Reviewer's report

Title: Hereditary Hemochromatosis (HFE) genotypes in heart failure: Relation to etiology and prognosis

Version: 1 Date: 4 February 2010

Reviewer: Christina Ellervik

Reviewer's report:

Minor

1) Abstract: I prefer that the aim is clearly stated in the abstract.

2) Introduction, 1st paragraph: You write that the prevalence of HH is 0.37-0.46: is that the clinical prevalence, the biochemical or the genetic prevalence?

3) I prefer using “polymorphisms” instead of “variants”

4) In the results, you discuss a result in relation to reference 17. Do not discuss results in the Results section. Furthermore, I wonder if the reference 17 is correct. Is it reference 24 instead?

5) Table 3: please make a footnote to “other”, “unknown” and “deceased”.

6) Please, put the log-rank p-values on the fig 1a-d. It seems as though C282Y carriers differ significantly from non-carriers.

7) Concerning genotyping, please also refer to the dbSNP rs-numbers for C282Y, H63D, and S65C in the Methods.

Major:

1) 2nd paragraph of Introduction and the whole discussion:

a) Danesh has written a meta-analysis in 1999 in Circulation on risk of IHD according to different iron parameters and van der A et al (Circ Cardiovasc Genet. 2008 Oct;1(1):43-50) has written the most comprehensive IPD meta-analysis on risk of HFE genotypes and IHD. Both of the studies conclude that increased iron parameters (Danesh) and HFE genotype (specifically C282Y/C282Y) do not associated with IHD (or MI). Please, correct the introduction and Discussion according to these studies.

b) Furthermore, please distinguish between the heart disease associated with the juvenile hemochromatosis, in which heart involvement is far more evident than in the adult-onset form (e.g. see Pietrangelo NEJM). This might also be the reason for you not finding the hemochromatosis gene mutations associated with HF in your population as this is far older.

2) You should sell the paper on the much more interesting finding that in a population of HF patients with HF not caused not by HH-variants, HFE-variants
may protect against mortality due to the fact that the patients do not get anemia.

3) Therefore I also suggest that you present a table of the results from the Cox-regression analyses: crude and adjusted.

4) Clinically and biochemically H63D/H63D is usually not related to HH. In the Discussion, I would prefer that you write C282Y/C282Y is not associated with IHD (van der A et al (se above)) but H63D/H63D may be associated with neurodegenerative disease and stroke (maybe due to a different mechanism other than iron overload).

5) In the Discussion you should point out the limitation on the number of patients making you unable to stratify on the more interesting genotype status for C282Y/C282Y homozygotes than the clinically less interesting and less useful carrier-status. Due to this limitation it would be helpful to have a power-calculation in the results.

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests