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Disease Course of Primary Dupuytren Disease: 5-Year Results of a Prospective Cohort Study

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Background: Predicting progression of Dupuytren disease becomes relevant in an upcoming era with progression-preventing treatment. This study aimed to determine the course of Dupuytren disease and identify factors associated with progression.

Methods: Two hundred fifty-eight patients with Dupuytren disease participated in this prospective cohort study, obtaining 17,645 observations in 5 years. Outcomes were disease extent (surface area) and contracture severity (total passive extension deficit). Demographics, lifestyle, health status, exposure to manual work, and genetic risk scores were gathered as potential predictors. Subject-specific, mixed-effects models were used to estimate disease course, and logistic regression with least absolute shrinkage and selection operator was used to evaluate factors associated with the presence of progression.

Results: On average, Dupuytren disease was progressive in all finger rays with regard to area [yearly increase, 0.07 cm^2 (95% CI, 0.02 to 0.13 cm^2) to 0.25 cm^2 (95% CI, 0.11 to 0.39 cm^2)]. Progression in total passive extension deficit was only present on the small finger side [yearly increase, 1.75 degrees (95% CI, 0.30 to 3.20 degrees) to 6.25 degrees (95% CI, 2.81 to 9.69 degrees)]. Stability or regression in area and total passive extension deficit was observed in 11 and 13 percent and 16 and 15 percent (dominant and nondominant hands), respectively. Smoking, cancer, genetic risk score, and hand injury were univariate associated with progression in area, but after multivariate variable selection, none of these associations remained. No predictors for progression in total passive extension deficit were found.

Conclusions: Dupuytren disease is progressive, especially with respect to disease extent. Progression in contracture severity is mainly present on the small finger side of the hand. None of the traditional risk and diathesis factors were associated with progression, indicating that new hypotheses about Dupuytren disease progression might be needed. (*Plast. Reconstr. Surg.* 149: 1371, 2022.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, III.

Dupuytren disease, with its prevalence ranging between 1 and 32 percent in the general population,[1] is the most common organ-specific fibrosis.[2] It has been associated with chronic diseases, such as diabetes mellitus,[3] but also with an increased risk of mortality due to several diseases, including cancer and cardiovascular and respiratory disease.[4–7]

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From a clinical point of view, it is often thought that Dupuytren disease is progressive. This is underlined by findings of lab studies indicating that disease extension and contracture formation is a self-propagating process.[8–10] The few studies evaluating natural course of Dupuytren disease, however, consistently show that the minority of the patients has progression.[11–14] The interpretation of these findings is hampered by the fact that progression is only presented as the percentage of hands progressing to a next disease stage.[11,12] Furthermore, previous studies often have only two measurements, making it impossible to determine the exact disease course profile.[13,14] Most importantly, none of the previous studies was aimed to identify predictors for a progressive disease course.

Precise knowledge about the disease course is important to gain insight in the development of the disease, to provide patients with evidence-based information during counseling, and to facilitate the timing of treatment. In addition, finding factors that predict progression helps to identify the subpopulation at highest risk of progression. This has become increasingly relevant, as recent scientific breakthroughs have resulted in the development of a potential treatment for preventing Dupuytren disease progression.[10,15] This treatment is costly and not fully without risks, however,[16,17] which demonstrates the urgency of being able to identify the target population who will benefit from future treatment aimed at preventing progression, and thereby limiting patient and economic burdens related to unnecessary treatment in those with nonprogressive disease.

This study was conducted to answer the following research questions: (1) What is the average and individual long-term natural course of Dupuytren disease? (2) What factors are associated with progression?

PATIENTS AND METHODS

Design

In this prospective cohort study, measurements took place with an interval of 6 months. Data gathered between May of 2012 and August of 2017 were included in this analysis.

Participants

A total of 462 adult patients who had primary (i.e., untreated) Dupuytren disease in one or both hands were asked to participate. Untreated hands of patients who were unilaterally treated were also eligible for inclusion. Participants were recruited from two sources: (1) a random age-stratified sample of the general elderly population of the city of Groningen (The Netherlands) who had been included in a previous study of our research group ($n = 179$, subclinical population)[18] and (2) patients with Dupuytren disease who visited the outpatient clinic of the Department of Plastic Surgery for a consult on Dupuytren disease ($n = 283$, clinical population). A sample size calculation was not performed as no data are available from comparable studies on long-term disease course. We estimated that, after 5 years, data of 200 participants would be sufficient for statistical analyses. Taking dropout into account, we aimed to include at least 250 participants.

This study was reviewed and approved by the institutional ethics committee of University Medical Center Groningen (METc2011/397) and conducted in accordance with the 1964 Declaration of Helsinki. All participants gave written informed consent.

Outcome Measures

The primary outcome measures were disease extent and severity of contracture. Disease extent was determined by physical examination of the hands, in which the nodules and cords were marked on the skin with a skin pencil. We used the surface area of nodules and cords measured with a tumorimeter to quantify disease extent,[19] which was summed per ray to obtain total area per ray. Contracture severity was determined by measuring the passive extension deficit (i.e., the inability to passively straighten the finger) of each finger joint, using a goniometer. These extension deficits were summed to obtain total passive extension deficit per finger. Total passive extension deficit was not measured in the thumb, as Dupuytren disease cords in the thumb rarely lead to functional restraints. Contractures of cords in the first web space can lead to functional problems, but this is not captured by measuring total passive extension deficit.

Predictor Variables

Predictor variables of progression were sex, age, age of onset, familial occurrence of Dupuytren disease, (past) exposure to vibration or heavy manual work during occupational or leisure activities, smoking and drinking habits, (past) hand injuries, abnormal scar formation, diabetes mellitus, liver disease, epilepsy, cancer, Ledderhose disease (fibromatosis on the soles of the feet), Peyronie

disease (fibromatosis in the penis), knuckle pads (fibrous masses on the dorsal side of the first finger joints), and weighted genetic risk score. These variables were obtained by an anamnestic interview during all follow-up measurements. In case of doubt about the presence of Ledderhose disease based on anamnesis, the feet were examined. The presence of knuckle pads was also determined by physical examination. A weighted genetic risk score was calculated from DNA derived from blood samples, based on the 26 single nucleotide polymorphisms currently known to be associated with Dupuytren disease,[20] using PLINK software (designed by Shaun Purcell).[21]

Procedures

Data of the first 1.5 years were gathered by the second author (R.L.), while the first author (D.C.B.) gathered data during subsequent visits. An interobserver agreement study was done to evaluate the necessity of adjustment for observer.[19] All measurements were done using the exact same instruments.

Every 6 months, the participants visited the outpatient clinic of the Department of Plastic Surgery for this study. In case the participant was unable to visit the hospital (e.g., due to injuries), the examiner visited the participant at home if possible. Some participants refused to visit the hospital every 6 months, and they were asked to continue participation with a yearly visit to prevent dropout.

Statistical Analysis

Characteristics of the cohort were described using descriptive statistics (i.e., frequencies, percentages, means, standard deviations, medians, and interquartile ranges) for predictors and outcome measures.

Missing values in the outcomes were scarce (89 of 17,645 observations), and most predictor variables had no missing values at all. Self-reported age of onset, weighted genetic risk score, heavy manual work, and hobbies with heavy manual work, however, all showed high proportions of missing values. We decided not to use multiple imputation, as these variables are not likely to be missing at random. These variables were excluded casewise.

Gathered data from dropped-out participants and preoperative data from participants who received treatment during the course of the study were included in the current analyses. The statistical analysis was applied to the surface area of nodules and cords and to the total passive extension deficit separately. These outcomes were summed per ray.

To answer the first research question, we fitted individual, linear trajectories using a subject-specific, mixed-effect model, as no evidence for nonlinearity was observed. Follow-up time was defined per finger ray and outcome separately, starting from the first time at which a clinical symptom was present (area or total passive extension deficit > 0). For the linear trajectories, the logarithm of the intercept (area/total passive extension deficit at baseline) and slope (progression) was considered bivariate normally distributed. We took the intercept lognormal to guarantee a positive area/total passive extension deficit at the first time point at which a clinical symptom was observed. The model was fitted using the NLMIXED procedure (version 9.4; SAS Institute, Inc., Cary, N.C.) The parameter estimates for intercept and slope, the correlation between intercept and slope, and the relative standard deviations are reported. The observations were predicted by the random effects derived from the subject-specific model, using best linear unbiased prediction. This was done to enable the calculation of R^2 values to evaluate how much variability between outcome and predictions is explained by the model, estimated with the GLM procedure (version 9.4; SAS Institute).

To answer the second research question, the observed area and total passive extension deficit were aggregated into observations in the dominant and nondominant hand. We analyzed the association of the baseline covariates with predicted progression (slope being positive or not) obtained from the analysis described above. The baseline covariates included in the model were sex, age, age of onset, smoking (never/ever), alcohol (never/ever), manual work during occupational and leisure activities, vibration, hand injury, Peyronie disease, Ledderhose disease, knuckle pads, abnormal scarring, diabetes, epilepsy, liver disease, cancer, having a first degree relative with Dupuytren disease, and genetic risk score. The latter was included as continuous variable in the model; the other variables were included as dichotomous. We assessed the effect of each covariate on progression separately, but variable selection was done using logistic regression with least absolute shrinkage and selection operator and the Bayesian information criterion on the variables that had a p value less than 0.05 at the variable screening stage. This analysis was done with the HPGENSELECT procedure (version 9.4; SAS Institute).

RESULTS

Of 462 eligible patients, 258 with untreated Dupuytren disease in at least one hand decided to participate; 111 subclinical patients were recruited from the general population, and 147 were recruited from the clinical population. A total of eight and 86 participants of the subclinical and clinical populations, respectively, were already treated in one hand at start of the study, so only their untreated hand was included in this study. Women and patients from the general population were more often willing to participate, compared with men and patients from the clinical population. (**See Table, Supplemental Digital Content 1**, which shows characteristics of the total invited population, comparing participants with nonparticipants, ***http://links.lww.com/PRS/F62***.) A total of 77 dropped out during the study for various reasons (Fig. 1), leaving 181 active participants after 5 years (Table 1).

The sample consisted of 163 men and 95 women, with a mean age of 64.7 ± 10.3 years at inclusion (Table 2). The majority of the participants were smokers or former smokers, and for those, a median of 16.3 pack years (interquartile range, 5.0 to 27.2 pack years) was found. Among the participants who consumed alcohol, a median of seven glasses per week (interquartile range, 2.8 to 13.5 glasses per week) was reported. The median time of follow-up was 4.9 years (interquartile range, 2.4 to 5.0 years), and in this period, 2215 patient examinations were performed.

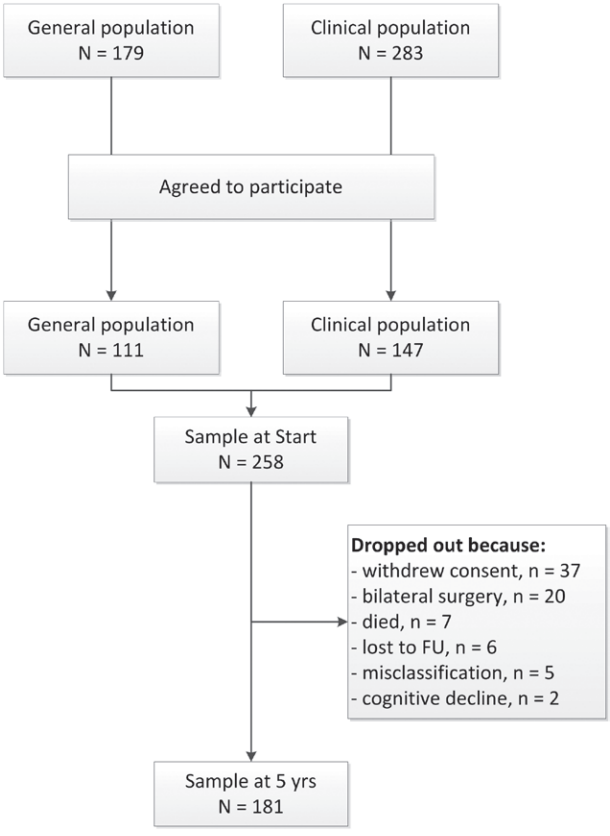

Fig 1. Flow-chart of the study, indicating the number of participants across time and reasons for dropout.

Natural Course of Dupuytren Disease: Area of Nodules and Cords

On average, the area of nodules and cords increased over time in all finger rays of both hands (Table 3). As example, the area of nodules and cords in the right thumb ray increased yearly by 0.23 cm^2 on average. This seems to be only a small increase, but this concerns an increase per year. Over the course of 5 years, surface area in the right thumb ray would increase on average by 1.15 cm^2, which is equivalent to the formation of a new cord with a length of 2.3 cm and width of 0.50 cm. The relatively wide confidence intervals (especially for the right index and left thumb, index, and small fingers) indicate that variability among participants was substantial. The disease extent at start of the study was not correlated to progression (Table 3, correlation), except for the right index finger ray. We observed no large differences in increase in area between the left and right hand, nor between left and right finger rays. In both hands, the ring finger ray was most often affected, followed by the small and middle finger rays. When the surface area of all fingers was summed per hand, we observed a yearly increase of 0.51 cm^2 (95 percent CI, 0.41 to 0.61 cm^2) in the dominant hand and 0.60 cm2 (95 percent CI, 0.49 to 0.72 cm^2) in the nondominant hand. The standard deviation in yearly increase between participants was 0.59 cm^2 (95 percent CI, 0.52 to 0.67 cm^2) in the dominant and 0.75 cm^2 (95 percent CI, 0.66 to 0.85 cm^2) in the nondominant hand, indicating substantial heterogeneity in progression. This is further underlined by the finding that 11.4 and 12.9 percent of the participants did not show an increase or even showed a decrease in area in the dominant and nondominant hand, respectively.

Natural Course of Dupuytren Disease: Total Passive Extension Deficit

We found that, on average, total passive extension deficit increased over time in the right ring finger and the left ring and small fingers (Table 4). In the other fingers, it was stable. It could not be estimated in the index finger

Table 1. Number of Participants and Subjects with Available Data Presented for Each Measurement Time*

	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Follow-up, yr	Start	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Participants, no.	258	252	245	231	218	206	201	196	188	185	181
Available data, no.	258	245	238	224	204	189	191	173	171	169	163

*The number of participants and cases with available data during each measurement time are not equal, since some participants were not able to attend each measurement time. The number of participants with available data is lower at T7 to T10, as not all participants were included at the same time.

because of the small number of participants with index finger contractures. A minority ($n = 126$) of the participants had or developed finger contractures during the course of the study, and among those, total passive extension deficit at start of the study was relatively small. There was no correlation between the total passive extension deficit at start of the study and the yearly increase. Contractures were most often present in the ring and small fingers, and half as often in the middle fingers. The standard deviations in yearly increase among participants ranged between 0.51 degrees (95 percent CI, 0.19 to 1.36 degrees) for the left small finger and 10.10 degrees (95 percent CI, 7.53 to 13.5 degrees) for the left ring finger, again indicating substantial heterogeneity. This is further underlined by the finding that 15.7 and 14.8 percent of the participants did not show a total passive extension deficit increase or even showed a decrease in the dominant and nondominant hands, respectively.

Table 2. Characteristics of the Cohort

	Value (%)	No. Missing (%)
Demographics		
Male sex	163 (63.2)	0 (0.0)
Mean age at inclusion, yr (SD)	64.7 (10.3)	0 (0.0)
Mean self-reported age of onset, yr (SD)	54.4 (11.9)	59 (27.2)
Mean wGRS (SD)*	6.134 (0.837)	34 (13.2)
Hand dominance		1 (0.4)
Left	21 (8.1)	
Right	233 (90.3)	
Bimanual	3 (1.2)	
Intrinsic risk factors		
First degree relative with DD	108 (41.9)	1 (0.4)
Diabetes	29 (11.2)	0 (0.0)
Liver disease	5 (1.9)	0 (0.0)
Epilepsy	3 (1.2)	0 (0.0)
Scarring		1 (0.4)
Normal	250 (96.9)	
Hypertrophic	3 (1.2)	
Keloid	4 (1.6)	
Ledderhose disease	27 (10.5)	0 (0.0)
Peyronie disease (only in men)	13 (8.0)	0 (0.0)
Knuckle pads	86 (33.3)	0 (0.0)
Cancer	5 (1.9)	0 (0.0)
Extrinsic risk factors		
Heavy manual work	102 (39.5)	34 (15.7)
Hobbies with heavy manual work	112 (43.4)	42 (16.3)
Exposure to vibration	173 (67.1)	6 (2.3)
Hand injury	108 (49.8)	5 (2.3)
Smoking status		0 (0.0)
Current	38 (14.7)	
Former	152 (58.9)	
Never	68 (26.4)	
Alcohol consumption		0 (0.0)
Current	215 (83.3)	
Former	11 (4.3)	
Never	32 (12.4)	

wGRS, weighted genetic risk score; DD, Dupuytren disease.
*Natural logarithm of weighted genetic risk score.

Factors Associated with Progression

In the univariate analyses on predictors of progression in disease extent (area), we found that smoking ($p = 0.010$), cancer ($p = 0.045$), and the weighted genetic risk score ($p = 0.024$) were associated with progression in the dominant hand. In the nondominant hand, ipsilateral hand injury ($p < 0.001$) was associated with progression. For total passive extension deficit in both hands, no associations were identified. After applying variable selection (multivariate analysis), no covariates were found to contribute to progression of area or total passive extension deficit in either hand. This indicates that the associations found are no strong predictors of progression.

DISCUSSION

Primary Findings

This study demonstrated that Dupuytren disease is progressive, especially with respect to disease extent (area). Progression in contracture severity (total passive extension deficit) is mainly present on the small finger side of hand. There was substantial heterogeneity among participants, with some having severe progression and also some who had stable or regressive disease in both area and total passive extension deficit. Surprisingly, we found no variables that predicted presence of progression after applying variable selection methods.

Findings in Relation to Literature

Our results on progression seem not to be in line with previous reports indicating that only 37

Table 3. Parameter Estimates and Model Fit of the Subject-Specific Model Examining the Surface Area at Start of the Study, Increase in Area over Time, and the Correlation between These Two Aspects*

Area	No. of Fingers	(A) Disease Extent at Start (cm^2)	(B) Yearly Increase (cm^2)	Correlation A – B	R^2
Right					
Thumb	85	0.91 (0.77; 1.08)	0.23 (0.15; 0.31)	0.18 (–0.19; 0.55)	84.8
Index	48	0.52 (0.35; 0.78)	0.13 (0.02; 0.24)	–0.52 (–0.91; -0.13)	86.0
Middle	121	0.90 (0.80; 1.02)	0.07 (0.02; 0.13)	0.13 (–0.09; 0.35)	90.5
Ring	163	1.44 (1.29; 1.60)	0.13 (0.08; 0.17)	0.10 (–0.09; 0.30)	90.5
Small	130	0.95 (0.81; 1.12)	0.17 (0.11; 0.23)	0.08 (–0.15; 0.31)	90.4
Left					
Thumb	98	0.86 (0.74; 1.00)	0.20 (0.13; 0.28)	–0.10 (–0.40; 0.19)	87.0
Index	40	0.56 (0.35; 0.91)	0.25 (0.11; 0.39)	0.38 (–0.04; 0.80)	94.2
Middle	134	0.90 (0.77; 1.04)	0.07 (0.02; 0.13)	–0.15 (–0.39; 0.09)	89.2
Ring	168	1.31 (1.15; 1.50)	0.17 (0.12; 0.22)	0.12 (–0.09; 0.33)	92.6
Small	138	0.97 (0.79; 1.17)	0.19 (0.09; 0.28)	–0.13 (–0.35; 0.08)	93.7

A, Disease extent at start (cm^2); *B*, yearly increase (cm^2); R^2, model fit.
*Data are expressed as value (95% confidence interval).

Table 4. Parameter Estimates and Model Fit of the Subject-Specific Model Examining the Total Passive Extension Deficit at Start of the Study, Increase in Total Passive Extension Deficit Over Time, and the Correlation between These Two Aspects*

TPED	No. of Fingers	(A) TPED at Start†	(B) Yearly Increase†	Correlation A – B	R^2
Right					
Middle	32	9.97 (6.45; 12.5)	1.25 (–0.65; 3.15)	–0.11 (–0.80; 0.58)	84.0
Ring	65	7.03 (5.01; 9.88)	4.59 (2.74; 6.45)	0.05 (–0.31; 0.42)	92.0
Small	57	10.1 (6.49; 15.6)	2.12 (–0.02; 4.26)	1.00 (NA; NA)	89.1
Left					
Middle	32	10.6 (7.34; 15.4)	–0.21 (–3.09; 2.67)	0.73 (0.34; 1.00)	90.7
Ring	60	7.19 (4.74; 10.9)	6.25 (2.81; 9.69)	0.38 (–0.09; 0.84)	85.8
Small	57	15.7 (11.2; 22.2)	1.75 (0.30; 3.20)	0.27 (–0.26; 0.81)	91.1

A, TPED at start; *B*, yearly increase; TPED, total passive extension deficit; R^2, model fit.
*Estimates at 95 percent confidence interval.
†Measured in degrees.

to 51 percent of the Dupuytren disease patients experience progression.[11,13,14] For individual progression, we showed that 84 to 89 percent of the participants had progression. However, if we apply a staging system similar to that of the cited studies, we would report a progression rate of 26 percent after 5 years of follow-up. Note that the duration of follow-up was different in the previous studies, and that two of the previous studies reported progression in a clinical population only,[11,14] possibly explaining the difference in progression rates.

The published interim analysis of this study showed that 44 to 95 percent of the participants did not have progression.[22] The difference with the current findings can be explained by the longer follow-up time, increasing the chance to capture progression.

To our surprise, we found that none of the Dupuytren disease risk factors reported in the literature were identified as predictors for progression. This indicates that risk factors for getting the disease are not prognostic of disease course. What surprised us even more was that none of the previously reported Dupuytren disease diathesis factors we evaluated (e.g., familial occurrence of Dupuytren disease, ectopic lesions, early age of onset, male sex)[23,24] were identified as predictors of progression in our cohort, although it is often suggested that patients having diathesis characteristics will have a rapidly progressive disease course. This might be related to a difference in definition of progression. In our study, every participant who had a positive yearly increase in area/total passive extension deficit was labelled as having progression. Other studies used recurrence after treatment as definition for progression,[24,25] thereby including a different part of the disease spectrum. Furthermore, by including only clinical populations, these previous studies may represent possible bias. Our study shows, based on a mixture of subclinical and clinical patients, that these variables are not strongly associated, indicating that subclinical patients share diathesis characteristics with clinical patients. Furthermore, Dupuytren disease diathesis factors were not associated with the histological staging,[26] partly confirming our results. Nevertheless, new biological and medical hypotheses should be posed, and subsequent

research should be conducted to help understand Dupuytren disease progression better.

Strengths and Limitations

We were able to describe the year-to-year disease course of Dupuytren disease. The prospective nature of this study limits the chance of missing values, which is often a problem in retrospective database or patient file studies. In addition, the frequent follow-up measurements enabled a reliable estimation of the exact disease course (R^2, 87.0 to 94.2 percent for area, 84.0 to 92.0 percent for total passive extension deficit).

Another strength is that we used area of nodules and cords to measure disease extent. In contrast to previous studies that recorded outcomes such as "progression to bilateral disease," "progression from nodules to cords" or defined progression as a change in disease stage,[11–14] we were able to quantify disease extent and thereby follow the disease course in participants with mild disease, without contractures. It should be noted, however, that area of nodules and cords has no clinical relevance, as patients are usually referred to the plastic surgeon when contractures are present.

Although measurement bias might have occurred when data collection was taken over by another observer, we performed an agreement study to determine whether the analyses required adjustment for this.[19] Acceptable to high intraclass correlations were obtained, so it is unlikely that measurement bias played a large role in determining area and total passive extension deficit. Recall bias might have occurred in determining the risk factors, however, as this was gathered anamnestically. It is therefore likely that Peyronie disease has been underreported in our study, as physical examination of the genital area was not part of the data collection.

Dropouts may have introduced selection bias, as it is possible that participants with mild Dupuytren disease were less motivated to continue long-term participation. Although we had several strategies to prevent dropout, a substantial number of participants (n = 37) still quit participation. However, we observed no differences in baseline disease extent and total passive extension deficit between those who quit participation versus those who were still participating. Selection bias did occur, however, because of severe disease progression, as postoperative data of participants who developed severe contractures were excluded from the current analyses because after treatment we could no longer observe the natural course. Furthermore, participants who dropped out were older and more often women than those who continued to participate (**see Table, Supplemental Digital Content 1**, ***http://links.lww.com/PRS/F62***).

Relevance of the Findings and Future Perspectives

We found that Dupuytren disease is progressive, but the speed of progression varies. More importantly, none of the factors that we assessed were strongly predictive of disease progression. This indicates that, when preventive treatments will be applied in the future, the Dupuytren disease diathesis factors may not be that important for selecting eligible patients. Our findings also show that we have a limited understanding of which patients will experience progression and that we need new hypotheses about disease progression. Future research should focus on this, making use of existing population-based cohort studies, as population stratification will soon become relevant when treatment preventing progression becomes available.

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