected family members were on average 5.2 years younger at the time of first surgery. Coert *et al.* investigated the same parameter and found no difference in mean ages at surgery between patients with and without family predisposition.[18] This may be due to the smaller effective size (N = 261) of their study.

Additionally, 1.3% of probands had affected family members in both parental lines. These probands were even younger at the time of first surgery. A possible explanation is that additive genetic effects lead to a more severe phenotype in these cases.

The male-to-female ratio was highest in 40-49 year old probands , underlining that men are affected earlier. Brenner *et al.* stated that the ratio goes down to 1 in the 10th decade of life.[2] We do see the same tendency but men are always overrepresented and numbers of very young

and very old patients are rather small. It has often been reported that the observed male-to-female ratio in DD is due to the later age of onset in females. However, in a recent cross sectional study, which was conducted in a non-surgical setting, a male-to-female ratio of 1.2 was found[5], and there was a low incidence of surgical intervention. These differences could indicate that either the course of disease is different in affected females with a less frequent need for surgery[5], or different types of DD exist with a milder form that is similarly present in males and females[27] and not identified by our study design. This is in line with our observation that more men than women underwent surgery for DD, which was still true for 80-89 years old probands. The same tendency was noted by Loos *et al*.[28]

Heavy smoking may be a risk factor for DD. In total, we found 19.1% current smokers, 25.8% former smokers, and 54.9% non-smokers in our study. The ratios for current and former smokers are somewhat lower than those in the general population in Germany (24% current smokers, 39% former smokers, 37% non-smokers; age and sex adjusted data from the Robert Koch Institute (2012)[29], the central German institution responsible for disease control and prevention). Smokers were significantly more frequent in the group of probands without positive family history, which might indicate that smoking is an independent risk factor. Smokers with DD were on average slightly younger at the time of first surgery than non-smokers. This age difference was just significant when all probands were considered. The ratio of ever smokers among probands with positive family history was about ten percentage points smaller than among probands without positive family history. In probands without familial predisposition the amount of cigarettes consumed per day did not correlate with the mean age at first surgery, while in probands with familial predisposition there was a ~5 year difference in the mean age at first surgery for heavy smokers compared to smokers who consumed less than five cigarettes per day (not significant). Thus the results on smoking are inconsistent, which is in line with findings from other studies. Loos *et al*. found no statistical correlation between heavy smoking (>20 cigarettes per day) and mean stage of disease after

Iselin's classification.[30] Brenner *et al.* noted a higher percentage of bilaterally affected patients among heavy smokers compared to patients who consumed less than 20 cigarettes per day.[2] A significant correlation between heavy smoking and the occurrence of DD was seen in the majority of cohort or epidemiological case/control studies[8-10,31,32] but not by Zerajic and Finsen[33]. A larger sample collective is desirable in order to test for this hypothesis. It would be important to subdivide probands into those with and without familiar predisposition when assessing the prevalence of heavy smoking or other suggestive risk factors in DD and correct for familial cases in cohort studies, respectively, because family predisposition is a strong risk factor for DD and might influence other risk factors.

We have not detected a correlation between alcohol consumption and DD in this study. About 17.2% of probands never drank alcohol. This is well comparable to the general German population (17% non-drinkers, 55% moderate drinkers, 28% alcohol abuse; age and sex adjusted data from the Robert Koch Institute (2012)[29]) but our data were not sufficiently comprehensive to elucidate possible correlations between alcohol intake and disease severity as we could only distinguish between regular and occasional alcohol consumers in the questionnaire.

Several studies have identified diabetes, epilepsy, and hypertension as potential further risk factors for DD. Diabetes type 2 is itself an ageing associated disease, we have therefore adjusted the frequency of diabetes patients for age but did not observe differences between the two groups. Only 0.9% of the probands took antiepileptic drugs. The studies by Loos *et al.*[28] and Brenner *et al.*[2] both found 1.3% epilepsy patients in their respective patient collectives (2919 and 566 patients, respectively), and Coert *et al.*[18] noted 1.9% epilepsy patients in a collective of 261 patients operated for DD. These numbers do not differ significantly from the prevalence in the population. For hypertension, we found a significantly higher ratio among

DD individuals without a positive family history but the overall frequency of hypertension in our study is comparable to that in the general population (31.6%).[34]

Interestingly, women tend to have a lower mean age at first surgery when the affected family member was in their paternal line. Because DD has a complex genetic basis, epigenetic factors may trigger and/or modulate disease severity. Possibly not only men are more frequently affected by DD and/or have a more severe course of the disease but parent of origin effects may also play a role in the development of the disease. Parent of origin effects have been shown to modulate disease severity for example in cystic fibrosis[35] and they can also have an effect in aging associated diseases such as Alzheimer's disease[36]. Thus it will be interesting to assess parent of origin effects more thoroughly in future genetic studies.

Conclusion

To our knowledge this is the largest study comparing the age at first surgery with risk factor assessment. A genetic predisposition is one of the most prominent risk factors for DD. We have shown that a positive family history is clearly linked to disease severity and represents the most important risk factor for DD, at least for the severe disease courses that need surgical intervention at some point. Individuals with positive family history require earlier surgical treatment and have more often ectopic lesions. Consistent with the complex genetic basis for DD, patients with affected family members in both parental lines exhibited an even more severe disease phenotype.

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Conflict of interest statement

The authors declare they have no conflict of interest.

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Tables

Table 1.

Age distribution of Dupuytren's disease. The ages at first surgery are summarized for male and female probands in various age groups represented in the study.

	All	men	women	gender ratio	familial cases	
Years of age	N	N	N		N	%
29-39	15	11	4	2.8:1	8	53.3
40-49	80	70	10	7.0:1	44	55.0
50-59	191	158	33	4.8:1	84	44.0
60-69	278	225	53	4.2:1	102	36.7
70-79	208	169	39	4.3:1	63	30.3
80-89	29	25	4	6.3:1	5	17.2
All	801	658	143	4.6:1	306	38.2

Table 2.

Risk factors for Dupuytren's disease and their association with positive family history.

	Probands with positive family history		Probands without positive family history			
	N (%)	N total	N (%)	N total	P-value[4]	Odds ratio (95% CI)[5]
Women	61 (19.9)	306	82 (16.6)	495	0.226	1.25 (0.87-1.81)
Ectopic manifestations	65 (22.0)	296[a]	35 (7.1)	495	1.08E-09	3.70 (2.38-5.74)
Knuckle pads	33 (11.2)	296[a]	25 (5.1)	495	1.45E-03	2.36 (1.37-4.05)
Ledderhose	27 (9.1)	296[a]	10 (2.0)	495	4.71E-06	4.87 (2.32-10.21)
Others[1]	5 (1.7)	296[a]	0 (0)	495	7.18E-03	x
Both hands affected	170 (59.7)	285[b]	214 (44.5)	481[b]	5.00E-05	1.84 (1.37-2.48)
Recurrence[2]	96 (32.4)	296[a]	102 (20.6)	495	2.03E-04	1.85 (1.33-2.56)
Diabetes	36 (11.8)	306	72 (14.5)	495	0.263	0.78 (0.51-1.20)
Diabetes, age adjusted					0.830	0.89 (0.29-2.72)
Hypertension	81 (26.5)	306	210 (42.4)	495	5.08E-06	0.49 (0.36-0.67)
Hypertension, age adjusted					0.011	0.52 (0.31-0.86)
Rheumatoid arthritis	4 (1.3)	306	14 (2.8)	495	0.220	0.46 (0.15-1.40)
Smokers[3]	120 (39.2)	306	241 (48.7)	495	8.85E-03	0.68 (0.51-0.91)
Regular alcohol consumers	62 (19.0)	306	119 (24.0)	495	0.092	0.74 (0.52-1.05)
Office workers	45 (24.5)	184[c]	46 (17.0)	271[c]	0.050	1.58 (1.00-2.51)

[a] Probands with positive family history (excl. 10 patients with both parental lines affected)

[b] Probands who reported the affected hand(s)

[c] Probands who stated their profession

[1] Others: one proband with frozen shoulder; four probands did not specify type of ectopic manifestation

[2] Recurrence: probands had previous surgeries at same hand (two or more surgeries at same hand)

[3] Former and current smokers

[4] P-values are those of χ^2 test; for other ectopic manifestations and rheumatoid arthritis we used Fisher´s exact test.

[5] CI – confidence interval.

Table 3.

Mean ages at first surgery for Dupuytren's contracture in probands with and without familial predisposition and depending on maternal and/or paternal inheritance.

	N	Mean age (CI 95%)[3]	Difference[1] (CI 95%)[3]	P-value[2] (vs. non-familial)	P-value[2] (vs. maternal line)	P-value[2] (vs. paternal line)
All patients	736			x	x	x
Non-familial	458	61.1 (60.0-62.2)		x	x	x
Familial	268	55.9 (54.4-57.4)	5.2 (2.7-7.7)	6.69E-08	x	x
Both parental lines	10	47.9 (40.4-55.4)	13.2 (4.6-21.8)	2.30E-03	x	x
Women	119[a]			x	x	x
Non-familial	71	62.9 (60.3-65.5)		x	x	x
Familial	48	58.8 (55.5-62.1)	4.1 (-1.8-10.0)	0.059	x	x
Maternal line	16	61.9 (57.3-66.5)		x	x	x
Paternal line	21	54.8 (49.2-60.4)	7.1 (-3.2-17.4)	x	0.073	x
Line unknown	11	61.9 (56.6-67.2)	0 (-9.9-9.9)	x	0.882	0.108
Men	607[a]			x	x	x
Non-familial	387	60.8 (59.6-62.0)		x	x	x
Familial	220	55.3 (53.7-56.9)	5.5 (2.7-8.3)	2.01E-07	x	x
Maternal line	63	54.5 (51.2-57.8)		x	x	x
Paternal line	108	55.0 (52.7-57.3)	0.5 (-6.1-5.1)	x	0.917	x
Line unknown	49	56.9 (53.9-59.9)	2.4 (-8.7-3.9)	x	0.387	0.312

[a] Probands with both parental lines affected were not included in the analyses considering women and men separately.

[1] The age difference is given in years.

[2] P-values are those of Mann-Whitney U test.

[3] CI – confidence interval.

Table 4.

Smoking behaviour of probands with Dupuytren's disease.

	N	Mean age at first surgery (CI 95%)[1]	P-value[2]
Positive family history	278		x
Non-smokers	169	55.62 (53.70-57.54)	x
All smokers	109	55.60 (53.41-57.78)	0.6045
Number of cigarettes unknown	21	59.52 (55.46-63.59)	x
Less than 5 cigarettes/day	22	58.18 (53.54-62.82)	x
Less than 20 cigarettes/day	39	53.87 (50.10-57.64)	x
More than 20 cigarettes/day	27	52.93 (48.46-57.39)	x
No positive family history	458		x
Non-smokers	236	62.67 (61.29-64.04)	x
All smokers	222	59.27 (57.66-60.88)	0.006748
Number of cigarettes unknown	43	60.69 (57.01-64.37)	x
Less than 5 cigarettes/day	37	58.89 (55.22-62.56)	x
Less than 20 cigarettes/day	88	58.84 (56.11-61.57)	x
More than 20 cigarettes/day	54	59.13 (56.12-62.14)	x

[1] CI – confidence interval.

[2] P-values are those of Mann-Whitney U test.