**Phenotype**

/H11350 2 occasions

definition: elevated fasting TS on

/0.60 [men] without other known causes (Simultaneous genetic and 0.50 NA NA Geno† HV PC OS AR DM F/A

C283Y and HFE alleles C282Y and H63D; phenotypic testing using TS; SF measurement

Iron overload: H63D mutations, serum iron, SF 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

1st- and 2nd-degree relatives, C282Y/C282Y homozygotes: 25 of 112 (calculated)

Controls: n 991 (random sample of 2337) Women: n 399 (n 60) 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‡

Others 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 168 patients were identified as having an index symptom (diabetes, AR, unexplained fatigue, abdominal pain, liver disease, ... 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: Exclusion: age >18 y Living in Picardy Attended a free health checkup clinic

Case-patients: HFE C282Y and H63D mutations, serum iron, SF

NA NA

Pheno HV PC OS AR DM F/A

TS > 0.40, % Pts w/ TS > 0.40 who are YY, n/n (%) 2/293 (0.07) NR 1/9 (1.1) 7/106 (6.6) 13/70 (18.6)

SF > 300 μg/L % Pts with SF > 300 μg/L who are YY, n/n (%) 5.8 NR 41 46.3 33.0

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### Appendix Table 10—Continued

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
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<th>Diagnostic Criteria</th>
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<th>Quality</th>
</tr>
</thead>
</table>
| Deugnier et al., 2002  | Men and women attending Health Appraisal Centres from September 1998 to December 2000 | 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 Centre; meeting age criteria  
Those who declined genotyping (4%) had no personal history of iron excess | n = 9396 (96% of total population)  
Men: n = 3367  
Women: n = 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, n/n (%):  
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) | Fair |
| Waalen et al., 2002  | Health appraisal center in San Diego, California May 1999–August 2001 | Cross-sectional study | n = 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: n = 15 362  
Women: n = 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 | 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, n/n (%):  
Men  
All CHD: 3/1796 (0.17)  
No CHD: 65/8540 (0.76)  
Women  
All CHD: 3/1074 (0.28)  
No CHD: 65/9117 (0.71) | Good |

**CHD, CAD**

**Men and women attending Health Appraisal Centres from September 1998 to December 2000**

**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 Centre; meeting age criteria**

**Those who declined genotyping (4%) had no personal history of iron excess**

**n = 9396 (96% of total population)**

**Men: n = 3367**

**Women: n = 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, n/n (%):**

**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)

**C282Y homozygotes by presence of chronic fatigue, n/n (%):**

**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, n/n (%):**

**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)

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Continued on following page
## Appendix Table 10—Continued

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<tbody>
<tr>
<td><strong>Liver disease clinics</strong></td>
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<tr>
<td>Poullis et al., 2003 (63)</td>
<td>Patients attending a liver clinic at a teaching district general hospital in south London 1997–2001 London, United Kingdom</td>
<td>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</td>
<td>667 outpatients referred for investigation of liver disease over 5 y</td>
<td>Afro-Caribbean/African: ND</td>
<td>Age range, 17–83 y (median, 51 y)</td>
<td>European: 68.6% (Celtic, 38.4%; other, 30.2%); Asian, 10.7%; Afro-Caribbean, 9.7%; Mediterranean, 7.9%</td>
<td>Previous diagnosis: hepatitis C, 28%; primary biliary cirrhosis, 6%; hepatitis B, 4%</td>
<td>Liver biopsy: n = 349</td>
<td>NA</td>
<td>TS cutoffs</td>
<td>Fair</td>
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<tr>
<td>Moodie et al., 2002 (64)</td>
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<tr>
<td><strong>Arthritis</strong></td>
<td>Specimens of patients with arthritis from the DNA archive of NOAR First diagnosed between 1989 and 1995 United Kingdom</td>
<td>Case-control study to determine the value of screening patients with inflammatory arthritis for hereditary HC-associated HFE gene</td>
<td>Case-patients: unselected inflammatory arthritis population collected by NOAR; prevalence of the hereditary HC-associated HFE genotypes compared with that in a large sample from unaffected populations Controls: 1000 individuals from the catchment area of the Norfolk and Norwich hospital, a large subset of the area covered by NOAR</td>
<td>People with inflammatory arthritis</td>
<td>Arthritis populations: n = 1000 Controls: 373 unaffected volunteers from screening trial and 541 patients undergoing full blood counts Mean age, 54 y</td>
<td>NA</td>
<td>NA</td>
<td>Variable Mean age, y C282Y homozygotes, n Predicted frequency of C282Y homozygotes (95% CI)</td>
<td>Arthritic Patients</td>
<td>Controls</td>
<td>Good</td>
</tr>
</tbody>
</table>

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).
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<tbody>
<tr>
<td>Swinkels et al., 2002 (66)</td>
<td>Department of General Internal Medicine of the University Medical Centre St. Radboud, Nijmegen, a Dutch tertiary CFS referral center</td>
<td>Cross-sectional study: to determine whether patients previously diagnosed as having CFS actually have primary HC</td>
<td>NR</td>
<td>Patients fulfilling criteria for CFS Patients had given permission to store serum for future CFS studies</td>
<td>88 self-referred patients previously diagnosed with CFS Mean age, 40 y (range, 20–66 y) Men: n = 23 Women: n = 65</td>
<td>TS: elevated if &gt;0.40 (women) and &gt;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 µg/L [men], 6–80 µg/L [premenopausal women], and 15–190 µg/L [postmenopausal women]) Elevated TS: n = 6 Elevated SF level: n = 2 Elevated TS and SF level: n = 0</td>
<td>NA</td>
<td>NR</td>
<td>None of the 8 patients with increased TS or increased SF levels were C282Y homozygotes or compound C282Y/H63D heterozygotes</td>
<td>Fair/ poor</td>
<td></td>
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</tbody>
</table>

* 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 ≤ 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.