The Heritability of Dupuytren's Disease: Familial Aggregation and Its Clinical Significance

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Purpose: Dupuytren's disease (DD) is a benign, fibroproliferative disease affecting the hands. The familial occurrence of DD and its presence in identical twins suggests a genetic basis for the condition. Our aims in this study were (1) to provide evidence for familial aggregation of DD by estimating the sibling recurrence-risk ratio and (2) to link previously associated environmental risk factors with family history of DD.

Methods: Patients diagnosed with DD between the ages of 58 and 81 years (N = 92) were interviewed to assess potential risks and the severity of their conditions. A clinical history and examination were performed and we attempted to interview every family member either in person or through a postal questionnaire.

Results: The sibling recurrence-risk ratio (λ_s) equaled 2.9 and ranged from 2.6 to 3.3 based on the 95% confidence intervals for the population prevalence. This suggests a high genetic basis for the causation of DD. A lower age of onset and greater severity of DD were associated significantly with a positive family history of DD. Other factors showed no statistical significance with familial aggregation of DD.

Conclusions: The familial clustering observed in DD likely is due to genetic influence rather than shared environment, as shown by the lack of association with exposure to environmental risk factors and family history. Understanding the genetic basis of DD is important for developing novel diagnostic, preventative, and therapeutic regimens in the future. (J Hand Surg 2006;31A: 204–210. Copyright © 2006 by the American Society for Surgery of the Hand.)

Type of study/level of evidence: Prognostic, Level II.

Key words: Dupuytren's disease, familial aggregation, genetics, heritability, sibling recurrence risk.

Dupuytren's disease (DD) is a benign fibroproliferative disorder that results in the characteristic formation of thick, scar-like tissue in the palmar fascia of the hand extending to any digit.[1] In its advanced stages DD leads to an irreversible, permanent, and progressive contracture of the involved digits. Dupuytren's disease in the hands is commonly bilateral but Dupuytren-like fibrotic tissue also can occur in the dorsum of the hand over the knuckles (Garrod's nodes), feet (also known as Lederhose's disease), and penis (also known as Peyronie's disease) of the same individual.[1]

Dupuytren's disease is most prevalent in northern European whites. It is considered to be one of the most commonly inherited connective-tissue disorders affecting whites of northern European descent. The prevalence of DD is more than 4% in the male population in England, with an incidence of more than 25% in the Celtic population aged over 60 years.[2]

Many environmental factors have been associated with the etiology of DD including a history of smoking, frozen shoulder, epilepsy, diabetes mellitus, and a high lipid profile. This mysterious etiology has kept DD a subject of immense interest, leading to many genetic and molecular studies trying to discover the underlying causes of this disabling condition. Conventional treat-

ment for DD is surgical correction; however, increasing severity and recurrence may lead to amputation of an affected digit, causing physical and psychologic distress.[3]

Dupuytren's disease is often familial and has been shown to be present in identical twins.[2] A familial preponderance for DD has been recognized since its early clinical description in the medical literature.[2–5]

Calculating the form of heritability for DD will assist in finding a genetic model for the condition. An estimate of relative risk[2] has been reported in the literature but there have not been any estimates of specific forms of heritability such as a sibling recurrence-risk ratio. The sibling recurrence-risk ratio is a measure of familial aggregation that is used widely.[6–7] This ratio indicates the heritability risk compared with the general population of an individual developing DD, given that a sibling is affected. Calculating the sibling recurrence-risk ratio is a standard method to estimate the statistical power to detect a disease locus[8]; hence this study may aid in understanding the genetic relationship of DD. To identify heritability, previously associated factors were investigated because they are believed by some researchers to play an important role in the pathogenesis of DD.[1,3]

In this study we evaluated a cohort of white patients with DD from northwestern England. Sibling recurrence-risk ratios were calculated for men and women affected with DD. We investigated the significance of environmental and other previously associated risk factors including age at onset and severity of disease with the presence of a positive family history of DD.

Materials and Methods

Study Population

A hospital-based, cross-sectional study design was used to recruit patients with a diagnosis of DD. We identified 300 white patients from northwestern England diagnosed with DD who had surgery between January 2000 and December 2003 from surgical records at Wrightington Hospital, Wigan, UK. Of these 300 patients 92 were examined randomly between May 20, 2004 and July 1, 2004. Eighty men (age range, 37–88 y; mean age, 65.6 y [SD = 8.3]) and 12 women (age range, 58–81 y; mean age, 68.8 y [SD = 8.1]) participated in the study after completing an ethically approved consent form.

A relevant thorough medical family history and clinical examination were performed by the first author based on a standard methodology agreed on by all authors. All patients, regardless of whether they reported a family history of DD, then were asked if their family members would take part in the study

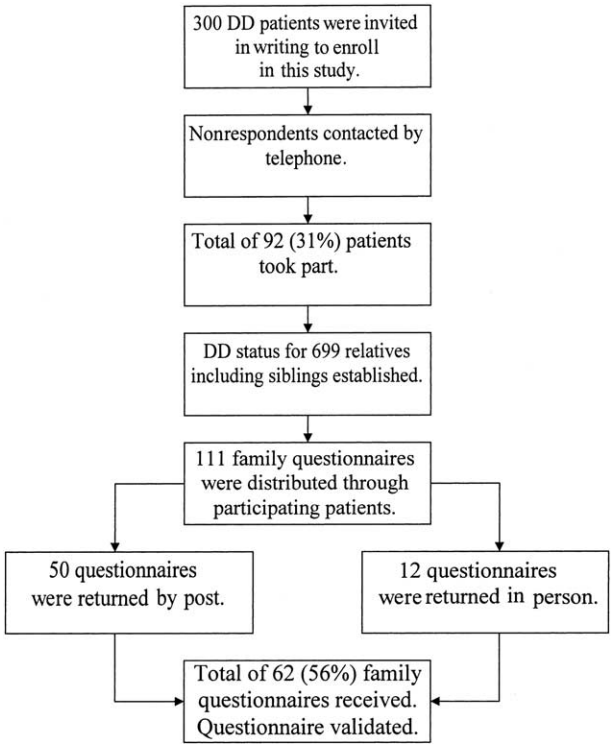

Figure 1. Total number of patients enrolled in the study and information obtained from family members.

and a second appointment was offered for patients to attend the clinic with family members. Relatives who were unable to attend the clinic were requested to return a family questionnaire to the hospital. One hundred eleven family questionnaires were distributed to patients; 62 questionnaires were received by mail and 12 of the 62 family members also were examined in the clinic. Each family member was asked to complete the family questionnaire before arrival at the clinic. Questionnaires then were checked with the participants, allowing for the validation of the family questionnaire (Fig. 1).

Data on associated risk factors were collected including a history of manual labor, diabetes mellitus, epilepsy, frozen shoulder, liver disease, hypercholestrolemia, smoking, and alcohol consumption. Clinical examination of the hands allowed for a modified severity score to be produced assessing disease severity in each patient. The severity score incorporated a validated staging system (Table 1).[9] The research and clinical audit department at Wrightington Hospital NHS Trust, England, UK granted full ethical approval for this study.

Prevalence Data

Because the study population sample was selected from northwestern England we used the population prevalence data that were calculated by using a cohort of DD patients from the same geographic area.[10]

Table 1. Severity of Dupuytren's Disease

Criteria	Score
Total surgical procedures for DD	Total for left and right hands
Recurrence of DD in affected digit	Total for each digit
Number of digits affected	Total for left and right hands
Number of nodules	Total for left and right hands
Number of pits	Total for left and right hands
Garrod's pads	Presence scores 1
DD on feet	Presence scores 1
For each digit stage DD[9]	Score according to stage (1–4). Total score for all digits. Flexion deformities to be measured with goniometer.
Stage 1 = TFD	1
Stage 2 = TFD	2
Stage 3 = TFD	3
Stage 4 = TFD	4
Bilateral/unilateral DD	1 for unilateral; 2 for bilateral
Total severity score	

Assessing the severity of DD using a modified scoring system incorporating an existing staging system for the disease.[9] TFD, total flexion deformity.

In addition to prevalence rate data from the United Kingdom we also used more recent prevalence rate data from another northern European population.[11]

Data Analysis

Data were entered into a database (Access; Microsoft, Redmond, WA). Family pedigrees for each patient were drawn by using pedigree drawing analysis software (Progeny 5; Progeny Software). For each patient the significance of associated risk factors against a positive family history was tested by using chi-square and Student *t* tests. The sibling recurrence-risk ratio (λ_s) then was calculated by using a known genetic statistical formula.[7,8] Statistical analyses were calculated by using software packages (Stata 8.0; StataCorp; Statsdirect, Statsdirect).

Results

Demographic Details

Of the 80 men and 12 women, 28 and 7, respectively, gave positive family histories of DD. Of the 92 patients 6 were not sure if there was a family history of DD. Data for these patients were excluded for the analysis of association of risk factors against a positive family history. Therefore 35 of 86 patients indicated a positive family history of DD.

Associated Risk Factors of DD in Patients

Of the 12 previously associated risk factors analyzed, 2 factors were associated significantly with a positive family history of DD: age at onset and severity of the disease (Figs. 2, 3). The mean age at onset in those

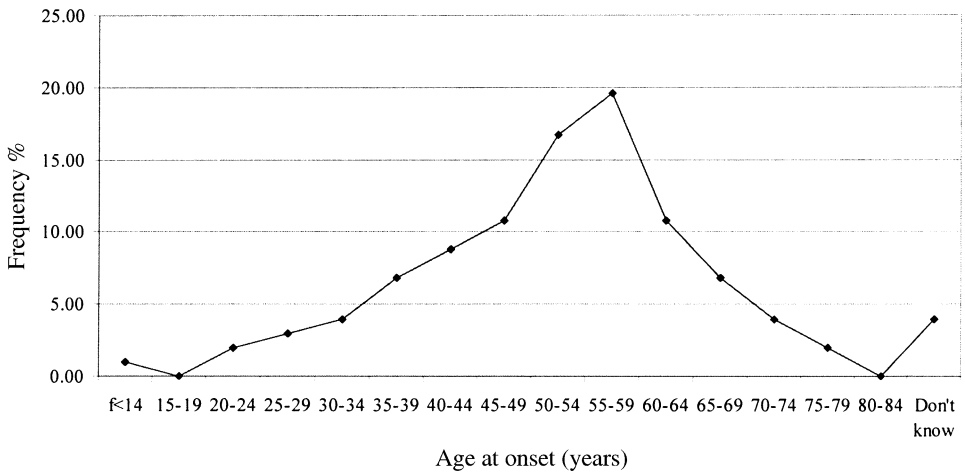

Figure 2. Age at onset of DD among the population cohort. Age at onset was defined as the first time the patient noticed either a nodule or pit in the palm. Mean age at onset of DD was 53 years.

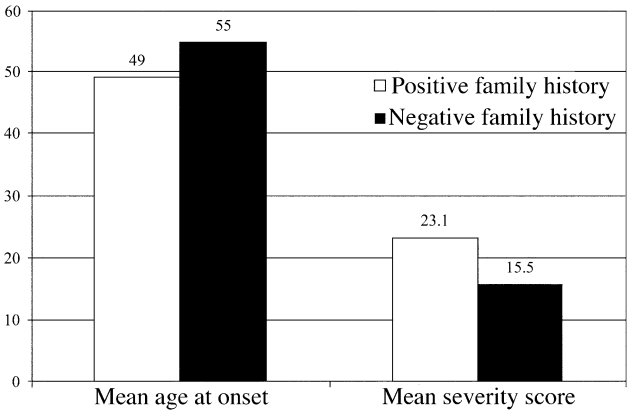

Figure 3. Results of 2 significant associations with a positive history of DD. Although mean age at onset and severity score appear to correlate closely there is a significant difference in those with and without a positive family history.

with a positive family history was 49 years compared with 55 years in those without a family history. The mean severity score for the whole study population was 18.7 (range, 4–53; SD = 10.9). The mean severity score for those with a positive family history was 23.1 (range, 6–53; SD = 13.5) compared with 15.5 (range, 4–38; SD = 7.5) for those with a negative family history of DD. Clinical examination of patients also indicated that the severity of DD was greater in those with a positive family history than in those without. Patients with a positive family history had a trend toward more digits being affected with more severe contractures, nodules, cords, and pits. They also were more likely to have ectopic DD tissue affecting the feet (Lederhose's disease) and knuckles (Garrod's pads) (Table 2).

Validation of Family Questionnaires

Because not all family members were examined clinically for DD status, DD status was ascertained from the data provided on the family questionnaires. Twelve family members completed the questionnaire and were examined. Of these 12 family members 10 showed clinical evidence of DD; however, only 7 reported signs of DD on the questionnaire. Three family members were misclassified on the questionnaire in this small sample, resulting in a questionnaire sensitivity of 70%, which showed that DD is likely to be underreported rather than overreported by family members.

Sibling Recurrence-Risk Ratio (λ_s)

Ninety-two patients were considered in this analysis. The family pedigree size ranged from 2 to 19 individuals (mean, 8; SD = 3). Data for 699 relatives were obtained; of these, 217 were siblings consisting of 119 brothers and 98 sisters. The mean age of the siblings was 63 years (range, 21–92 y; SD = 12.7 y).

Table 2. Associated Factors of DD in Patients and Their Association With a Positive Family History

Clinical Finding/ Environmental Exposure	Value for the 35 Patients with Positive Family History	Significance
Mean age at onset (y)	49	$p < .05$
Mean severity score	23.1	$p < .05$
Male (%)	39	NS
Female (%)	58	NS
Manual work (%)	40	NS
Diabetes mellitus (%)	11	NS
Epilepsy (%)	0	NS
Frozen shoulder (%)	23	NS
Liver disease (%)	3	NS
Smoking history (%)	57	NS
Alcohol history (%)	86	NS
High cholesterol (%)	26	NS

Association between associated risk factors of DD and significance to a positive family history. A positive family history is associated with a lower age at onset and greater severity of DD. A history of manual work appears to be related to a positive family history; however, results were not significant. This suggests that environmental exposure may not be a cause in the etiology of DD.
NS, not significant.

The number of siblings ranged from 0 to 7 (mean, 2; SD = 2); 13 of the 92 patients had no siblings. Of those 79 patients who had siblings the presence of DD was unknown in 5 siblings. The mean age of brothers and sisters with DD was 66 years (SD = 7.1 y) and 69 years (SD = 10.9 y), respectively. The compositions of affected siblings among male and female patients then were calculated to derive the sibling recurrence-risk based on a standard formula.[7,8]

Calculation of the sibling recurrence-risk ratio (λ_s) is derived by dividing the sibling recurrence risk (K_s) by the population prevalence (Table 3). Two population prevalences were used, 1 from the Lancashire and Cheshire region, England[10] and 1 from Reykjavik, Iceland.[11]

Table 3. Sibling Recurrence–Risk Ratio (λ_s) for DD

K_s (%)	Prevalence Rate (%)	Prevalence Rate 95% CI	λ_s	λ_s Range
10.3	3.5*	3.1–4.0	2.9	2.6–3.3
10.3	13.3†	11.8–14.7	0.8	0.7–0.9

Prevalence rates are combined for males and females.
*Based on population prevalence in northwestern England.[10]
†Based on population prevalence in Iceland.[11]

Discussion

The etiopathogenesis of DD remains an enigma. The relevance of some of the many implicated etiologic factors such as alcohol abuse, cirrhosis, smoking, diabetes, and anticonvulsant medication in DD formation has been questioned[12]; however, 2 elements in the etiology of DD clearly continue to stand out. One is the familial nature of the disease and the other is that DD appears to be an extremely common disorder mainly affecting whites of northern European ancestry.[1,13]

This study further showed the importance of familial aggregation present in DD. Sibling recurrence-risk ratios (λ_s) were shown to average 2.9 and ranged from 2.6 to 3.3 based on the 95% confidence intervals for the population prevalence. This suggests a high genetic basis for the causation of DD. A lower age of onset and greater severity of DD also were associated significantly with a positive family history. Other factors had no statistical significance with familial aggregation of DD. The familial clustering observed in DD likely is caused by genetic influence rather than shared environment, as indicated by the lack of association with exposure to environmental risk factors and family history.

One of the potential weaknesses of this study design is that patients with a positive family history may be ascertained preferentially, leading to inflated estimates of K_s. Patients were selected randomly from surgical records and it was not assumed that each patient had a positive family history of DD. Each nonresponding patient was telephoned and requested to take part and told that a positive family history was not the only reason to participate and that other possible links to DD were being investigated.

Forty-one percent of patients reported a positive family history; this is consistent with a previous figure of 44%, further suggesting no bias in our ascertainment stratgy.[14] Our results suggest that both the incidence of a positive family history and the number of affected relatives may be underestimated. The relatively late age at onset of DD, even in affected families, may lead to younger siblings being misclassified in a cross-sectional study design. The progressive and perhaps early stages (nodules only) of DD also may result in underreporting of positive DD status among family members. This issue has been raised by Ling,[15] who showed that after the examination of patients' relatives the rate of a positive family history increased from 16% to 68%. From the small sample that completed both the questionnaire and physical examination we observed a high specificity but lower sensitivity for the questionnaire. This suggests that more efficient and accurate methods to investigate DD status are required. Designing and validating a new telephone questionnaire is likely to provide more accurate results in identifying those affected with DD and is likely to improve response rates among selected subjects than the use of postal questionnaires.

After the calculation of λ_s we had evidence that familial aggregation exists for DD when the prevalence data from the same geographic populations were used. This is the ideal population from which to draw a prevalence rate; however, this estimate was based on a wider age range than that of our patients. We therefore also used a prevalence rate from the Icelandic population—a less suitable population but with a more similar age range. There is a considerable difference of λ_s estimates when the 2 prevalence rates are compared. The prevalence of DD varies according to gender; we did not calculate a gender-specific λ_s because of the extremely small female population because this may have resulted in an overestimate of λ_s in the female population. Based on recently calculated population prevalence rates from the Reykjavik study,[11] which are greater than those in England, λ_s equaled 0.8 and ranged from 0.7 and 0.9, suggesting no familial clustering caused by either genetic or environmental factors. The prevalence of DD varies widely in different populations, ranging from 2% to 42%.[16] This difference in prevalence may be caused by age range differences within each study or, alternatively, caused by a genuine difference in the prevalence rate in northern England and Iceland. Prevalence rates used in the Reykjavik study[11] were for ages between 46 and 74 years compared with all ages assessed in the study by Early.[10] Early[10] had used a selected population in a relatively small region compared with a random selection used in the Reykjavik study. This may suggest that the prevalence in England is likely to be higher than predicted because the familial nature of the disease is likely to affect people at a younger age, agreeing with the Reykjavik study.

Calculations of λ_s using population prevalence rates for both countries differ greatly: using the population prevalence rates from the Reykjavik study suggested no familial clustering for our population. Prevalence data from a more appropriate population, however, did suggest substantial evidence for familial clustering. The results presented here will require further validation using more recent population prevalence rates for England. There is also likely to be strong familial aggregation in the Icelandic population if the λ_s is calculated using a population from Reykjavik.

We have shown that many of the factors associated with DD are not associated significantly with a pos-

itive family history of DD. This may not indicate nonassociation or lack of power, nor does it exclude these factors from being risk factors for DD *per se,* only from being more important in familial or nonfamilial DD.

Our results agree with those of others[17–19] who also have shown an insignificant relationship between alcohol consumption and DD. Therefore it is unlikely that alcohol consumption acts as an environmental influence to increase the risk of DD in susceptible individuals, suggesting that familial clustering of DD is not associated with alcohol as a shared environmental risk factor. Although diabetes mellitus is associated positively with DD and the severity of DD[12,13] the presence of diabetes mellitus among our patients did not result in a significant association with a positive family history of DD. Although DD is 8 times more likely to develop in those with a history of frozen shoulder,[20] its association was not associated significantly with familial aggregation of DD. Smoking has been a recognized risk factor for DD for some time[21,22]; however, in this cohort of patients smoking does not appear to be linked statistically with DD. Biochemical markers were not measured to assess the presence of high cholesterol levels in our patients. For the purpose of this study, however, we accepted confirmation of high, normal, or low cholesterol status from each patient's self-reported cholesterol levels. Nevertheless there was no significant statistical association between a high lipid profile and a positive family history of DD. Many have stated that manual work is associated with DD either as a result of chronic trauma or because of retirement from manual labor preventing maximum physiologic normality.[23–25] Analysis from this study has shown that a history of manual labor is not associated significantly with familial clustering of DD.

On the other hand a positive family history of DD is associated significantly with a lower age at onset and greater severity of DD. The time of onset given by each patient was specific to the first time they noticed a nodule or pit and not the time of digit contracture. This ensured minimizing bias in our data collection. Although results with our derived scoring system are significant the scoring system will require validation.

The negative association of risk factors cannot act as confounders in the study but suggest a higher genetic component compared with environmental exposure (ie, greater heritability) in the etiology of DD.

It is evident from this study that further research is required to unravel the genetic basis of DD. Confirming familial aggregation also will require a revised population prevalence rate of DD for England. The sibling recurrence-risk ratio (λ_s) also is required for other ethnic origins and populations for comparison with the findings of this study. Although familial aggregation is evident in DD it is necessary to conduct a sophisticated analysis of heritability, which may be conducted in twin subjects.

We have not identified any measured environmental factor that could account for the degree of familial clustering indicated by our calculation of λ_s; therefore we believe this estimate is attributable to genes rather than a shared familial environment. For the causes of DD in general, although we have shown heritability, it is clear from our reported value that environmental factors still play a large role in the cause of DD, either those reported previously or factors as yet unidentified. The early age at onset and more severe disease observed in those with a family history also supports a genetic component and is consistent with other complex diseases. The underreporting of DD and potentially inaccurate prevalence data will affect this estimation; however, this measurement error is far more likely to reduce the magnitude of the true genetic component of DD that may be elucidated by complex genetic analysis.

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References

1. Thurston AJ. Dupuytren's disease. J Bone Joint Surg 2003; 85B:469–477.
2. Burge P. Genetics of Dupuytren's disease. Hand Clin 1999; 15:63–71.
3. Hayton MJ, Gray ICM. Dupuytren's contracture: a review. Curr Orthop 2003;17:1–7.
4. Maza KM, Goodman RM. A family with Dupuytren's contracture. J Hered 1968;59:155–156.
5. Matthews P. Familial Dupuytren's contracture with predominantly female expression. Br J Plast Surg 1979;32:120–123.
6. Olson JM, Cordell HJ. Ascertainment bias in the estimation of sibling genetic risk parameters. Genet Epidemiol 2000; 18:217–235.
7. James JW. Frequency in relatives for an all-or-none trait. Ann Hum Genet 1971;35:47–48.
8. Rybicki BA, Elston RC. The relationship between the sibling recurrence-risk ratio and genotype relative risk. Am J Hum Genet 2000;66:593–604.
9. Tubiana R. Dupuytren's disease of the radial side of the hand. Hand Clin 1999;15:149–159.
10. Early PF. Population studies in Dupuytren's contracture. J Bone Joint Surg 1962;44B:602–613.

11. Gudmundsson KG, Arngrimsson R, Sigfusson N, Bjornsson A, Jonsson T. Epidemiology of Dupuytren's disease: clinical, serological, and social assessment. The Reykjavik study. J Clin Epidemiol 2000;53:291–296.
12. Arkkila PE, Kantola IM, Viikari JS, Ronnemaa T, Vahatalo MA. Dupuytren's disease in type 1 diabetic patients: a five-year prospective study. Clin Exp Rheumatol 1996;14: 59–65.
13. Stradner F, Ulreich A, Pfeiffer KP. Die Dupuytrensche Kontraktur als Begleiterkrankung des Diabetes mellitus. [Dupuytren's contracture as a concomitant disease in diabetes mellitus.] Wien Med Wochenschr 1987;137:89–92.
14. Skoog T. Dupuytren's contracture with special reference to aetiology and improved surgical treatment, its occurence in epileptics, note on knuckle pads. Acta Chir Scand 1948; 96(suppl 139):25–175.
15. Ling RS. The genetic factor in Dupuytren's disease. J Bone Joint Surg 1963;45B:709–718.
16. Saar JD, Grothaus PC. Dupuytren's disease: an overview. Plast Reconstr Surg 2000;106:125–134.
17. Attali P, Ink O, Pelletier G, Vernier C, Jean F, Moulton L, Etienne JP. Dupuytren's contracture, alcohol consumption, and chronic liver disease. Arch Intern Med 1987;147:1065–1067.
18. Noble J, Arafa M, Royle SG, McGeorge G, Crank S. The association between alcohol, hepatic pathology and Dupuytren's disease. J Hand Surg 1992;17B:71–74.
19. Gudmundsson KG, Arngrimsson R, Jonsson T. Dupuytren's disease, alcohol consumption and alcoholism. Scand J Prim Health Care 2001;19:186–190.
20. Smith SP, Devaraj VS, Bunker TD. The association between frozen shoulder and Dupuytren's disease. J Shoulder Elbow Surg 2001;10:149–151.
21. Burge P, Hoy G, Regan P, Milne R. Smoking, alcohol and the risk of Dupuytren's contracture. J Bone Joint Surg 1997; 79B:206–210.
22. An HS, Southworth SR, Jackson WT, Russ B. Cigarette smoking and Dupuytren's contracture of the hand. J Hand Surg 1988;3:872–874.
23. Liss GM, Stock SR. Can Dupuytren's contracture be work-related? Review of the evidence. Am J Ind Med 1996;29: 521–532.
24. de la Caffiniere JY, Wagner R, Etscheid J, Metzger F. Travail manuel et maladie de Dupuytren Resultat d'une enquete informatisee en milieu siderurgique. [Manual labor and Dupuytren disease. The results of a computerized survey in the field of iron metallurgy.] Ann Chir Main 1983;2:66–72.
25. Heuston JT, Seyfer AE. Some medicolegal aspects of Dupuytren's contracture. Hand Clin 1991;7:617–631.