

Dupuytren's Contracture in Alabama *HFE* Hemochromatosis Proband

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Abstract

Background: Dupuytren's contracture (DC) and *HFE* hemochromatosis occur in some of the same at-risk populations and present with similar comorbid conditions.

Methods: We estimated DC prevalence in two cohorts of white Alabama hemochromatosis probands (294 C282Y homozygotes, 67 C282Y/H63D compound heterozygotes) in a retrospective study. We performed logistic regressions on DC using the following independent variables: age, body mass index, heavy ethanol consumption, serum ferritin, elevated serum AST/ALT, non-alcoholic fatty liver disease, viral hepatitis, cirrhosis, and diabetes.

Results: One man and two women with C282Y homozygosity had DC (prevalence 1.02%; 95% CI 0.35%–2.96%). A man with C282Y/H63D had DC (prevalence 1.49%; 95% CI 0.26%–7.98%). DC occurred as an autosomal dominant trait in his kinship. In regression analyses, no single variable predicted DC. We observed no new DC cases after the diagnosis of hemochromatosis (mean follow-up 12.9 ± 7.5 years (1 SD), and 9.0 ± 5.1 years, respectively).

Conclusions: Our prevalence estimates of DC in white Alabama hemochromatosis probands are similar to those found in the white US population cohorts. DC risk was unrelated to the variables we studied.

Keywords: Dupuytren's contracture, epidemiology, hemochromatosis, iron overload, prevalence

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Introduction

Dupuytren's contracture (DC) is a distinctive but heterogeneous fibroproliferative disorder of the palmar fascia characterized by nodular growth and proliferation; cord development and contracture;^{1,2} increased hexosamine and collagen contents; and an elevated ratio of Type 3 to Type 1 collagen.³ DC is common in some northwestern European populations, especially those of Viking or Celtic descent,⁴⁻⁷ suggesting that there may be a genetic predisposition to develop DC. Lifestyle and occupational factors and comorbid conditions may also increase one's risk of developing DC.^{6,8-10}

HFE hemochromatosis is usually a result of homozygosity in the human leukocyte antigen (HLA)-linked C282Y mutation of the *HFE* gene (chromosome 6p21.3). *HFE* C282Y homozygosity occurs in 0.003–0.006 of persons of northwestern European descent.^{11,12} Iron overload, especially if severe, may cause cirrhosis, primary liver cancer, diabetes mellitus, other endocrinopathy, arthropathy, and cardiomyopathy.¹³⁻¹⁵ The prevalence of *HFE* C282Y homozygosity is relatively high in Alabama,¹⁶ like it is in Iceland, Norway, and the British Isles.¹⁷⁻²³ The *HFE* genotype C282Y/H63D occurs in ~0.021 of white Americans, of whom 10.8% of men and 7.8% of women have elevated serum transferrin saturation and ferritin levels.¹²

Persons with *HFE* hemochromatosis may have increased risk to develop DC because at-risk populations and some co-morbid conditions in *HFE* hemochromatosis and DC cohorts are similar, but we were unable to identify a report of the occurrence of these two disorders in the same patient. Thus, we reviewed the medical records of 361 adult white Alabama hemochromatosis probands (294 *HFE* C282Y homozygotes and 67 *HFE* C282Y/H63D compound heterozygotes) in a retrospective study. We estimated the prevalence of DC at the diagnosis of hemochromatosis and compiled data on associated lifestyle variables, comorbid conditions, and evidence of familial transmission of DC. Our findings are discussed in the context of pertinent observations regarding DC in non-hemochromatosis populations of American and northwestern European adults.

Methods

Selection of hemochromatosis probands

The performance of this work was approved by the Institutional Review Board of Brookwood Medical

Center. We conducted computerized and manual searches of medical records and hemochromatosis databases to identify all patients evaluated for hemochromatosis because they had elevated values of transferrin saturation or serum ferritin (SF). Each patient selected for this study was Caucasian and was the first in his/her family to be diagnosed with hemochromatosis (proband). We included persons who: (a) were diagnosed with hemochromatosis in non-screening venues; (b) had *HFE* C282Y homozygosity or *HFE* C282Y/H63D compound heterozygosity; (c) attained iron depletion after treatment with phlebotomy if SF levels at diagnosis were elevated (men > 300 µg/L; women > 200 µg/L);^{13,24} and (d) resided in central Alabama. Hand examinations were performed on each patient at diagnosis to detect evidence of hemochromatosis arthropathy. Each proband was also evaluated for other complications associated with iron overload, as appropriate.^{13,25}

Diagnosis of Dupuytren's contracture

The diagnosis of DC was established in three patients during physical examination. These patients fulfilled the following clinical criteria for the diagnosis of DC: nodularity and cord-like thickening of the palmar fascia and the presence of fixed flexion contractures of the metacarpophalangeal joint or proximal interphalangeal joint of 20 degrees or more in one or more digits. In a fourth patient, we reviewed the history, operative report of surgery for DC, and pathologists' interpretation of tissue removed at surgery and deemed this case to be consistent with DC as defined in the three other patients. In all cases, phenotype mimics of DC were excluded as appropriate. These mimics include scar formation from trauma or burns, various benign cysts and nodules, sequelae of reflex sympathetic dystrophy, recurrent digital fibroma of childhood, and palmar epithelioid sarcoma.

Laboratory methods

SF levels were measured using automated clinical methods. *HFE* mutation analysis was performed as previously described.²⁶ Analyses were performed using buffy coat or DNA specimens obtained from probands who were diagnosed with hemochromatosis before the discovery of *HFE* in 1996.¹¹ HLA typing of probands and their first-degree relatives, and assignment of HLA-A and -B haplotypes in probands were



performed as described elsewhere in detail.²⁷ We defined an ancestral hemochromatosis haplotype as any chromosome 6p bearing *HFE* C282Y and either A*03, B*07, or A*03, B*14.^{28,29}

Sections of liver biopsy specimens were stained using hematoxylin and eosin, Masson's trichrome, and Perls' Prussian blue techniques. Intrahepatocytic iron was graded according to the method of Scheuer et al.³⁰ Routine methods were used to detect HB_sAg, HB_sAb, HB_cAb, and the hepatitis C antibody.

Diagnosis of liver conditions

We defined five liver conditions as: elevated serum level(s) of hepatic aminotransferase levels; non-alcoholic fatty liver disease (NAFLD); heavy ethanol consumption; chronic hepatitis B or C; and cirrhosis.³¹ Patients were classified as having elevated aminotransferase levels if either their serum aspartate or alanine aminotransferase (AST, ALT, respectively) level was higher than the respective upper reference limit (>2 SD above the mean). NAFLD was defined as steatosis or steatohepatitis detected on liver biopsy specimens or by a typical increase in hepatic echogenicity detected by ultrasonography in the absence of self-reports of heavy ethanol consumption. Heavy ethanol consumption was defined as the self-reported consumption of ≥ 60 g/d for five or more years. Chronic hepatitis B or C was defined as positivity for HB_sAg or hepatitis C antibody, respectively, in association with clinical or liver biopsy abnormalities consistent with chronic viral hepatitis.

Liver biopsy was typically performed in probands who had SF > 1000 μ g/L at diagnosis, or in whom there was evidence of unexplained liver disease regardless of SF level.²⁴ Cirrhosis was defined by pathologists' interpretations of liver biopsy specimens.

Treatment of iron overload manifestations

Iron depletion therapy, defined as the periodic removal of blood to eliminate storage iron, was performed as described in detail elsewhere.^{13,24} An attempt to achieve iron depletion by phlebotomy was made in each proband with elevated SF levels. Hepatic, cardiac, endocrinologic, and rheumatologic manifestations of iron overload were evaluated and treated as described previously.^{13,24}

Statistics

One analytic data set consisted of observations on 294 Alabama hemochromatosis probands with *HFE* C282Y homozygosity (188 men, 106 women). A second analytic data set consisted of observations on 67 Alabama hemochromatosis probands with C282Y/H63D compound heterozygosity. We compiled the following general characteristics of each proband: age at diagnosis; sex; presence or absence of DC; SF level at diagnosis; date of diagnosis; elevated serum level of ALT or AST; NAFLD; heavy ethanol consumption; chronic viral hepatitis; cirrhosis; and diabetes.

All living patients were so confirmed on May 1, 2012. The dates of death of other patients were confirmed by review of office and hospital records and by the Social Security Death Index (<http://ssdi.rootsweb.ancestry.com/>). Duration of follow-up after diagnosis was computed using the date of diagnosis and either May 1, 2012 (living patients) or date of death, as appropriate.

SF levels were converted to natural logarithms (ln) to normalize them for univariable comparisons. Mean SF results are displayed as anti-ln of mean ln SF (95% confidence interval (CI)). Descriptive statistics are displayed as enumerations, percentages, or mean \pm 1 standard deviation (SD). Comparisons of continuous data were made using Student's two-sided *t*-test; percentages were compared using Fisher's exact or chi-square test, as appropriate. We performed independent logistic regression analyses on the diagnosis of DC (dependent variable) to identify significant predictors (positive or negative associations) in 294 probands with C282Y homozygosity and in 67 probands with C282Y/H63D compound heterozygosity. Values of $P < 0.05$ are defined as significant. Analyses were performed using GB-Stat[®] v. 8.0 (Dynamic Microsystems, Inc, Silver Spring, MD) and Microsoft Excel 2000[®] (Microsoft Corp, Redmond, WA).

Results

Characteristics of Alabama hemochromatosis probands with DC

Three of the 294 patients with *HFE* C282Y homozygosity had DC (prevalence 1.02%; 95% CI 0.35%–2.96%) (Table 1). Each of the three patients had involvement of the palmar fascia corresponding to the third digit (long finger); none had DC of the fifth digit. One of the three patients had bilateral involvement. Two of the three patients gave

**Table 1.** Characteristics of four hemochromatosis probands with Dupuytren's contracture^a.

Characteristic	Proband 1	Proband 2	Proband 3	Proband 4
<i>HFE</i> genotype	C282Y/C282Y	C282Y/C282Y	C282Y/C282Y	C282Y/H63D
Age, sex	46 F ^b	30 M	60 F	57 M
BMI, kg/m ²	30.3	22.6	27.7	32.8
Report of chronic occupational hand trauma	–	+	+	–
Hand, digit with DC	R 3	L 3	L 2, 3, 4; R 2, 3, 4	R 5; L 4, 5
Serum ferritin, µg/L	>5000	822	637	468
Elevated serum ALT/AST	–	–	+	+
HLA-A, B haplotypes	A*24, B*07; A*24, B*44	A*03, B*07; A*29, B*44	A*03, B*07; A*11, B*14	n.a.
Cirrhosis	+	–	–	–
Diabetes mellitus	–	–	+	–
Follow-up interval, y	23.4	17.7	12.7	5.2

Notes: ^aCharacteristics are those at diagnosis of hemochromatosis; ^bunderwent surgery to correct DC before diagnosis of hemochromatosis. No proband reported ethanol consumption \geq 60 g/d for five or more years or had non-alcoholic fatty liver disease or viral hepatitis.

Abbreviations: BMI, body mass index; DC, Dupuytren's contracture; AST/ALT, aspartate and alanine aminotransferases, respectively; HLA, human leukocyte antigen; n.a. not available.

reports of chronic occupational trauma to the palmar area (Table 1). Two of the three patients were heterozygous for the ancestral haplotype as defined by HLA-A*03, B*07. None of the three patients reported a significant change of DC manifestations after the diagnosis of hemochromatosis and all achieved iron depletion by phlebotomy. Two of the three patients with DC had first-degree relatives who also had hemochromatosis and C282Y homozygosity, but none of these relatives had DC by our examination. None of the three patients with DC had a family history of DC. We observed no new cases of DC after the diagnosis of hemochromatosis. Mean follow-up of all 294 patients was 12.9 ± 7.5 years.

One of the 67 patients with *HFE* C282Y/H63D compound heterozygosity had DC (prevalence 1.49%; 95% CI 0.26%–7.98%) (Table 1). He had bilateral DC of his fifth digits. He had a family history of DC that occurred as an autosomal dominant trait, including involvement of the plantar fascia in his eldest sister (Fig. 1). He reported that his paternal and maternal ancestors were Irish. None of his family members underwent evaluation for hemochromatosis or iron overload (Fig. 1). This man reported no significant change of DC manifestations after he achieved iron depletion by phlebotomy. We observed no new cases of DC after diagnosis of hemochromatosis. Mean follow-up of all 67 probands was 9.0 ± 5.1 years.

Characteristics of Alabama hemochromatosis probands without DC

Observations of the 291 patients with *HFE* C282Y homozygosity who did not have DC are displayed in Table 2. Men comprised 63.9% of these patients. The prevalence of reports of heavy ethanol consumption, mean SF level, and proportion of patients with elevated AST/ALT, viral hepatitis, and diabetes mellitus were significantly greater in men than women. Observations of the 66 patients with *HFE* C282Y

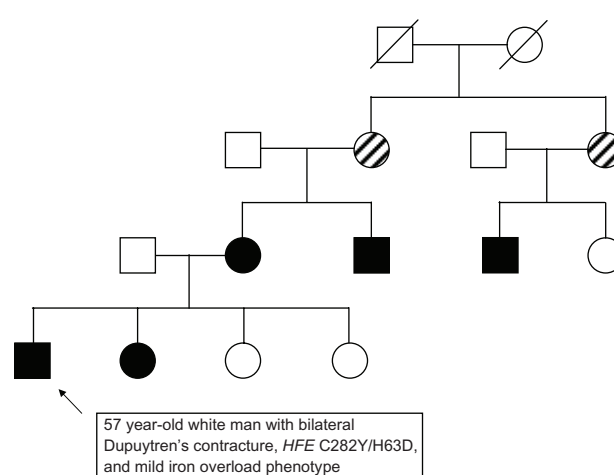


Figure 1. Pedigree of Proband 4, a man with *HFE* C282Y/H63D compound heterozygosity and Dupuytren's contracture (DC) (arrow).

Notes: The proband's eldest sister had DC and similar involvement of her plantar fascia. Only the proband underwent evaluation for iron phenotype and *HFE* genotype. The proband reported that his paternal and maternal relatives were Irish. Black figures = DC. Shaded figures = deduced DC carriers.

**Table 2.** Characteristics of 291 white hemochromatosis probands with *HFE* C282Y homozygosity without Dupuytren's contracture^a.

Characteristic	Men (n = 186)	Women (n = 105)	Value of P ^b
Mean age at diagnosis, y (±1 SD)	48 ± 13	51 ± 14	0.1032
Mean BMI, kg/m ² (±1 SD)	28.2 ± 5.1	26.1 ± 5.5	0.2515
Heavy ethanol consumption, % (n) ^c	23.1 (43)	5.7 (6)	0.0001
Mean serum ferritin, µg/mL (95% CI)	1019 (901, 1154)	541 (448, 654)	<0.0001
Elevated AST/ALT, % (n)	38.7 (72)	26.7 (28)	0.0378
NAFLD, % (n)	18.3 (34)	17.1 (18)	0.8079
Viral hepatitis, % (n)	7.0 (13)	1.0 (1)	0.0218
Cirrhosis, % (n)	17.2 (32)	9.5 (10)	0.0734
Diabetes mellitus, % (n)	24.2 (45)	9.5 (10)	0.0021

Notes: ^aCharacteristics are those at diagnosis of hemochromatosis; ^bcomparisons were made using student's *t*-test, Chi-square test, or Fisher's exact test, as appropriate. Mean SF results are displayed as antilog of mean ln SF (95% confidence interval (CI)); ^cself-report of ethanol consumption of ≥60 g/d for five or more years.

Abbreviations: BMI, body mass index; SD, standard deviation; CI, confidence interval; AST/ALT, aspartate and alanine aminotransferases, respectively; NAFLD, non-alcoholic fatty liver disease.

homozygosity who did not have DC are displayed in Table 3. Men comprised 57.6% of these patients. The mean SF level was significantly greater in men than women.

Comparisons of Alabama hemochromatosis probands with and without DC

Among *HFE* C282Y homozygotes, Proband 1 had SF at diagnosis of >5000 ng/mL (Table 1). This is higher than the upper 95% confidence limit for the 291 patients (men and women) without DC (Table 2). This patient also had cirrhosis, a characteristic of only 9.5% of the 105 female probands with C282Y homozygotes who did not have DC (Table 2). The SF level of Proband 2 was below the lower 95% confidence limit for men with C282Y homozygosity (Table 2). Proband 3 had diabetes mellitus. This complication was observed in only 9.5% of the 105 women with C282Y homozygosity who did not have DC (Table 2). The single man with *HFE* C282Y/H63D compound heterozygosity and DC had characteristics similar to those of the 66 other probands with

Table 3. Characteristics of 66 white hemochromatosis probands with *HFE* C282Y/H63D homozygosity without Dupuytren's contracture^a.

Characteristic	Men (n = 38)	Women (n = 28)	Value of P ^b
Mean age at diagnosis, y (±1 SD)	48 ± 13	51 ± 15	0.3963
Mean BMI, kg/m ² (±1 SD)	29.2 ± 4.7	26.4 ± 6.5	0.2515
Heavy ethanol consumption, % (n) ^c	15.8 (6)	10.7 (3)	0.4146
Mean serum ferritin, µg/mL (95% CI)	482 (379, 613)	242 (152, 386)	0.0104
Elevated AST/ALT, % (n)	39.5 (15)	21.4 (6)	0.1198
NAFLD, % (n)	39.5 (15)	21.4 (6)	0.1198
Viral hepatitis, % (n)	0.0 (0)	7.1 (2)	0.1762
Cirrhosis, % (n)	7.9 (3)	7.1 (2)	0.6442
Diabetes mellitus, % (n)	7.9 (3)	7.1 (2)	0.6442

Notes: ^aCharacteristics are those at diagnosis of hemochromatosis; ^bcomparisons were made using student's *t*-test, Chi-square test, or Fisher's exact test, as appropriate. Mean SF results are displayed as antilog of mean ln SF (95% confidence interval (CI)); ^cself-report of ethanol consumption of ≥60 g/d for five or more years.

Abbreviations: BMI, body mass index; SD, standard deviation; CI, confidence interval; AST/ALT, aspartate and alanine aminotransferases, respectively; NAFLD, non-alcoholic fatty liver disease.

C282Y/H63D compound heterozygosity who did not have DC.

Logistic regressions on occurrence of DC

We performed logistic regressions on the presence of DC (dependent variable) in 294 probands with *HFE* C282Y homozygosity using age, body mass index, report of heavy ethanol consumption, SF level, elevated serum levels of AST/ALT, NAFLD, viral hepatitis, cirrhosis, and diabetes (independent variables). None of the independent variables was significantly associated with the diagnosis of DC. Logistic regressions on DC in 67 probands with C282Y/H63D compound heterozygosity using the same independent variables did not reveal any significant associations.

Discussion

The present observations demonstrate that the prevalence of DC in white Alabama hemochromatosis probands with either *HFE* C282Y homozygosity or *HFE* C282Y/H63D compound heterozygosity is approximately 1.0%. This is consistent with early prevalence estimates of DC in the general white



American population of 1%–2% and 1.2%–1.7%,^{32,33} respectively. A more recent estimate of the prevalence of DC in Caucasians derived from a Department of Veterans Affairs database is 734/100,000 (0.7%).³⁴ The estimated global prevalence of DC in Caucasians is 3%–6%.^{4,35}

The prevalence of DC is much higher in some northwestern European populations, especially those of Viking or Celtic descent, than in Americans. In Iceland, for example, 19.2% of 1297 males and 4.4% of 868 female participants in a random population sample between the ages of 46 and 74 years old presented with clinical signs of Dupuytren's disease.⁶ In Norway, the prevalence of DC approaches 30% in persons aged 60 years or older.³⁶ In Northeast Scotland, 39% of men and 21% of women aged more than 60 years had DC.⁵ DC was present in 13.75% of 400 elderly ex-servicemen from England or Ireland living at the Royal Hospital Chelsea.³⁷ These modern estimates agree with historic accounts of DC in Europe.^{38–40}

The prevalence of *HFE* C282Y homozygosity is relatively high in Alabama,^{16,26} like it is in Iceland,^{17,18} Norway,^{19,20} Northeast Scotland,²¹ England,²² and Ireland.²³ Hemochromatosis probands from Alabama with C282Y homozygosity indicated that they are predominantly from the British Isles and proportional British Isles ancestry was significantly higher in hemochromatosis probands than in Caucasian Alabama control subjects.⁴¹ Regardless, our prevalence estimate of DC in Alabama hemochromatosis probands is similar to that in American Caucasians, but is much lower than that in general populations that reside in some areas of northwestern Europe.^{5,6,37} This suggests that the inheritance of *HFE* C282Y homozygosity alone is not associated with an increased risk of DC.

DC is often inherited as an autosomal dominant trait with variable penetrance that has been observed most frequently among people of Nordic descent.³⁶ This is consistent with the occurrence of DC in Proband 4 and his family members who reported having Irish ancestry. The pattern of inheritance of DC occurs rarely as an autosomal recessive or matrilinear trait.^{42,43} We obtained no family history of DC in three other hemochromatosis probands with DC, although this does not exclude a contribution of heritable factors to DC phenotypes.

Many candidate chromosomes, genes, and single-nucleotide polymorphisms that might explain

DC have been identified in family, linkage analysis, genome-wide associations, and other studies.⁴² There is a significant positive association of DC with HLA-DRB1-*15 (chromosome 6p21.3).⁴⁴ In patients of northwest European ancestry with multiple sclerosis in Victoria and Tasmania, the results of linkage disequilibrium and log linear modeling analyses suggest that the frequency of *HFE* C282Y is increased in these patients because C282Y is in linkage disequilibrium with the ancestral DR15 susceptibility haplotype (C282Y-HLA-A*0301-B*0702-DRB1*1501-DQB1*0602). Moreover, the results indicate that C282Y does not play an independent role in one's predisposition to developing multiple sclerosis.⁴⁵ The extended major ancestral hemochromatosis haplotype is D6S248(5), D6S265(1), HLA-A*03, HLA-F*02, D6S105(8).^{28,29,46} In many hemochromatosis patients of northwestern European ancestry, HLA-B*07 (or B*14) is also linked to HLA-A*03 and other ancestral haplotype markers.^{27,46} In 118 Alabama hemochromatosis probands with *HFE* C282Y homozygosity, the haplotype frequency of A*03, B*07 was 0.2966, and in 1,321 controls the frequency was 0.0331 ($P < 0.0001$; odds ratio 12.3).²⁷ Two of the three present C282Y homozygotes with DC were heterozygous for HLA-A*03, B*07 (haplotype frequency $2/6 = 0.3333$), consistent with our previous report.²⁷ Testing for positivity of HLA-DRB1-*15 was beyond the scope of the present work.

The increased frequency of HLA-DRB1-*15 in patients with DC suggests a possible role of the ancestral haplotype HLA-A1-B8-DR3.⁴⁷ The frequency of the HLA-A*01, B*08 haplotype was similar in 118 Alabama hemochromatosis probands and 1,321 white control subjects (0.0720 and 0.0669, respectively).²⁷ None of the three *HFE* C282Y homozygotes with DC in the present study had HLA-A*01, B*08. In Sweden, the HLA-A*01, B*08 haplotype occurs with greater frequency in hemochromatosis patients in some local populations than in the general population,⁴⁸ although there are no reports of the prevalence of DC in these patients.

The prevalence of DC among Native Americans in the US is lower than that in Caucasians.³⁴ Approximately one-quarter of Alabama hemochromatosis probands and controls reported being of Native American ancestry.⁴¹ Native American ancestry could account in part for the relatively low prevalence of



DC that we observed in the present hemochromatosis probands, and it may also account for the lower prevalence estimates of DC in other population samples of Americans^{32–34} when compared to northwestern Europeans.^{5,6,36,37}

The present results suggest that there is no significant association of risk of DC in hemochromatosis probands and their severity of iron overload. In the four probands who had DC, SF levels at diagnosis varied widely. The mean SF level at diagnosis in the present *HFE* C282Y homozygotes was much higher than that in C282Y/H63D compound heterozygotes, in agreement with previous reports.¹⁴ Regardless, the prevalence of DC in C282Y homozygotes did not differ significantly from that found among C282Y/H63D compound heterozygotes (1.02% vs. 1.49%, respectively; $P = 0.5551$). Our observations are also consistent with those of Hnaniček and colleagues who reported that among individuals from the Czech Republic, there was no significant difference in the serum iron measures and allele frequencies of controls and of *HFE* C282Y and H63D patients without a diagnosis of hemochromatosis who underwent surgery for DC.⁹

Lifestyle, occupational factors, and comorbid disorders in western Europeans have been reported to be associated with an increased risk of DC. These factors and disorders include: (1) cigarette smoking;⁸ (2) low body mass index;⁶ (3) heavy ethanol consumption;⁹ (4) elevated blood glucose levels;⁶ and (5) occupational hand trauma.^{6,9,10} In contrast, another large study did not confirm a significant relationship between DC and cigarette smoking, heavy ethanol consumption, or diabetes.⁷ We observed no association of body mass index, heavy ethanol consumption, or diabetes with DC in the present cohort.

Our prevalence estimates may be conservative because some probands may have had other fibroproliferative conditions associated with DC that we did not assess, including Peyronie disease, knuckle pads, congenital generalized fibromatosis, juvenile fibromatosis, or frozen shoulder.⁴⁹ Our relatively low prevalence estimates of DC may have decreased our ability to detect significant predictors of DC, if they exist, using logistic regressions. Because the prevalence of DC increases with age, it is possible that other hemochromatosis probands in our cohorts will eventually develop DC. On the other hand, none of

the present probands developed DC after diagnosis of hemochromatosis. The relatively long follow-up intervals for both of the present hemochromatosis cohorts suggest that the number of any future cases of DC may be small.

Conclusions

The prevalence of DC in Caucasian hemochromatosis probands who reside in central Alabama is similar to that reported in other US Caucasian population cohorts, and the severity of iron overload and other characteristics of hemochromatosis typically assessed at diagnosis are not significant predictors of the occurrence of DC. The relatively high proportion of Native American ancestry among white Alabama hemochromatosis probands and in white control subjects could account in part for the lower prevalence estimates of DC in US whites than in whites who reside in northwestern Europe.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Author Contributions

JaCB conceived this work and examined all probands. JaCB and JCIB tabulated data and performed statistical analyses. JaCB wrote the first draft of the manuscript. JaCB and JCIB revised and approved the manuscript in its final form.

Disclosures and Ethics

As a requirement of publication, the author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted



material. The authors have no disclosures to make. The external blind peer reviewers report no conflicts of interest.

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