

Appendix Table 10. Studies of High-Risk Groups for C282Y Homozygosity or Hereditary Hemochromatosis*

Study, Year (Reference)	Setting, Time Frame, Country	Study Design	Sample	Risk Group Definition	Inclusion and Exclusion Criteria	Population	Initial Screening Sequence	Definition of Clinical HC	Diagnostic Criteria	Results	Quality																																																																															
Family setting																																																																																										
Barton et al., 1999 (57)	Southern Iron Disorder Center and Brookwood Medical Center No dates reported United States	Cross-sectional study: to compare phenotyping and HFE genotyping for diagnosis of hereditary HC in 150 family members of 61 probands	Probands diagnosed during routine medical care delivery from June 1996 to June 1998 (Genetic testing not used to diagnose probands before family members were identified—only 73.8% were C282Y/C282Y homozygotes) 150 family members of 61 probands (did not report what percentage of total)	Relatives of people with iron overload (probands: 16% had cirrhosis and 5% had diabetes attributable to iron overload)	Inclusion: willingness of probands and a family member to participate Exclusions: NR	72 (48%) men 78 (52%) women Mean age, 46 (SD, 15) y (All were adults except one 11-year-old) 94 were 1st-degree relatives; 56 were 2nd-degree non-blood relatives	Simultaneous genetic testing for HFE alleles C282Y and H63D; phenotype testing using TS; SF measurement	Phenotype definition: elevated fasting TS on ≥ 2 occasions without other known causes (>0.60 [men] and >0.50 [women]) Iron overload: elevated SF level (>300 μg/L [men] and >200 μg/L [women]), increased hepatic iron content determined by using hepatic biopsy, or iron >4 g (mobilized by TP) No genetic criteria used Hepatic cirrhosis and diabetes criteria not reported	HC phenotype: presence of elevated TS or iron overload or both	1st- and 2nd-degree relatives, C282Y/C282Y homozygotes: 25 of 112 (calculated) C282Y/C282Y homozygotes, n/n (%): Siblings: 14/42 (33) Parents: 3/16 (19) Offspring: 5/36 (14) Other blood relatives: 3/18 (16) 22 of 61 probands: blood relative with hereditary HC (36%); all were C282Y/C282Y Phenotype, n/n (%): First-degree relatives: 30/94 (31.9) Non-first-degree relatives: 4/56 (7.1)	Good/fair																																																																															
Other targeted screening																																																																																										
Cadet et al., 2003 (61)	Multiple settings: primary care patients were recruited from 3 Oxfordshire practices, and secondary care patients were recruited from patients attending specialist clinics at Amiens University Hospital No dates reported France	Cohort study: to determine the optimal means of identifying patients with undiagnosed hereditary HC using HFE genotype or phenotype	Primary care: 4022 consultations, during which 169 patients were identified with an index symptom (diabetes, AR, unexplained fatigue, abdominal pain, liver disease, abnormal LFT results, impotency, premature amenorrhea, or cardiac arrhythmia), of whom 88 were age 25–70 y and offered a genetic test for HC; 60 patients were tested Secondary care: Several groups of patients attending specialty clinics at a hospital Rheumatology clinics: 221 rheumatoid factor-negative patients with OS or AR Endocrinology clinics: 121 diabetic patients from 1 endocrine department	Patients with presenting conditions possibly related to HC	Case-patients: Exclusions: families or patient previously diagnosed with hereditary HC Controls: Inclusion: age >18 y Living in Picardy Attended a free health checkup clinic	Case-patients: OS n = 159 Sex: NR Age: 64 (SD, 12) y AR n = 62 Sex: NR Age: 61.3 (SD, 13.9) y Diabetes n = 121 Women: n = 42 Men: n = 79 Age: 54.8 (SD, 8.3) y F/A n = 227 Women: n = 144 Men: n = 83 Age: 58.3 (SD, 15.6) y Controls: n = 991 (random sample of 2337) Women: n = 483	HFE C283Y and H63D mutations, serum iron, SF	NA	NA	<table border="1"> <thead> <tr> <th>Genot</th> <th>HV (n = 991)</th> <th>PC (n = 60)</th> <th>OS (n = 159)</th> <th>AR (n = 62)</th> <th>DM (n = 121)</th> <th>F/A (n = 227)</th> </tr> </thead> <tbody> <tr> <td>HH/CC</td> <td>60.9</td> <td>68.3</td> <td>56.0</td> <td>59.7</td> <td>42.1‡</td> <td>44.9‡</td> </tr> <tr> <td>HD/CC</td> <td>26.4</td> <td>23.3</td> <td>29.0</td> <td>25.8</td> <td>24.0</td> <td>21.6</td> </tr> <tr> <td>HH/CY</td> <td>6.8</td> <td>5.0</td> <td>10.0</td> <td>8.0</td> <td>14.9§</td> <td>10.6</td> </tr> <tr> <td>DD/CC</td> <td>2.7</td> <td>3.3</td> <td>2.5</td> <td>6.5</td> <td>5.0</td> <td>9.3‡</td> </tr> <tr> <td>HD/CY</td> <td>2.9</td> <td>0</td> <td>1.9</td> <td>0</td> <td>8.3‡</td> <td>7.9§</td> </tr> <tr> <td>HH/YY</td> <td>0.2</td> <td>0</td> <td>0.6</td> <td>0</td> <td>5.8‡</td> <td>5.7‡</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Pheno</th> <th>HV (n = 991)</th> <th>PC (n = 60)</th> <th>OS + AR (n = 221)</th> <th>DM (n = 121)</th> <th>F/A (n = 227)</th> </tr> </thead> <tbody> <tr> <td>TS > 0.40, %</td> <td>29.6</td> <td>NR</td> <td>4.1</td> <td>87.6</td> <td>30.8</td> </tr> <tr> <td>Pts w/ TS >0.40 who are YY, n/n (%)</td> <td>2/293 (0.07)</td> <td>NR</td> <td>1/9 (11.1)</td> <td>7/106 (6.6)</td> <td>13/70 (18.6)</td> </tr> <tr> <td>SF >300 μg/L, %</td> <td>5.8</td> <td>NR</td> <td>4.1</td> <td>46.3</td> <td>33.0</td> </tr> <tr> <td>Pts with SF >300 μg/L who are YY, n/n (%)</td> <td>0/57 (0)</td> <td>NR</td> <td>1/9 (11.1)</td> <td>6/56 (10.7)</td> <td>13/75 (17.3)</td> </tr> </tbody> </table>	Genot	HV (n = 991)	PC (n = 60)	OS (n = 159)	AR (n = 62)	DM (n = 121)	F/A (n = 227)	HH/CC	60.9	68.3	56.0	59.7	42.1‡	44.9‡	HD/CC	26.4	23.3	29.0	25.8	24.0	21.6	HH/CY	6.8	5.0	10.0	8.0	14.9§	10.6	DD/CC	2.7	3.3	2.5	6.5	5.0	9.3‡	HD/CY	2.9	0	1.9	0	8.3‡	7.9§	HH/YY	0.2	0	0.6	0	5.8‡	5.7‡	Pheno	HV (n = 991)	PC (n = 60)	OS + AR (n = 221)	DM (n = 121)	F/A (n = 227)	TS > 0.40, %	29.6	NR	4.1	87.6	30.8	Pts w/ TS >0.40 who are YY, n/n (%)	2/293 (0.07)	NR	1/9 (11.1)	7/106 (6.6)	13/70 (18.6)	SF >300 μg/L, %	5.8	NR	4.1	46.3	33.0	Pts with SF >300 μg/L who are YY, n/n (%)	0/57 (0)	NR	1/9 (11.1)	6/56 (10.7)	13/75 (17.3)	Fair
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			(including those with unstable diabetes) Internal medicine clinics: 227 patients with chronic fatigue and AR Controls: recruited from 2337 persons >18 y from health appraisal center			Men: <i>n</i> = 508 Age: 42.5 (SD, 14.9) y OS based on radiographic analysis; AR based on clinical diagnosis Diabetes divided into 3 groups: type 1, type 2, and could not be classified F/A defined by referral to internal medicine for chronic problem					
Deugnier et al., 2002 (51)	Men and women attending Health Appraisal Centres from September 1998 to December 2000 France	Cross-sectional study	Men: age 25–40 y Women: age 35–50 y	Family history of iron excess Chronic fatigue Increased ALT levels	Included: Attending Health Appraisal Centres; meeting age criteria Those who declined genotyping (4%) had no personal history of iron excess	<i>n</i> = 9396 (96% of total population) Men: <i>n</i> = 3367 Women: <i>n</i> = 6029	Questionnaire: age, sex, BMI, awareness of a family relative regularly having TS for iron excess, personal history of blood donation, chronic fatigue, chronic distal AR, diabetes HFE C282Y mutation testing, and if C282Y homozygote Fasting serum iron status (iron, TS, and SF) and genetic counseling	HFE C282Y mutation testing	NA	C282Y homozygotes by family history of iron excess, <i>n/n</i> (%): Men Family history: 3/83 (3.6) (calculated) No family history: 7/3904 (0.2) (calculated) Women Family history: 12/16 (75) (calculated) No family history: 21/175 (12) (calculated) <hr/> C282Y homozygotes, <i>n/n</i> (%) All participants: 54/9396 (0.006) Men: 10/3367 (0.003) Women: 44/6029 (0.007) <hr/> C282Y homozygotes by presence of chronic fatigue, <i>n/n</i> (%): Men Chronic fatigue: 7/828 (0.85) (calculated) No chronic fatigue: 3/2180 (0.14) (calculated) Women Chronic fatigue: 12/2253 (0.53) (calculated) No chronic fatigue: 28/3361 (0.83) (calculated) C282Y homozygotes by increased ALT level, <i>n/n</i> (%): Men ALT level increased: 1/176 (0.57) (calculated) ALT level not increased: 9/3181 (0.28) (calculated) Women ALT level increased: 3/322 (0.62) (calculated) ALT level not increased: 42/5694 (0.74) (calculated)	Fair
CHD, CAD											
Waalén et al., 2002 (62)	Health appraisal center in San Diego, California May 1999–August 2001 United States	Cross-sectional study: to examine the relationship between 2 HFE mutations (C282Y and H63D) and the prevalence of CHD in a large white adult population	<i>n</i> = 35 792 All white, non-Hispanic adult patients age ≥25 y who attended a health appraisal center between May 1999 and August 2001	History of CHD, defined as “yes” to questions “Have you had a heart attack for which you were hospitalized for at least 3 days?” or “Do you have angina pectoris?” or an ICD-9 code of 410 or 412 in the medical record	Inclusion: white, non-Hispanic, age 25–98 y attending Health Appraisal Center of an HMO 46% gave consent for HFE mutation testing	Men: <i>n</i> = 15 362 Women: <i>n</i> = 15 554 All participants were white, non-Hispanic	400-Item questionnaire supplemented with medical record review to ensure ascertainment of all CHD events Serum iron, TS, and SF values HFE C282Y and H63D mutations	NA	TS > 0.55 (men) or >0.45 (women), SF level >250 μg/L (men) and >200 μg/L (women) were used to define elevated levels based on clinical criteria	C282Y/C282Y, <i>n/n</i> (%): Men All CHD: 3/1798 (0.17) No CHD: 65/8540 (0.76) Women All CHD: 3/1074 (0.28) No CHD: 65/9117 (0.71)	Good

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Appendix Table 10—Continued

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Liver disease clinics													
Poullis et al., 2003 (63) Moodie et al., 2002 (64)	Patients attending a liver clinic at a teaching district general hospital in south London 1997–2001 London, United Kingdom	Cross-sectional data: to examine the value of routine TS testing of new liver clinic attendees over a 5-y period in detecting previously unrecognized cases of hereditary HC	667 outpatients referred for investigation of liver disease over 5 y Afro-Caribbean/ African: ND Asian: majority originated from the Indian subcontinent, but also included 2 Chinese persons and 4 Iranian persons Mediterranean: families originated from Portugal and countries bordering the Mediterranean Sea Northern European: ND Celtic: parents or grandparents from Cornwall, Wales, Scotland, or Ireland	Outpatients referred to a liver clinic for investigation of liver disease	Exclusion: previous diagnosis of hereditary HC	<i>n</i> = 667 Age range, 17–83 y (median, 51 y) European: 68.6% (Celtic, 38.4%; other, 30.2%); Asian, 10.7%; Afro-Caribbean, 9.7%; Mediterranean, 7.9% Other, 3.1% Previous diagnoses: hepatitis C, 28%; primary biliary cirrhosis, 6%; hepatitis B, 4% Liver biopsy: <i>n</i> = 349 Previous diagnosis: 60% >30 units per week alcohol consumption, present or past history	Nonfasting TS; those with TS >0.45 or a liver biopsy had <i>HFE</i> genotyping Indications for biopsy included C282Y homozygosity, C282Y/H63D compound heterozygosity, elevated TS (>0.60), unexplained parenchymal liver disease, persistently abnormal LFT results, and liver disease of known cause necessitating staging or assessment of disease progression	NA	TS cutoffs	11 of 156 (7.1%) patients with TS >0.45 were C282Y/C282Y 1 of 349 (0.03%) patients with liver disease who had liver biopsy were C282Y/C282Y Prevalence of new cases of hereditary HC cases in patients of European origin attending a liver clinic, detected by phenotypic screening over a 5-y period, was 2.8% (12 of 458) (calculated) (Europeans only)	Fair		
Arthritis													
Willis et al., 2002 (65)	Specimens of patients with arthritis from the DNA archive of NOAR First diagnosed between 1989 and 1995 United Kingdom	Case-control study; to determine the value of screening patients with inflammatory arthritis for hereditary HC-associated mutations in the <i>HFE</i> gene	Case-patients: unselected inflammatory arthritis population collected by NOAR; prevalence of the hereditary HC-associated <i>HFE</i> genotypes compared with that in a large sample from unaffected populations Controls: 1000 individuals from the catchment area of the Norfolk and Norwich hospitals, a large subset of the area covered by NOAR	People with inflammatory arthritis	Case-patients: Inclusion: Sequential DNA samples from patients for whom adequate DNA samples remained and who were first diagnosed between 1989 and 1995; >1 swollen joint lasting for > 6 wk Controls: Exclusions: Patients with HC and people with foreign names	Arthritis populations: <i>n</i> = 1000 Controls: 373 unaffected volunteers from screening trial and 541 patients undergoing full blood counts Mean age, 54 y	<i>HFE</i> C282Y and H63D mutation testing	NA	NA	Variable Mean age, y C282Y homozygotes, <i>n</i> Predicted frequency of C282Y homozygotes (95% CI)	Arthritic Patients 54 5 1 in 287 (190–403)	Controls 54 5 1 in 236 (170–335)	Good

Appendix Table 10—Continued

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CFS											
Swinkels et al., 2002 (66)	Department of General Internal Medicine of the University Medical Centre St. Radboud, Nijmegen, a Dutch tertiary CFS referral center 1992 The Netherlands	Cross-sectional study; to determine whether patients previously diagnosed as having CFS actually have primary HC	NR	Patients fulfilling criteria for CFS Patients had given permission to store serum for future CFS studies	NR	88 self-referred patients previously diagnosed with CFS Mean age, 40 y (range, 20–66 y) Men: $n = 23$ Women: $n = 65$	TS: elevated if >0.40 (women) and >0.45 (men) All patients who could be located with elevated TS (15 of 19) were asked to provide a new fasting blood sample for a second TS and SF Genotyping done if TS or SF levels were elevated (reference values: SF: 15–280 $\mu\text{g/L}$ [men], 6–80 $\mu\text{g/L}$ [premenopausal women], and 15–190 $\mu\text{g/L}$ [postmenopausal women]) Elevated TS: $n = 6$ Elevated SF level: $n = 2$ Elevated TS and SF level: $n = 0$	NA	NR	None of the 8 patients with increased TS or increased SF levels were C282Y homozygotes or compound C282Y/H63D heterozygotes	Fair/poor

* ALT = alanine aminotransferase; AR = arthropathy; BMI = body mass index; CAD = coronary artery disease; CFS = chronic fatigue syndrome; CHD = coronary heart disease; DD/CC = H63D homozygous; DM = diabetes mellitus; F/A = fatigue and arthralgia; Geno = genotype; HC = hemochromatosis; HD/CC = H63D heterozygous; HD/CY = compound heterozygous; HH/CC = wild type; HH/CY = C282Y heterozygous; HH/YY = C282Y homozygous; HMO = health maintenance organization; HV = healthy volunteer; ICD-9 = International Classification of Diseases, Ninth Revision; LFT = liver function test; NA = not applicable; ND = not determined; NOAR = Norfolk Arthritis Register; NR = not reported; OS = osteoporosis; PC = primary care; Pheno = phenotype; Pts = patients; TP = therapeutic phlebotomy; TS = transferrin saturation; YY = C282Y/C282Y.

† Values are percentages.

‡ $P \leq 0.001$; chi-square test was used to determine the significance in each genotype versus healthy volunteers.

§ $P < 0.01$; chi-square test was used to determine the significance in each genotype versus healthy volunteers.