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Hereditary Hemochromatosis Is Characterized by a Clinically Definable Arthropathy That Correlates With Iron Load

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Objective. **To determine the frequency and character of arthropathy in hereditary hemochromatosis (HH) and to investigate the relationship between this arthropathy, nodal interphalangeal osteoarthritis, and iron load.**

Methods. **Participants were recruited from the community by newspaper advertisement and assigned to diagnostic confidence categories for HH (definite/probable or possible/unlikely). Arthropathy was determined by use of a predetermined clinical protocol, radiographs of the hands of all participants, and radiographs of other joints in which clinical criteria were met.**

Results. **An arthropathy considered typical for HH, involving metacarpophalangeal joints 2–5 and bilateral specified large joints, was observed in 10 of 41 patients with definite or probable HH (24%), all of whom were homozygous for the C282Y mutation in the HFE gene, while only 2 of 62 patients with possible/unlikely HH had such an arthropathy ($P = 0.0024$). Arthropathy in definite/probable HH was more common with increasing age and was associated with ferritin concentrations >1,000 μg/liter at the time of diagnosis (odds ratio 14.0 [95% confidence interval 1.30–150.89], $P = 0.03$). A trend toward more episodes requiring phlebotomy was also observed among those with arthropathy, but this was not statistically significant (odds ratio 1.03 [95% confidence interval 0.99–1.06], $P = 0.097$). There was no significant association between arthropathy in definite/probable HH and a history of intensive physical labor ($P = 0.12$).**

Conclusion. **An arthropathy consistent with that commonly attributed to HH was found to occur in 24% of patients with definite/probable HH. The association observed between this arthropathy, homozygosity for C282Y, and serum ferritin concentrations at the time of diagnosis suggests that iron load is likely to be a major determinant of arthropathy in HH and to be more important than occupational factors.**

Hereditary hemochromatosis (HH) is a common inherited metabolic disorder characterized by systemic iron overload (1–3). It is possible that levels of other divalent metals could also be increased in HH (4). HH affects approximately 1 of 200 people and is common in persons of Northern European origin. Organ damage in the pancreas, liver, heart, endocrine glands, skin, and joints has been described in HH. The frequency and extent of organ damage may be changing with time, perhaps due to earlier diagnosis and treatment (5). In persons of Northern European origin, homozygosity for the C282Y mutation in the HFE gene is present in >90% of patients with unequivocal HH, whereas as many as 30% of cases in patients of Southern European origin may be heterozygous or wild-type (WT) for this mutation (6–8).

Schumacher first described arthropathy as a manifestation of HH in 1964 (9). Since then it has become accepted that arthropathy is frequent in HH. Arthropathy in HH is usually persistent, refractory to phlebot-

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omy, and structurally irreversible (10–12). It is a major cause of morbidity, disability, and reduced quality of life in a substantial proportion of HH patients, regardless of whether they were treated or untreated (13). A putative unique and relatively specific form of arthropathy affecting the finger metacarpophalangeal (MCP) joints 2–5 in particular and/or other joints such as the hip, ankle, radiocarpal, elbow, shoulder, and knee joints and also the lumbar spine has been described (14). The frequency of arthropathy in HH has been reported to be as high as 81% depending considerably on diagnostic criteria and the method of case ascertainment (15,16). It remains unknown why arthropathy affects only a subset of patients with HH, whether this subset can be predicted, and whether the arthropathy in HH is clinicoradiographically differentiable from other arthropathies, as is widely believed.

The aim of this study was to investigate the arthropathy attributed to HH and to specifically determine 1) the frequency of this and other arthropathies in HH; 2) the relationship between iron overload and the development of finger MCP joint arthropathy and other types of arthropathy in this disorder; 3) whether the development of the arthropathy is related to the concentration of other commonly measured divalent metals such as lead, copper, or zinc; and 4) whether the topography of the arthropathy usually associated with HH, which we have previously postulated to be analogous to type 2 polyarticular osteoarthritis (OA), can be distinguished from that of the common form of nodal interphalangeal (IP) OA, designated type 1 polyarticular OA (17).

PATIENTS AND METHODS

Study participants. Volunteers age ≥40 years in whom HH had been diagnosed by a family or specialist physician were recruited between 2006 and 2009. Recruitment was by regular newspaper advertisement, which covered the state of Western Australia. Persons were asked to volunteer for a medical study. No reference in the advertisement was made to arthritis, in order to minimize ascertainment bias for arthropathy. The study was approved by the local institutional ethics and human rights committee.

Participants were evaluated by an experienced rheumatologist (GJC) with an interest in OA and hemochromatosis. They were interviewed, and historical data were obtained. Duration of disease was determined from the time of diagnosis, not from the time when symptoms, particularly musculoskeletal symptoms, first began. Participants were asked to estimate the number of times they had undergone a phlebotomy procedure. A musculoskeletal examination was performed to determine the presence or absence of Heberden's nodes and which joints met predetermined range of motion and other criteria for arthropathy, as shown in Table 1.

Table 1. Clinical examination criteria for qualifying to undergo radiography*

Joint	Criteria
MCP2–5	Passive flexion <70°†
Radiocarpal	Passive extension <50° or passive flexion <40°
Elbow	Passive extension deficit of at least 10° or passive flexion <120°
Hip	Passive flexion <100° or passive internal rotation <20°
Knee	Passive extension deficit of at least 10° or passive flexion <120°
Ankle	Passive plantar flexion <20°
MTP1	Passive extension <60°

* MCP2–5 = metacarpophalangeal joints 2–5; MTP1 = first metatarsophalangeal joint.
† All patients had hand radiographs.

Volunteers were excluded from the study if they had clinical evidence of rheumatoid arthritis (RA), gout, or other inflammatory arthropathies. All participants were asked to undergo anteroposterior (AP) radiographic examination of the hands. Those who fulfilled the criteria for reduced range of motion in other prespecified joints were asked to undergo radiographic examination of those joints (AP views and, in the case of the elbow and ankle joints, lateral views as well). The number of views was limited in an effort to minimize radiation exposure. Blood samples were collected for HFE genotyping and for assays of blood lead and serum copper and zinc.

Diagnostic classification. Whenever possible, the earliest prephlebotomy iron studies, including serum ferritin concentrations and transferrin saturation, were sourced from the volunteers themselves, family physicians, and pathology laboratory databases; however, ascertainment of results was incomplete (58%). Thus, to determine the likelihood that volunteers had HH and to classify them in terms of diagnostic probability, other diagnostic data including HFE genotyping and phlebotomy history were reviewed in conjunction with the available iron study findings by an independent physician experienced in the diagnosis and management of HH (JKO), who did not have access to any of the other clinical or radiographic findings or laboratory data. Volunteers were assigned to the categories of definite, probable, possible, or unlikely HH and for the purpose of further analysis were grouped into the categories of definite/probable HH or possible/unlikely HH.

Occupation. We administered a validated questionnaire used to ascertain occupation and to classify volunteers according to the duration and intensity of heavy physical labor (see Appendix A) (18). On the basis of this assessment, volunteers were assigned a grade from 1 to 4. Higher grades signify heavier physical labor in terms of extent and duration in hours per week and years over an occupational lifetime.

Analysis of radiographic findings. Radiographs were read by an experienced musculoskeletal radiologist (WHB) who did not have access to any of the clinical or laboratory data and who was blinded to the diagnostic categories assigned. In the hands, 32 joints (distal IP [DIP] joints, proximal IP [PIP] joints, MCP joints, the first carpometacarpal joint, and the

scaphotrapezotrapezoidal joint) were assessed and graded for OA using the Kellgren/Lawrence (K/L) scoring system applied to OA. This method of grading was deemed to represent the most appropriate system available, given that no validated instrument exists for measuring the arthropathy associated with HH (19,20). We also recorded the presence or absence of chondrocalcinosis at any site in the hand joints or other imaged joints or hook-like osteophytes at MCP joints 2–5. Other joints were graded on the basis of the K/L scoring system where a valid K/L reference was available, and otherwise on the basis of the presence or absence of osteophytes and/or sclerosis and the degree of joint space narrowing. The principles of the K/L scoring system were applied for those joints for which a valid K/L reference was unavailable (e.g., ankle joints).

Participants were considered to have the arthropathy typical for HH in MCP joints 2–5 if the sum of the K/L grades for the 2 hands was ≥6. Neither bilateral disease nor any degree of symmetry was required. There was no requirement for hook-like osteophytes or chondrocalcinosis. To be considered to have an arthropathy consistent with HH in the hip, ankle, radiocarpal, elbow, or knee joints, participants were required to have at least K/L grade 2 disease bilaterally (those who had undergone fusion or joint arthroplasty were assigned a K/L grade of 4). Thus, participants were deemed to have an arthropathy consistent with HH if they met the predetermined K/L grade in MCP joints 2–5 and/or if they met prespecified criteria for at least 1 set of large joints bilaterally. Participants were also evaluated to determine whether they satisfied criteria for the type 1 polyarticular OA phenotype on the basis of findings in the hands alone (17). Predefined radiography criteria were used for this purpose. Participants were deemed to have type 1 polyarticular OA if the sum of the K/L grades for DIP joints 2–5 and PIP joints 2–5 in both hands was ≥8 and the sum of the K/L grades for MCP joints 2–5 was also ≤2.

HFE genotyping. HFE gene mutations corresponding to the C282Y and H63D mutations in the gene product were determined in buffy coat DNA by polymerase chain reaction amplification using previously described methods, followed by restriction enzyme cleavage and analysis on a 3% agarose gel. Participants were assessed for C282Y using the unique *Rsa* I digestion site. H63D was determined using the unique *Mbo* I digestion site. Subjects were classified as WT homozygotes, single C282Y/WT or WT/H63D heterozygotes, compound C282Y/H63D heterozygotes, C282Y homozygotes, and H63D homozygotes (21).

Assays for blood lead and serum copper and zinc. Blood lead and serum copper and zinc were measured by PathWest Laboratories using inductively coupled plasma mass spectrometry on a Varian 820-MS unit.

Statistical analysis. Data were entered into an Excel spreadsheet for the purpose of collation and statistical analysis. Median values and ranges were determined using function options within Excel. Data were exported to Quickcalcs GraphPad Statistics for statistical analysis online or evaluated via Prism offline (GraphPad Software). The significance of differences was determined by Fisher's exact test or chi-square test for categorical variables according to cell numbers, and by *t*-test for continuous variables assumed to be normally distributed. Two-tailed *t*-tests were performed throughout. Where data were not normally distributed, nonparametric tests were used. Univariate and multivariate statistical analyses were performed using logistic regression models. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are provided. *P* values less than 0.05 were considered significant. No corrections were made for multiple testing.

Table 2. Characteristics of the study participants*

	Subjects with definite/probable HH (n = 41)	Subjects with possible/unlikely HH (n = 62)
Male, no. (%)	18 (44)	25 (40)
Age, median (range) years	58 (43–77)	60 (41–83)
Duration of HH, median (range) years	7 (1–20)	4 (1–30)
Right hand dominant, %	94	86
Occupational category (1–4), mean ± SD	2.0 ± 1.1	2.4 ± 1.06
Had undergone hysterectomy, no. (%)	5 (22)	15 (41)

* There were no significant differences between the groups. HH = hereditary hemochromatosis.

RESULTS

One hundred four volunteers attended an initial interview to receive further information about the study before consent to participate was requested. One subject who provided a credible history of RA was excluded. After being fully informed, no subjects declined to participate. Thus, 103 subjects were enrolled. Forty-one participants were assigned to the category of definite or probable HH, and 62 were assigned to the category of possible or unlikely HH. These latter participants served as a control population against whom it was considered appropriate to compare those with definite or probable HH on the basis that they had been recruited under identical circumstances and evaluated in accordance with the same study protocol before being assigned to a diagnostic category. The age, sex, and duration of putative HH for participants in each of these categories are shown in Table 2. Ninety-six (93%) of those who agreed to participate in the interview and to undergo an examination and then radiography actually presented for radiography, either at or subsequent to the first visit and after a single written reminder and/or at least 2 telephone reminders. Thirty-eight of the 103 participants had radiographs of other joints as per protocol. Participants were well matched with respect to age, sex, disease duration, hand dominance, and occupational grade.

There was a marked predominance of C282Y homozygous participants in the definite/probable HH category (85%) (Table 3), as would be expected in classic HH, compared with a majority of heterozygous

Table 3. HFE genotype according to diagnostic category*

HFE genotype	Subjects with definite/probable HH (n = 41)	Subjects with possible/unlikely HH (n = 62)
C282Y/C282Y	35 (85)	19 (31)
C282Y/H63D	4 (10)	17 (27)
C282Y/WT	0 (0)	10 (16)
WT/WT	2 (5)	5 (8)
WT/H63D	0 (0)	10 (16)
H63D/H63D	0 (0)	1 (2)

* Values are the number (%) of subjects. HH = hereditary hemochromatosis; WT = wild-type.

(compound and single), WT homozygous, and H63D homozygous participants collectively in the possible/unlikely HH control group (69%).

Table 4 provides the frequency of reported arthralgia and the clinical and radiographic features of arthropathy for definite/probable HH and for possible/unlikely HH. Either arthropathy of MCP joints 2–5 or bilateral prespecified large joint arthropathy was observed in 10 of the 41 subjects (24%) with definite/probable HH. The frequency of such arthropathy among persons age ≥60 years was still higher at 36% (8 of 22 subjects). Our results are similar to the findings reported by Valenti et al (22) in a survey of well-documented Italian patients with HH in a tertiary hospital setting. Those investigators observed MCP arthropathy typical for HH in 36% of patients and at least unilateral hip arthropathy in 35% of patients. In our study, arthropathy of MCP joints 2–5 alone, bilateral hip arthropathy, and bilateral prespecified large joint arthropathy as a whole were observed significantly more frequently in the definite/probable HH group. Bilateral ankle arthropathy alone was not found to be significantly more frequent in definite/probable HH (n = 2).

Hook-like osteophytes, which are a well-recognized feature of the hand arthropathy in HH, were also found significantly more often in the definite/probable HH group. Moreover, all subjects with hook-like osteophytes were homozygous for the C282Y mutation in the HFE gene. Arthralgia was just as frequent in the subjects with definite/probable HH as it was in the controls. Likewise, Heberden's nodes and the hand equivalent of the type 1 polyarticular OA phenotype were found with very similar frequency in these 2 groups. Bilateral OA of the first MTP joint was not

Table 4. Clinical and radiographic findings in the study participants*

	Subjects with definite/probable HH (n = 41)	Subjects with possible/unlikely HH (n = 62)	*P*†
Reported arthralgia	32 (78)	49 (79)	1.00
Heberden's nodes	17 (41)	24 (39)	0.84
At least 1 clinically abnormal joint	21 (51)	16 (26)	0.0202
Hook-like osteophytes‡	7 (17)	1 (2)	0.0207
Chondrocalcinosis	2 (5)	2 (3)	1.0000
Arthropathy of MCP2–5 based on sum of the K/L grades ≥6	6 (15)	1 (2)	0.0467
Bilateral hip arthropathy based on K/L grade ≥2§	4 (10)	1 (2)	0.0144
Bilateral ankle arthropathy based on K/L equivalent grade ≥2¶	2 (5)	0 (0)	0.1561
Bilateral prespecified large joint arthropathy	7 (17)	2 (3)	0.0282
STT joint arthropathy based on the sum of the K/L grades ≥2 for the left and right joints	11 (27)	13 (21)	0.6345
Bilateral arthropathy of MTP1 based on K/L grade ≥2	4 (10)	4 (6)	0.7099
Arthropathy of either MCP2–5 or bilateral prespecified large joints (radiocarpal, elbow, hip, knee, ankle)#	10 (24)	2 (3)	0.0024
Hand equivalent of type 1 polyarticular OA phenotype	7 (17)**	13 (21)**	0.80

* Values are the number (%) of subjects. STT = scaphotrapezotrapezoidal; MTP1 = first metatarsophalangeal joint.
† *P* values less than 0.05 were considered significant.
‡ All 7 subjects with definite/probable hereditary hemochromatosis (HH) and hook-like osteophytes had the C282Y/C282Y HFE genotype. The 1 subject with possible/unlikely HH and hook-like osteophytes had the H63D/H63D HFE genotype.
§ No subject had unilateral hip arthropathy.
¶ The principles of the Kellgren/Lawrence (K/L) scoring system were applied for measuring ankle arthropathy since a valid K/L reference was unavailable. Only 1 subject (classified as having possible HH) had unilateral ankle arthropathy.
# Two subjects had grade 3 elbow arthropathy, 1 (classified as having probable HH) with unilateral arthropathy and 1 (classified as having possible HH) with bilateral arthropathy. No subjects met the predetermined clinical criteria for knee osteoarthritis (OA). No subjects were found to have OA of K/L grade ≥2 in the radiocarpal joints. All 10 subjects with definite/probable HH and arthropathy of either metacarpophalangeal joints 2–5 (MCP2–5) or bilateral prespecified large joints had the C282Y/C282Y HFE genotype. Of the 2 subjects with possible/unlikely HH and arthropathy of either MCP2–5 or bilateral prespecified large joints, 1 had the C282Y/wild-type HFE genotype and 1 had the C282Y/H63D HFE genotype.
** Four female subjects and 3 male subjects with definite/probable HH and 10 female subjects and 3 male subjects with possible/unlikely HH.

Table 5. Characteristics of the participants with definite or probable HH with and without arthropathy*

	Arthropathy of MCP2–5 or bilateral prespecified large joint arthropathy (n = 10)	Neither MCP2–5 arthropathy nor bilateral prespecified large joint arthropathy (n = 31)		Univariate analysis (logistic regression model)	
			P†	OR (95% CI)	*P*
Age, median (range) years	68 (49–77)	55 (41–75)	0.029‡	1.11 (1.02–1.31)	0.014
Male/female	6/4	17/14	0.78	1.24 (0.29–5.26)	0.775
HFE genotype	10 C282Y/C282Y	25 C282Y/C282Y, 4 C282Y/H63D, 2 WT/WT	0.58	3.03§	0.328
Duration of HH, median (range) years	13 (1–20)	7 (1–17)	0.21	1.11 (0.98–1.27)	0.106
Family history of HH in at least 1 sibling, no./total no. (%)	5/9 (56)	10/31 (32)	0.255	–	–
High iron load (ferritin >1,000 μg/liter at diagnosis), no./total no.	5/6	5/19	0.023‡	14.0 (1.30–150.89)	0.03
Phlebotomies required because of iron load, median (range) [no. of patients]	56 (30–180) [7]	38 (0–88) [30]	0.136‡	1.03 (0.99–1.06)	0.097
Occupational grade, mean ± SD¶	2.50 ± 1.30	1.87 ± 0.97	0.115	–	–
Occupational grade, no. with 3 or 4/no. with 1 or 2	6/4	8/21	0.124	–	–

* Data for some variables could not be traced and were therefore incomplete (e.g., serum ferritin at diagnosis, number of phlebotomies).
HH = hereditary hemochromatosis; MCP2–5 = metacarpophalangeal joints 2–5; OR = odds ratio; WT = wild-type.
† *P* values less than 0.05 were considered significant.
‡ By nonparametric statistical test (Kolmogorov-Smirnov test).
§ Upper limit of 95% confidence interval (95% CI) could not be estimated; lower limit was 0.39.
¶ Higher grade indicates more physical labor.

found to be significantly more frequent in the definite/probable HH group. No differences were observed in mean occupational grade between those with definite/probable HH who had arthropathy of MCP joints 2–5 and bilateral prespecified large joint arthropathy and those with possible/unlikely HH who had no arthropathy of MCP joints 2–5 and no bilateral prespecified large joint arthropathy (2.5 and 2.4, respectively; $P = 0.79$).

Table 5 provides selected clinical features and measures of iron load in participants with definite/probable HH who had either arthropathy of MCP joints 2–5 or bilateral prespecified large joint arthropathy and compares them with those in participants with definite/probable HH who had neither arthropathy of MCP joints 2–5 nor bilateral prespecified large joint arthropathy. In participants with definite/probable HH, arthropathy was found to be associated with age (OR 1.11 [95% CI 1.02–1.31], $P = 0.014$) but not with disease duration. A univariate analysis showed that ferritin concentrations in excess of 1,000 μg/liter at the time of diagnosis were strongly associated with the development of arthropathy (OR 14.0 [95% CI 1.30–150.89], $P = 0.03$). Insufficient data were available for a more robust multivariate analysis to be conclusive. However, after adjusting for age, participants with ferritin concentrations >1,000 μg/liter at the time of diagnosis were still found to be at significantly greater risk of arthropathy (OR 16.98 [95% CI 1.09–263.92]). It should be noted that serum ferritin concentrations at the time of diagnosis were available for the purpose of this study in only 27 of the 41 participants with definite or probable HH; likewise, the number of phlebotomies performed was available for only 39 of these 41 participants. A trend toward more episodes requiring phlebotomy was also observed among those with arthropathy, but this was not statistically significant (OR 1.03 [95% CI 0.99–1.06], $P = 0.097$).

A positive family history of HH was observed more often in participants with definite/probable HH who had arthropathy (56%) than in those who did not (32%), but the difference was not statistically significant ($P = 0.26$). All 10 of the participants with definite/probable HH who had arthropathy were homozygous for C282Y (OR 3.03); however, this was not statistically significant ($P = 0.328$). A trend toward higher occupational grades (more physical labor) was observed in those with arthropathy, but this difference also was not statistically significant ($P = 0.12$).

Concentrations of other divalent metals including blood lead and serum copper and zinc were measured in all participants. Those with definite/probable HH and arthropathy had higher blood lead concentrations than those with definite/probable HH without arthropathy (mean ± SD 3.5 ± 1.1 μg/100 ml versus 2.4 ± 1.2 μg/100 ml; $P = 0.0272$); however, the importance of this observation is uncertain, since a smaller and statistically

nonsignificant difference in lead concentration was observed when those with definite/probable HH and arthropathy were compared with those with possible/unlikely HH, in whom arthropathy was uncommon (mean ± SD 3.5 ± 1.1 μg/100 ml and 3.0 ± 1.6 μg/100 ml, respectively; $P = 0.3592$). In no participant was the blood lead concentration above the upper limit of the clinically accepted normal range. Serum copper concentrations were found to be lower in those with definite/probable HH and arthropathy than in those with possible/unlikely HH (mean ± SD 15.0 ± 2.1 μmoles/liter versus 17.2 ± 3.4 μmoles/liter; $P = 0.0391$).

DISCUSSION

An arthropathy involving either the finger MCP joints or bilateral prespecified large joints and determined a priori to be characteristic of HH was found to complicate definite or probable HH, confirming and extending previous observations (9–11,14,22). In clinical practice and in our study, this arthropathy can be readily distinguished from the type 1 polyarticular OA phenotype. The latter, which is common in the same age group, occurred just as often in definite or probable HH as in possible or unlikely HH. In contrast, arthropathy of MCP joints 2–5 or bilateral prespecified large joint arthropathy was found to occur in 24% of participants with definite/probable HH, but in only 3% of those with possible/unlikely HH. Arthropathy was associated with age (OR 1.11) and was thus more common late in the course of the disease. It occurred mostly in the absence of chondrocalcinosis, which in our study was an infrequent disease manifestation. Furthermore, serum ferritin concentrations >1,000 μg/liter at the time of diagnosis were found to be a strong predictor of arthropathy independent of age (OR 14.0).

This study of arthropathy in HH has a number of strengths and weaknesses. Perhaps its chief strength is that unlike previous studies, our study was community based. In contrast, previously reported studies have been retrospective observational series and have assessed patients with idiopathic hemochromatosis or HH who were mainly in tertiary referral centers where more severe cases were likely to have been concentrated and where arthropathy may have been overrepresented. Our study more likely reflects the wider spectrum of HH disease severity in the population. Furthermore, ascertainment bias with respect to arthritis was minimized by the nondisclosure of an arthritis focus in the newspaper advertising used to recruit participants. Assessment according to a predetermined clinical protocol together with the requirement for hand radiographs in all participants and other joint radiographs where predetermined clinical criteria were satisfied added rigor to the study. The application of a recognized grading system for radiographic findings and the use of "blinded assessment" (radiographs graded without knowledge of the clinical classification of participants) represent additional strengths. Another important aspect of the study is the availability of an internal control group. This was possible because a substantial number of volunteers for the study did not meet criteria for assignment to the category of definite/probable HH and were assigned to the category of possible/unlikely HH.

The study also has a number of weaknesses. Because participants were not referred by physicians and since they usually did not have accessible hospital records, diagnostic laboratory data were limited. Furthermore, some participants had putative HH of very long duration and/or had changed their family physician since diagnosis, which hindered the tracing of initial laboratory results. For example, the iron studies that supported the initial diagnosis could not be traced in ~40% of the study population. The relatively small number of patients with verifiable arthropathy limited the statistical power of the study.

The main findings in our study relate to the confirmation of an arthropathy consistent with HH (arthropathy of MCP joints 2–5 or bilateral prespecified large joint arthropathy), the distinction of this arthropathy from that conforming to nodal generalized OA (classified here as type 1 polyarticular OA in the hand), and the identification of a serum ferritin concentration >1,000 μg/liter at the time of diagnosis as an important predictor of arthropathy in HH. Occupational factors, and particularly long-term heavy physical labor, could not be shown to contribute to the development of arthropathy.

Other investigators have reported a strong relationship between iron load in arthropathy in HH in general and MCP arthropathy in the hand in particular (22). It is not clear to what extent genetic factors account for susceptibility to arthropathy in HH. In our study and in those by others, arthropathy was strongly associated with homozygosity for C282Y (all 10 participants with definite/probable HH who met criteria for arthropathy consistent with HH were C282Y homozygous) (22). It is possible that arthritis susceptibility genes are coinherited with HFE mutations. However, it is worth noting that a very similar form of MCP arthropathy has been reported in juvenile hemochromatosis in which iron overload occurs on a different genetic background (23).

Thus, whatever the mechanism, iron load may be the crucial determinant, and genetic factors may act to facilitate or hinder the development of arthropathy and/or the number and the topography of the joints affected.

Our results are consistent with those of Bulaj et al (24), who determined the frequency of MCP joint arthropathy by radiographic assessment (criteria not defined) in clinically unselected C282Y homozygous relatives of probands with HH with and without iron overload. In our study, 3 of 23 men with definite or probable HH had finger MCP arthropathy (mainly of MCP joints 2 and 3) (13%) as did 3 of 19 women (16%). Bulaj et al reported MCP arthropathy consistent with HH in 17 of 113 male C282Y homozygous relatives with iron overload (15%) and in 3 of 69 C282Y homozygous female relatives with iron overload (4%). Our results are also similar to those of Schumacher (9), who in his initial description of arthropathy in hemochromatosis reported that 5 of 23 males (22%) with idiopathic hemochromatosis had a clinically recognizable peripheral arthritis.

The observation that the arthropathy of HH is found more often in older patients is consistent with the possibility that an iron deposition threshold may need to be reached in order for osteochondral damage to occur (15,16). It is noteworthy that regular phlebotomy and thus systemic iron depletion in HH patients with arthropathy is seldom helpful for symptom relief (10–12). Moreover, iron depletion seems not to retard or reverse the progressive deterioration in joint structure. It is possible that in HH, iron may become sequestered or trapped in joint tissues and no longer available for removal by phlebotomy, unlike in other tissues/organs such as the liver. The detection of appreciable hemosiderin in synovium from HH patients with arthropathy at the time of joint surgery, but not in synovium from patients with OA or RA, supports this proposition (25). Moreover, the consistent finding of hemosiderin in the synovium of HH patients after extensive phlebotomy attests to the persistence of iron in the synovial tissue despite systemic iron depletion. Taken together, these observations suggest that iron may progressively accumulate in joint tissues where it persists despite regular phlebotomy and eventually produces irreversible osteochondral damage accompanied by intractable symptoms.

One of us (GJC) previously obtained a specimen of synovial fluid (SF) from a pathologic joint in a patient with proven C282Y homozygous HH who had a severe form of arthropathy typical for HH. SF was collected from the patient's left hip joint immediately after the joint was opened in preparation for a hip arthroplasty. In this patient, the SF ferritin concentration was found to be 5,374 μg/liter, while at the same time the serum ferritin concentration was 1,366 μg/liter. Further studies comparing SF ferritin with serum ferritin in patients with HH and in other arthropathies may help to clarify whether, despite phlebotomy, the SF ferritin level remains high in treated HH patients. The observation that concentrations of ferritin are higher in SF from OA patients who have HFE gene mutations than in SF from WT OA patients is also consistent with the possibility that localized iron deposition may contribute, although to a lesser extent, to joint damage in idiopathic OA (26). Ferritin has recently been shown to act as a proinflammatory cytokine and could contribute directly to joint injury (27). Importantly, in hepatic stellate cells, at nanomolar concentrations similar to those observed in the SF of the patient described above, ferritin was found to be a potent and rapid inducer of interleukin-1 (IL-1) gene expression (27). IL-1 is strongly implicated in cartilage and bone resorption (28–32). Accordingly, it may be an important mediator of osteochondral damage in the joints of patients with HH.

Intriguingly, a clinically and radiographically similar arthropathy, closely resembling arthropathy of MCP joints 2–5 with or without similar large joint arthropathy, occurs commonly in a subset of patients with polyarticular OA in whom HH has been excluded (17). It has long been recognized that MCP arthropathy closely resembling but not due to HH occurs commonly in the hand, and more recently several teams of investigators have reported that hand joint arthropathy and particularly MCP joint arthropathy are associated with mutations in the HFE gene (33–35). In the more extended phenotype designated type 2 polyarticular OA, 75% of patients who met strict clinicoradiographic criteria for this classification were found to have one or more HFE gene mutations, most commonly the H63D mutation (17). Higher serum ferritin concentrations were also found in these patients. It is possible that in patients with idiopathic polyarticular OA in whom the arthropathy closely resembles that typical for HH (putative type 2 polyarticular OA) and in whom HFE gene mutations are common, a less severe degree of articular iron deposition may contribute to joint damage.

In conclusion, an arthropathy consistent with that reported commonly in HH was found to occur in approximately one-fourth of patients with definite or probable HH recruited from the community. The association observed between this arthropathy, homozygosity for C282Y, and iron load as reflected by serum ferritin concentrations $>$1,000 μg/liter at the time of

diagnosis suggests that iron load is likely to be a major determinant of arthropathy in HH and to be more important than occupational factors.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Carroll had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Carroll, Breidahl, Bulsara, Olynyk.

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APPENDIX A: OCCUPATIONAL HISTORY QUESTIONNAIRE

The following occupational history questionnaire was used to ascertain and identify participants according to occupation and intensity of hard physical labor during an occupational lifetime.

1. During the years that you have been in paid employment what has been your main occupation?

   Answer: _____

2. Which of these 4 categories best describes what you have done in the course of your main occupation?

   a) mainly sedentary work
   b) job includes mainly standing and walking or light handling of materials without heavy physical loading
   c) in addition to standing and walking the job includes (included) frequent lifting and carrying
   d) hard manual work

3. In the course of your working life were you involved in any occupation that required hard manual work for **more than 5 years**?

   Yes ☐
   No ☐

   If yes, please complete the following:

   For up to 5 hours per week ☐
   For 5 to 10 hours per week ☐
   For more than 10 hours per week ☐