Reviewer's report

Title: Impact of HFE genetic testing on clinical presentation of hereditary hemochromatosis: new epidemiological data

Version: 2 Date: 15 April 2005

Reviewer: Robert Britton

Reviewer's report:

General

-----------------------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The data presented do not support the conclusion that the availability of HFE genotyping resulted in earlier diagnosis (because the age at diagnosis was not significantly decreased, and actually increased in males). Therefore, some changes are required to the text (e.g., on p 8, lines 18-20: delete the sentence HH can now be unambiguously diagnosed earlier than it could be before the test was available and this greatly modifies the epidemiology of the disease.). Other textural changes are included in the next section.

2. In Table 1, the headings Yes and No are switched.

-----------------------------------------------------------------------------------------------

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

P 2, line 4: change to discovery on the clinical presentation and epidemiology of HH.

P 2, beginning on line 9: change to The profile of HH patients at diagnosis changed after the DNA test became available. Serum ferritin and iron values were lower and there was a reduced frequency of clinical signs displayed at diagnosis, particularly skin pigmentation (20.1 vs 40.4%, OR=0.37, p<0.001) and hepatomegaly (11.0 vs 22.7%, OR=0.42, p=0.006). In contrast, fatigue became a more common symptom at diagnosis (68.0 vs 51.2%, OR=XX, p=0.004). Conclusions: This study highlights the importance of the HFE gene discovery, which has simplified the diagnosis of HH and modified its clinical presentation and epidemiology. This study precisely measures these changes. Enhanced diagnosis of HFE-related HH at an early stage and implementation of phlebotomy treatment are anticipated to maintain normal life expectancy for these patients.

P 3, line 5: change to (encoding for transferrin receptor 2)

P 3, line 14: change to by increases in serum iron parameters (transferrin saturation, ferritin).

P 3, line 17: change to non-specific symptoms such as persistent fatigue and arthralgias, and at a later stage, clinical signs such as skin pigmentation,

P 3, line 20: change Hereditary hemochromatosis to HH

P 3, line 22: change to disease may progress towards irreversible damage such as cirrhosis and
hepatocellular carcinoma

P 4, line 9: change to HFE gene, a DNA test was proposed to confirm

P 4, line 11: change to enabled pre-symptomatic or early diagnosis in some patients. If phlebotomy treatment is implemented before the appearance of irreversible damage, the excess iron can be removed and patients have a normal life expectancy.

P 4, starting on line 13: change to the impact of HFE genetic testing on the clinical presentation and epidemiology of HH in a cohort of 415 patients homozygous for the C282Y mutation who were followed in a blood centre in western Brittany, France. This report contains objective data to measure this impact.

P 5, line 4: should s be changed to symbol for standard deviation?

P 5, starting on line 20: change to After introduction of molecular testing, the symptom of unexplained and persistent fatigue was more commonly present at diagnosis of HH. The frequency

P 5, line 25: change increased to changed

P 6, line 4: delete "parameter"

P 6, line 9: change to adjustment for age..

P 6, line 10: change to (>60 g/day; n=33) comprising 9.9% of the patients..

P 6, line 11: change to A decrease was not observed for the third iron parameter, transferrin saturation (79.5 vs 79.4%, p=0.93), for which an elevated value (>45%) was used as a selection criterion for this study.

P 6, line 20: change to genetic testing although these changes did not reach statistical significance

P 6, line 22: change to were significantly less frequent following implementation of molecular testing:

P 7, line 3: change hereditary hemochromatosis to HH

P 7, starting on line 7: change to Niederau et al. showed that the percentage of patients with early diagnosis increased 3-fold during the period of 1970-1981 compared to the period of 1947-1969, and that there was a further 20-25% increase in the early diagnosis rate during the period of 1981-1991 (37). These changes occurred before the discovery of the HFE gene, and were probably the consequences of improved education of physicians and the implementation of HLA testing for family members of probands.

P 7, line 12: start new paragraph with The current study highlights the importance of the discovery of the HFE gene in 1996 and demonstrates how the clinical presentation and epidemiology of HH have changed since the availability of the DNA test. Our results objectively measure these changes, and show that

P 7, line 16: change to changed: the patients have lower iron parameter values (serum ferritin and iron) and a lower frequency

P 7, line 24: should therefore be even greater than reported here.

P 8, line 8: change to thus genetic testing for confirmation..
P 8, line 11: change to non-specific symptoms

P 8, line 12: change to classical signs

P 8, line 18: change to iron overload that is expressed only at

P 8, lines 18-20: delete the sentence HH can now be unambiguously diagnosed earlier than it could be before the test was available and this greatly modifies the epidemiology of the disease.

P 8, line 25: change to patients who exhibit..

P 9, line 1: change the sentence beginning Even if HH to Until more data are available on the penetrance of the C282Y homozygous state, population screening using HFE genotyping remains controversial (27 and add new reference: Njajou OT, Alizadeh BZ, van Duijn CM. Is genetic screening for hemochromatosis worthwhile? Eur J Epidemiol 2004;19(2):101-8).

P 9, line 6: change to non-specific symptoms

P 9, line 8: change to diagnosed with the symptom of fatigue..

P 9, line 9: change to has already increased since 1996. With astute clinical assessment and HFE genetic testing, patients can be diagnosed and treated before

P 9, line 13: change to possible to analyze the transmission of HLA haplotypes

P 9, line 16: change to introduction of HFE genotyping was similar..

P 9, line 17: change to family testing did not alter our findings.

P 9, line 18: change to The impact of the HFE gene test on the identification of HH through family testing is expected to be higher in other regions where family testing was not practiced as

P 9, line 20: change to HH and follow-up phlebotomy treatment should prove efficacious in..

P 9, line 21: change to life expectancy for patients (43). Early detection can

P 9, line 23: change to through analysis of a cohort of patients..

P 9, line 24: change to was similar to that in the general population (43).

P 9, starting on line 26: change to determination of serum iron parameters as a criterion for the diagnosis of HH. This has increased the proportion of women diagnosed with HH and has decreased the frequency of certain clinical signs at diagnosis. The method of diagnosis of HH

P 10, line 2: change to sex ratio reduced to close to 1.0 and..

P 11, line 7: change to who presented with transferrin saturations of greater

P 11, line 9: add Of all patients enrolled in this phlebotomy program, 15 had no HFE mutation (among whom 4 were diagnosed before the implementation of the HFE gene test). The proportion of homozygous C282Y patients before and after the implementation of the genetic test did not change significantly.

P 11, line 21: change concentrations to parameters
P 11, line 22: change to ..after a 12-hour fast, confirmation by at least 2 measurements)

P 12, line 1: delete performant

P 12, line 3: change to Family testing combines the collection of biochemical and clinical evidence of iron overload for the patients relatives

P 12, line 11: change to as means and standard deviations, 

P 12, line 19: change to which were made separately for males and females, were adjusted for age at diagnosis and for alcohol consumption, because we showed previously that excessive alcohol consumption (>60 g/day) increased HH expressivity (33).

P 12, line 23: change to wine, beer and liquor)

P 12, line 25: change to (i.e. before or after availability of HFE genotyping)

P 12, line 26: change to assessed by calculating the odds-ratio (OR) and its 95% confidence interval (CI).

P 13: change to were involved in genetic analysis and revised the paper.

Table 1: delete the headings Biochemical parameters and Socio-demographic characteristics
Table 1: replace liter with L
Table 1: change footnote to *adjusted for age at diagnosis and alcohol consumption

Figure 1: change gender labels to Male and Female

Figures 2a and 2b: change title to main clinical signs and symptom at the time..
Figures 2a and 2b: change y-axis label to Frequency (%) and use scale of 0 to 100 (instead of 0,0 and 100,0)

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.