Reviewer's report

Title: New epidemiological data on hereditary hemochromatosis

Version: 1 Date: 23 November 2004

Reviewer: Claus Hellerbrand

Reviewer's report:

General

Scotet et al. aimed to assess the impact of the discovery of the HFE gene on the epidemiology of hemochromatosis (HH). Overall this approach is interesting. However, the critical question to be answered is whether HFE genotyping has impact on the morbidity and mortality of hemochromatosis (HH) patients. Unfortunately, the present study contributes little to the answer of this question. Moreover, there are major concerns regarding the quality of the data presented and the conclusions drawn from these data.

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

The authors mention that the "results were adjusted for .. alcohol consumption" and state that there was a "subgroup ... of patients having no excessive alcohol consumption" (page 6, last sentence). Does this mean that most patients had (excessive) alcohol consumption? Based on the major impact of alcohol on iron metabolism and the damaging effect of iron overload particularly in hepatic tissue, respectively, this is critical. The authors have to state precisely 1. How data concerning alcohol consumption were collected. 2. What was the definition of "excessive alcohol consumption"? 3. How many patents consumed "excessive amounts of alcohol"? This numbers have to be given for all patients before and after 1996.

The only clinical sign based on which the diagnosis HH was made that differed significantly prior and after 1996 in male patients was fatigue. 1. it remains unclear whether fatigue, arthritis, hepatomegaly etc. had been clinical signs leading to the diagnosis HH or whether there was a follow up investigating whether the patients actually had diabetes, hepatomegaly/liver damage etc. after the diagnosis was made. Only the later is important regarding the above mentioned question. 2. Obviously, fatigue is quite an unspecific clinical sign. It may be suspected that "fatigue" was not the only (clinical) sign that led to the use of HFE genotyping.

It is well known that TFS is the critical parameter reflecting body iron overload. However, this parameter was not different prior and after 1996. Instead, the authors base their discussion on serum ferritin and iron. However, particularly serum iron has no value for the diagnosis of HH or the estimation of body iron overload, respectively.

There is no logic explanation why the age at onset of women - but not the one of men - decreased. Particularly, since the TFS did not change. The author's explanation that differences in women are not significant due to the small number of women analyzed may be correct in part but does not explain the missing difference in men.

The authors distinguish patients included before and after 1996 in their venesection program, since the HFE mutation was first described in 1996. However, rather they should divide the subgroups
"diagnosis based on HFE genotyping" or not, respectively. It seems more than unlikely, that in all patients starting venesection in 1996 and thereafter HH was based on HFE genotyping.

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

Precise information should be given with regards to the methods of genotyping and the origin of the genomic material was used?

Had there been standardized conditions for the collection of the serum and the measurement of the serum iron parameters? Repeated measurements? Was the serum collected after 12h starving?

Was there information available concerning liver iron content?

How many cases diagnosed before 1996 revealed no HFE mutations?

Had the statistical tests be performed one-sided or two-sided? Here, only two-sided statistical testing is appropriate. If done differently, the p-values have to be corrected.

Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because scientifically unsound

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests’