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Short Report

The importance of genetic susceptibility in Dupuytren's disease

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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. We have collected clinical data from 736 unrelated individuals with DD who underwent surgical treatment from Germany and Switzerland. We evaluated a standardised questionnaire, assessed the importance of different risk factors and compared subgroups with and without positive family history. We found that family history clearly had the strongest influence on the age at first surgery compared to environmental factors, followed by male sex. Participants with a positive family history were on average 55.9 years of age at the first surgical intervention, 5.2 years younger than probands without known family history ($p = 6.7 \times 10^{-8}$). The percentage of familial cases decreased with age of onset from 55% in the 40–49 years old 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.

Conflict of interest

The authors have declared no conflict of interest.

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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 and 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. The prevalence of DD is around 4% in England (1) and 2.5% in Germany (2), and it increases drastically with age (3–5).

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 (6–9). Reports also said that DD was common among diabetes mellitus type 2 patients but they may be in general less severely affected (10).

Frequent familial occurrence of DD indicates a genetic basis for the disease. A recent whole genome association study identified nine genetic susceptibility loci for DD (11). DD most likely has a complex genetic basis, where different genetic risk loci contribute to disease susceptibility (12). 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 large case study individuals undergoing surgery for DD were recruited through the hand surgery departments of nine hospitals distributed over Germany and one in Switzerland. Some probands were recruited through the collaboration with the German patient support group. Participants provided written informed consent, with institutional review board approval. All subjects were informed about the importance of family history but probands were not selected on the basis of their family predisposition.

Each participant completed a standardised, 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).

Probands 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. Few probands participated in the study but did not undergo surgery.

Statistical methods

The age at first surgery is assumed 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 performed with Microsoft Excel®. Associations in single tests were considered significant if the p-value was <0.05.

Results

Age at surgery

The questionnaire was completed between 2007 and 2012 by 801 unrelated individuals with DD [639 from Germany, 162 (20.2%) from Switzerland]. One hundred and thirty-two (19.1%) were women, giving an overall male/female ratio of 4.6:1. 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 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 88.7% of these cases a parent was affected. We then compared the two groups of subjects with and without positive family history for the presence of ectopic lesions, bilateral affection status and recurrence of disease (Table 2). In addition,

Table 1. Age distribution of first surgery in Dupuytren's disease. The ages are summarised for male and female probands in various age groups represented in the study

	All	Men	Women		Familial cases	
Years of age	*n*	*n*	*n*	Gender ratio	*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. Features of Dupuytren's disease and association of risk factors with positive family history

	Probands with positive family history		Probands without positive family history			
	n (%)	*n* total	*n* (%)	*n* total	p-value[g]	Odds ratio (95% CI)
Women	61 (19.9)	306	82 (16.6)	495	0.226	1.25 (0.87–1.81)
Ectopic manifestations	65 (22.0)	296[d]	35 (7.1)	495	1.08E – 09	3.70 (2.38–5.74)
Knuckle pads	33 (11.2)	296[d]	25 (5.1)	495	1.45E – 03	2.36 (1.37–4.05)
Ledderhose	27 (9.1)	296[d]	10 (2.0)	495	4.71E – 06	4.87 (2.32–10.21)
Others[a]	5 (1.7)	296[d]	0 (0)	495	7.18E – 03	x
Both hands affected	170 (59.7)	285[e]	214 (44.5)	481[e]	5.00E – 05	1.84 (1.37–2.48)
Recurrence[b]	96 (32.4)	296[d]	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[c]	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[f]	46 (17.0)	271[f]	0.050	1.58 (1.00–2.51)

CI, confidence interval.
[a]Others: one proband with frozen shoulder; four probands did not specify type of ectopic manifestation.
[b]Recurrence: probands had previous surgeries at same hand (two or more surgeries at same hand).
[c]Former and current smokers.
[d]Probands with positive family history (excl. 10 probands with both parental lines affected).
[e]Probands who reported the affected hand(s).
[f]Probands who stated their profession.
[g]p-values are those of χ^2 test; for other ectopic manifestations and rheumatoid arthritis we used Fisher´s exact test.

we collected a severity score for all probands based on the disease staging of Tubiana (13). 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)].

Participants 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 (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. In total, we found 19.1% current smokers, 25.8% former smokers, and 54.9% non-smokers in our study. 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 at first surgery. When cases were divided into probands with and without familial predisposition the age difference between smokers and

Table 3. Mean ages at first surgery for Dupuytren's contracture in probands with and without positive family history and depending on maternal and/or paternal inheritance

	n	Mean age (CI 95%)	Difference (years) (CI 95%)	p-value[a] (*vs* non-familial)	p-value[a] (*vs* maternal line)	p-value[a] (*vs* paternal line)
All probands	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[b]			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 to 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 to 17.4)	x	0.073	x
Line unknown	11	61.9 (56.6–67.2)	0 (−9.9 to 9.9)	x	0.882	0.108
Men	607[b]			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 to 5.1)	x	0.917	x
Line unknown	49	56.9 (53.9–59.9)	2.4 (−8.7 to 3.9)	x	0.387	0.312

CI, confidence interval.
[a]*p*-values are those of Mann–Whitney *U* test.
[b]Probands with both parental lines affected were not included in the analyses considering women and men separately.

non-smokers was more pronounced in participants without familial predisposition and not seen in the group with familial predisposition (Table S1, Supporting information).

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.

Discussion

DD is a common genetic disorder with a strong increase of prevalence in persons over 50 years of age. Although several epidemiological studies of DD have been conducted, the contribution of genetic predisposition and environmental risk factors remains mostly unclear. We have therefore studied risk factors in a large case series of individuals with DD seeking surgical treatment.

We have compared mainly two groups of DD cases: the first group includes all individuals with a known family history and the second group consists of all participants for whom a family history was not noted. The ratio of cases with positive family history was 38.2% in our study and between 12.5% and 44% in other studies (1, 2, 14–16). It is still possible that the actual rate is underestimated: Ling showed 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 (17). The first group predominantly included subjects who had an affected parent, and the disease appears to be transmitted in a dominant mode of inheritance, at least in two generations. Thus the group with positive family history encompasses individuals who carry genetic factors that strongly contribute to the disease; we probably miss individuals who carry weaker genetic risk factors that do not result in an evident family history. The second group contained individuals in whom a family history was overlooked or could not be determined because the disease may be caused predominantly by environmental factors such as heavy manual work, trauma, or drug intake.

In both groups genetic and environmental factors are supposed to interact to cause the disease in each individual. We found that participants with both parents affected have an even lower mean age of first surgery than participants with one parental line affected. Accordingly, genetic factors might act additively and the inheritance of DD is oligogenic. Many studies that link the disease to non-genetic factors were enriched in cases with an exposition to environmental factors, for instance in epilepsy patients or patients with diseases resulting from alcohol abuse (6, 7, 18–21). In line with our findings, more recent studies identified a minor effect of epilepsy or alcoholism on the manifestation of DD.

In all age classes, more men than women were recruited and the male-to-female ratio was highest in 40- to 49-year-old probands, underlining that men are earlier referred to surgery. 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 with a low incidence of surgical intervention (16). These differences could indicate that the course of disease is different in affected females resulting in a less frequent need for surgery (16, 22).

Heavy smoking may be a risk factor for DD. A significant correlation between heavy smoking and the occurrence of DD was seen in the majority of cohort or case/control studies (6–8, 21, 23). The number of cases in our subgroups are still rather small to identify modifying effects but we assume that smoking modulates the disease and has a different contribution in cases with and without a strong genetic basis. Similarly, other environmental risk factors appeared to be more effective in cases without a positive family history, pointing to environmental factors as additional, independent risk factors.

In summary, our findings show that genetic predisposition indicated by positive family history is the most prominent risk factor for DD that needs surgical intervention. Individuals with positive family history require earlier surgery and have more often ectopic lesions. Consistent with the complex genetic basis for DD, probands with affected family members in both parental lines needed earlier treatment, and environmental risk factors played a larger role in cases with a negative family history.

Supporting Information

The following Supporting information is available for this article:

Tables S1. Smoking behaviour of probands with Dupuytren's disease

Additional Supporting information may be found in the online version of this article.

Acknowledgements

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Supplementary Tables

Supplementary Table 1.

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.

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.