SCIENTIFIC ARTICLE

Dupuytren Diathesis and Genetic Risk

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Purpose Dupuytren disease (DD) is a benign fibrosing disorder of the hand and fingers. Recently, we identified 9 single nucleotide polymorphisms (SNPs) associated with DD in a genome-wide association study. These SNPs can be used to calculate a genetic risk score for DD. The aim of this study was to test whether certain clinical characteristics (including the DD diathesis features) of patients with DD are associated with a high genetic risk score.

Methods Between 2007 and 2010, we prospectively invited all DD patients (1,120 in total) to participate. Clinical characteristics were noted using patient- and doctor-completed questionnaires, and blood was obtained for DNA analysis. We analyzed a total of 933 subjects with genetic and clinical data. The 9 previously identified DD SNPs were used to calculate a weighted genetic risk score. Patients were categorized into high and low genetic risk score groups, according to their weighted genetic risk score. Logistic regression was performed to study the association of clinical characteristics with a high genetic risk score.

Results In a univariate regression model, patients with an age of onset of DD younger than 50 years, a family history positive for DD, knuckle pads, and Ledderhose disease were statistically significantly associated with a high genetic risk score. In an additional analysis using high and low genetic risk groups that deviate further from the median, Ledderhose disease was no longer significantly associated with DD.

Conclusions Patients with DD who present with these diathesis features, and predominantly patients with knuckle pads, are more likely to carry more risk alleles for the discovered DD SNPs than patients without these diathesis features.

Clinical relevance These markers may prove useful in predicting disease progression or recurrence.

Key words Dupuytren diathesis, Dupuytren disease, Dupuytren contracture, genetics, genetic risk score.

DUPUYTREN DISEASE (DD) is a benign fibrosing disorder of the palmar fascias of the hand and fingers leading to the formation of nodules and cords. Often these cords contract, causing flexion contractures of the fingers. The prevalence of DD has been reported to vary between 0.2 and 56%.[1] The prevalence of DD rises with increasing age,[2] and DD is found most frequently in white males.[3] Standard treatment consists of collagenase injection and percutaneous division or surgical excision of the nodules and cords.[4,5] At present, the disease is incurable and recurrence rates following treatment vary from 8% to 66%, depending on

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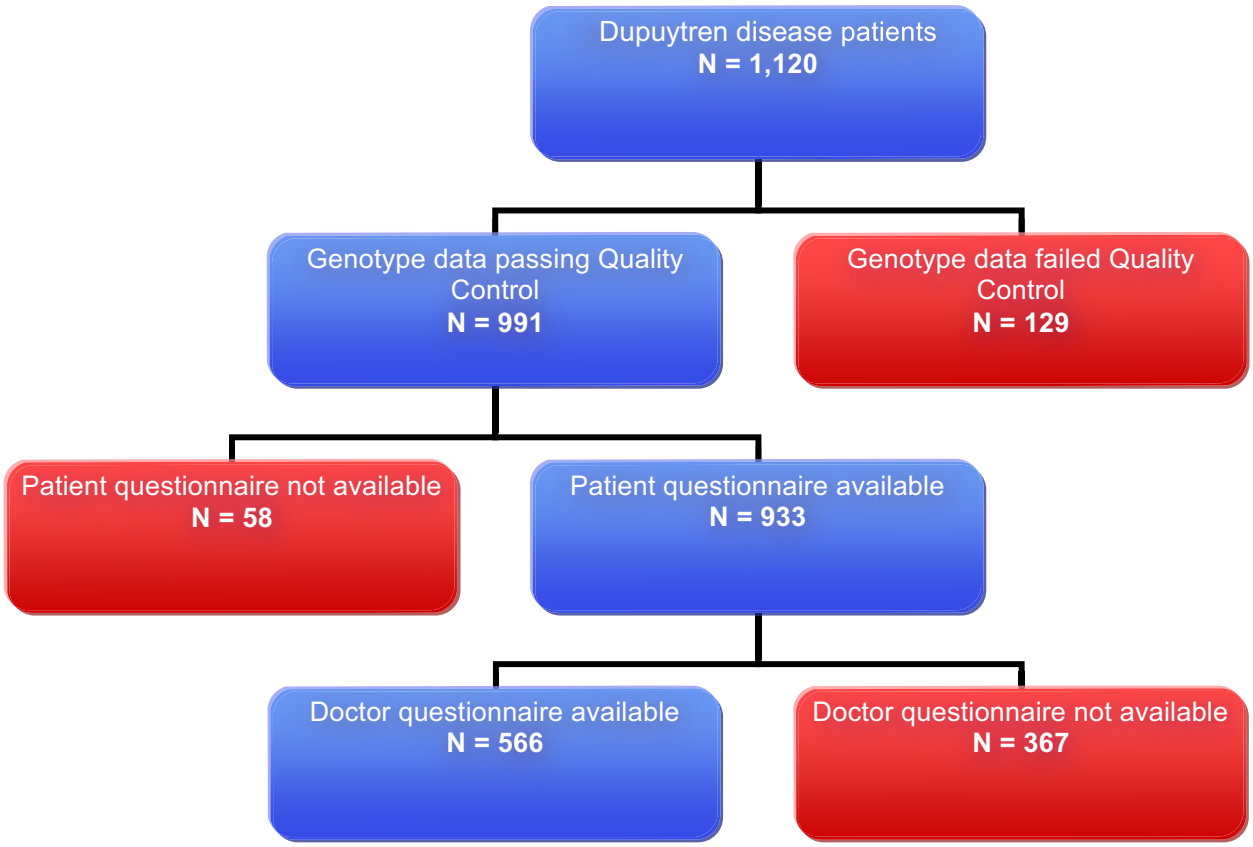

FIGURE 1: Inclusion flow chart.

the treatment modality and definition of recurrence.[5–7] DD is associated with several environmental factors, such as alcohol consumption, smoking, and antiepileptic drug use, as well as with diseases such as diabetes mellitus and liver disease.[8]

The way DD develops varies over time. Some clinical characteristics of patients with DD are related to a more aggressive course of the disease or diathesis. In 1963, Hueston[9] postulated the idea of a DD diathesis and described 4 factors defining this subset of disease: early onset of disease, bilateral involvement, positive family history, and the presence of ectopic lesions (knuckle pads, Ledderhose disease, and Peyronie disease). In 2006, male sex as a diathesis factor was added, "early onset of disease" was refined to age of onset younger than 50 years, and the ectopic lesions were restricted to the presence of knuckle pads only.[2] Features of the DD diathesis were used also in a scoring system by Abe et al.[10] in 2004 to evaluate the risk of recurrence and extension of DD for a Japanese population, implicating a more aggressive course of the disease. These authors suggested the addition of radial side involvement and little finger involvement to the diathesis scoring list.

The clustering of DD in families has long been recognized and most genetic studies have reported an autosomal dominant inheritance pattern.[11,12] Recently, we suggested that DD is a complex genetic disorder, in which several genetic and environmental risk factors are involved, each contributing to disease susceptibility.[13] Nine SNPs associated with DD were identified in a 2-stage genome-wide association study in 2,325 DD patients and 11,562 population controls. These SNPs represent the presently known genetic DD profile and can be used to calculate a genetic risk score for DD in each patient; the more risk alleles a patient carries, the higher the genetic risk score will be for that patient.[14]

We hypothesized that there is an association between certain clinical characteristics and the genetic risk score of patients with DD. Therefore, the aim of this study was to test whether clinical characteristics (including the diathesis features) of DD patients are associated with a high genetic risk score.

MATERIALS AND METHODS

Between 2007 and 2010, we prospectively invited all patients evaluated for a diagnosis of DD at the outpatient clinics of the plastic surgery departments of 6

TABLE 1. Relevant Clinical Characteristics, Patient's Questionnaire (N = 933)

Clinical Characteristics	Full Group n (%)	Doctor's Questionnaire Present n = 566 (%)	Doctor's Questionnaire Absent n = 367 (%)	Chi-square
Sex				
Male	711 (76)	421 (74)	290 (79)	$P = .104$
Female	222 (24)	145 (26)	77 (21)	
Age of onset (y)				
< 50	355 (39)	208 (37)	147 (41)	$P = .251$
≥ 50	561 (61)	350 (63)	211 (59)	
Family history for DD				
Positive	461 (50)	270 (48)	191 (52)	$P = .208$
Negative	468 (50)	293 (52)	175 (48)	

DD, Dupuytren disease.

hospitals in the Netherlands to participate. In this period, a total of 1,120 patients gave their consent (see flow chart, Figure 1). Patients were diagnosed by plastic surgeons with substantial clinical experience in treating DD. The diagnosis was based on the presence of characteristic nodules and/or cords in the palm of the hand and/or digits, with or without contracture of the digits. Written informed consent was acquired from all patients, with institutional review board approval. Patients were asked to complete a questionnaire inquiring about details concerning their clinical characteristics including age of onset, familial involvement, level of education, hand labor, medical history, and medications. A positive family history was defined as the presence of at least 1 other affected family member as noted by the patient. For 58 patients, the patient's questionnaire was not available (Figure 1). The plastic surgeons completed a separate questionnaire on the clinical characteristics of these patients, including passive extension deficits in metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints, unilateral or bilateral disease, the number of rays involved, and the presence of ectopic deposits (knuckle pads, Ledderhose disease, and Peyronie disease). For 367 patients, the doctor's questionnaire was not available (Figure 1). We did not collect clinical data concerning radial side involvement and little finger involvement as used in the scoring system by Abe et al.[10] Blood was obtained from all patients for DNA analysis.

TABLE 2. Relevant Clinical Characteristics, Doctor's Questionnaire (N = 566)

Clinical Characteristics	N (%)
Number of affected rays	
< 3	390 (74)
≥ 3	139 (26)
Total passive extension deficit	
< 45°	298 (54)
≥ 45°	253 (46)
Knuckle pads present	
Yes	82 (15)
No	465 (85)
Ledderhose disease present	
Yes	72 (13)
No	475 (87)
Peyronie disease present	
Yes	22 (4)
No	339 (60)
Bilateral involvement	
Yes	330 (59)
No	226 (41)

Genetic and statistical analysis

Details about genotyping and quality control steps have been described previously.[13] One hundred twenty-nine DNA-samples did not pass standard quality control and were excluded from further analysis (Figure 1). The 9 SNPs that were found to be associated with DD were at an individual basis used to calculate a weighted genetic risk score (wGRS).

The wGRS of each patient was calculated by multiplying the number of risk alleles per SNP by the weight for that SNP, taking the sum across the SNPs, and

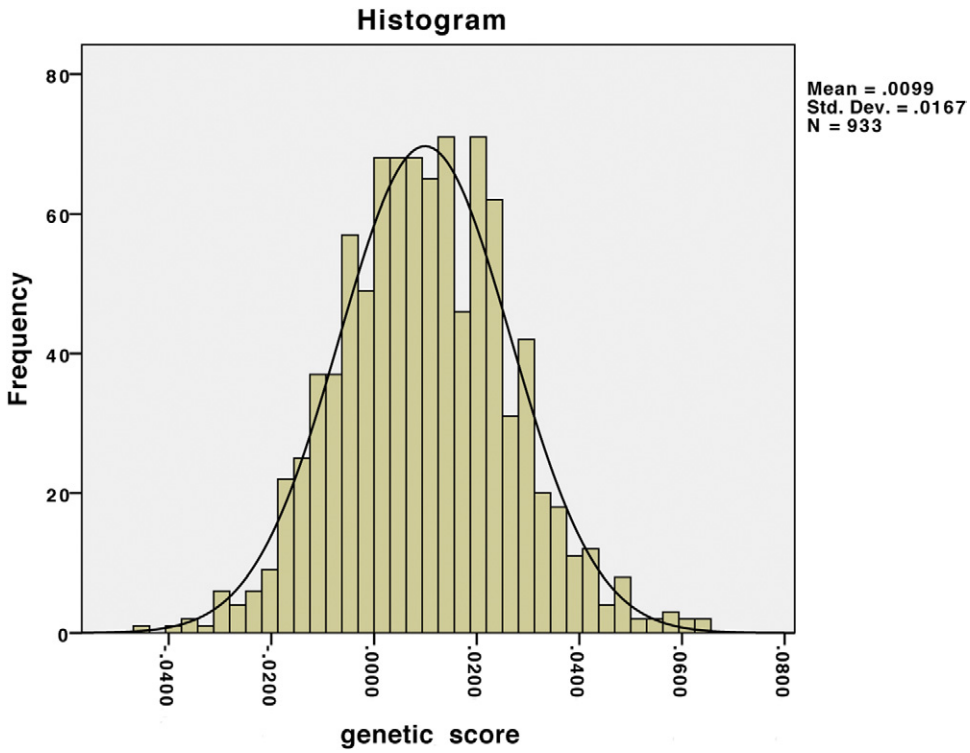

FIGURE 2: Histogram of genetic risk scores.

dividing this number by the 9 SNPs according to the following formula:

$$\text{wGRS} = \frac{\sum_{i=1}^{n} w_i X_i}{n}$$

where i is the SNP, n is the number of SNPs, w_i is the weight for SNP i, and X_i is the number of risk alleles. The natural log of the odds ratio (OR) for each allele was used for the weight. For this wGRS calculation, PLINK software (version 1.07),[15] a tool set for genetic analysis, was used.

The more risk alleles that are carried by a patient, the higher the wGRS. The wGRS scores were primarily divided in 2 categories (low and high score), where all scores below the median were considered as low score and all the scores equal to or higher than the median were considered as high score. An additional analysis was performed in which the groups were subdivided into categories that deviated further from the median. The low genetic risk score group was defined as a wGRS lower than 1 standard deviation (SD) from the median and the high genetic risk score group as a wGRS higher than 1 SD from the median. These categories were designed arbitrarily.

All data were transcribed categorically by using binary variables. Because the doctor's questionnaire was not available for all patients, a chi-square test was used to compare the patient groups with and without a doctor's questionnaire. We thereafter performed univariate logistic regression to study the association of clinical characteristics with the presence of a high genetic score and calculated ORs and 95% confidence intervals. $P < .05$ was considered as statistically significant.

TABLE 3. Prediction of Characteristics, Patient's Questionnaire, on High Genetic Risk Score Using a Univariate Logistic Regression Analysis

Variable	OR	95% CI	*P*
Sex			
Male	1.28	0.94–1.73	.11
Female	1		
Age of onset			
< 50	1.35	1.04–1.77	.03
≥ 50	1		
Family history for DD			
Positive	1.58	1.22–2.04	.001
Negative	1		

CI, confidence interval; DD, Dupuytren disease; OR, odds ratio.

TABLE 4. Prediction of Characteristics, Doctor's Questionnaire, on High Genetic Risk Score Using a Univariate Logistic Regression Analysis

Variable	OR	95% CI	*P*
Number of affected rays			
≥ 3	0.87	0.59–1.28	.47
< 3	1		
Total passive extension deficit			
≥ 45 °	1.22	0.87–1.71	.24
< 45 °	1		
Knuckle pads present			
Yes	1.95	1.20–3.18	.01
No	1		
Ledderhose disease present			
Yes	1.66	1.00–2.76	.05
No	1		
Peyronie disease present			
Yes	1.26	0.53–3.03	.60
No	1		
Bilateral involvement			
Yes	1.29	0.92–1.80	.15
No	1		

CI, confidence interval; OR, odds ratio.

TABLE 5. Prediction of the Significant Diathesis Features on High Genetic Risk Score in an Additional Analysis Using Univariate Logistic Regression*

Variable	OR	95% CI	*P*
Age of onset			
< 50	1.92	1.18–3.12	.009
≥ 50	1		
Family history for DD			
Positive	1.92	1.20–3.10	.007
Negative	1		
Knuckle pads present			
Yes	4.40	1.76–10.98	.001
No	1		
Ledderhose disease present			
Yes	1.44	0.59–3.51	.42
No	1		

CI, confidence interval; OR, odds ratio.
*For this additional analysis, the low genetic risk score group was defined as a wGRS lower than 1 SD from the median and the high genetic risk score group as a wGRS higher than 1 SD from the median.

RESULTS

An overview of the clinical characteristics noted in the patient's and doctor's questionnaires is shown in Table 1 and Table 2, respectively. Of the 933 patients who completed the patient's questionnaire, 711 (76%) were male and 222 (24%) were female. There were no differences in the frequencies of clinical characteristics between the patients with or without a completed doctor's questionnaire (Table 1).

The median wGRS of the 933 patients was 0.009 (ranging from −0.044 to 0.064; see also Fig. 2). Based on the wGRS, 461 patients were below the median and classified as the low genetic risk score group (including 282 patients with a completed doctor's questionnaire), and 472 patients were above the median and classified as the high genetic risk score group (including 284 patients with a completed doctor's questionnaire).

The OR of having a high genetic risk score were significantly greater in patients with an age of onset of DD Younger than 50 years of age, a family history positive for DD, knuckle pads, and Ledderhose disease (Tables 3 and 4). An additional analysis was performed, in which the low genetic risk score group was defined as a wGRS lower than 1 SD from the median and the high genetic risk score group as a wGRS higher than 1 SD from the median. Age of onset of DD younger than 50 years of age, a family history positive for DD, and knuckle pads significantly predicted a high genetic score in this additional analysis (Table 5).

DISCUSSION

The goal of this study was to test whether selected clinical characteristics of patients with DD were associated with a high genetic risk score. Patients were categorized into high and low genetic score groups according to their wGRS. In a univariate regression model, age of onset of DD younger than 50 years of age, a family history positive for DD, knuckle pads, and Ledderhose disease were significantly associated with a high genetic risk score.

The ORs of the significant diathesis features varied from 1.35 to 1.95, each having only a moderate effect on predicting a high genetic risk score. This is related to the fact that the study population was primarily divided into 2 large subgroups (genetic risk scores higher or lower than the median), in which most patients had a genetic score with a value almost equal to the median. When the groups were further subdivided into categories that deviated 1 SD from the median, age of onset of DD younger than 50 years of age, a family history

positive for DD, and knuckle pads remained significant with, as expected, larger effect sizes (Table 5). The presence of Ledderhose disease ceased to be significant in the additional analysis and was only just significant in the primary analysis. Further research has to demonstrate whether Ledderhose disease is really associated with a high genetic risk score.

The clinical characteristics that were statistically significant in this study are all features of the DD diathesis defined by Hueston[9] and later revisited by Hindocha et al.[9] In the revisited DD diathesis, the definition of ectopic lesions was restricted to the presence of knuckle pads.[2] In our study, the presence of knuckle pads revealed the highest OR of all the significant clinical characteristics. Therefore, the presence of knuckle pads can be seen as the diathesis feature predominantly associated with a high genetic risk score.

Male sex and bilateral disease, 2 other DD diathesis features, were not associated with a high genetic score. The former can be easily explained, because the 9 DD susceptibility SNPs are not located on the sex chromosomes. Therefore, an analysis using these SNPs will not show differences related to sex. The latter we consider as a less specific characteristic, because bilateral disease occurs in many patients over time and the survey time point influenced this factor. Peyronie disease was also not associated with a high genetic score. In 36% of doctor's questionnaires, Peyronie disease was not scored (Table 2), perhaps because of hesitance of the doctor to ask about this issue. This might have had an effect on the results.

The strengths of this study were the prospective design and the large cohort of patients who have been characterized. Limitations of this study were the lack of follow-up, the use of nonvalidated questionnaires, and the fact that, in only 566 patients, the doctor's questionnaire was completed. Because patients presented to the outpatient clinics for evaluation of their disease, presumably because of concern about their condition, there might have been a selection bias.

DD patients who present with an age of onset younger than 50 years, a positive family history, or ectopic disease (particularly with knuckle pads) are more likely to carry more risk alleles for the discovered DD SNPs than patients without these diathesis features. It is reassuring to find that there was a relation between certain diathesis features and the recently identified DD risk genotypes.

We know that the diathesis features of DD can lead to a more aggressive disease. It is to be expected that the more risk alleles a patient carries (the higher the genetic risk score), the more aggressive the disease will be. We are currently planning the follow-up for patients in this study to answer this question. It would be interesting to investigate the relationship between genetics and the course of the disease and especially the occurrence of recurrent disease.

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