Reviewer's report

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

Version: 1 Date: 15 February 2010

Reviewer: Dairena Gaffney

Reviewer’s report:

Comments

1. The authors could be considered to be selectively interpreting the literature. For example Rasmussen et al 2001 is quoted as supporting the fact that the C282Y is associated with increased risk of coronary heart disease but the authors themselves are much less didactic about this interpretation. But in fact there is so much conflicting literature about this subject (Heart disease and HFE genotype) that it is possible to find support for either side of the case.

2 Earlier published studies are contradictory and any effects are small. It does not seem likely that any HFE genotyping, especially S65C genotyping, will ever be a test for predicting outcome for heart failure cases. The authors were presumably interested in whether HFE genotype could, by some mechanism, predict the outcome for Heart Failure patients. From earlier studies, I would have thought that narrowing the diagnostic criteria to try and get a uniform set of patients would be more likely to reveal a genetic connection rather than including individuals with different reasons for their heart failure.

3 I think it is rather an overstatement that individuals with genotype CCDD are predisposed to iron overload. There are an enormous number of CCDD individuals in any Celtic population with no iron overload so it is possible that the very small number of CCDD individuals who present with minor iron overload are presenting for some reason other than their HFE genotype. In the same way, individuals with genotype CC HH SS can, and do present with iron overload. The recommendations for Predictive Referral, genotype CCDD from King C, Barton DE. (Best practice guidelines for the molecular genetic diagnosis of Type 1 (HFE-related) hereditary haemochromatosis. BMC Med Genet 2006;7:81) are very cautious. Again, the literature is contradictory about this, although American Web sites encouraging mass genotyping for HFE mutations would probably encourage all to think otherwise (for example see www.healthcheckusa.com).

Major Compulsory Revisions

4 I do not see the need for figure 1. If anything, it’s confusing as it gives equal visual impact to the very small number of S65C carrier individuals who died during the 4 year period compared with those with C282Y or H63D. The same data has been adequately presented in the text and on Figure 3.
5 I would change the wording of the last paragraph from "therefore it seems that performing HFE genotype... to "Therefore it seems that performing HFE genotype screening in heart failure patients has no value unless of course they display clear clinical signs of HH." And I think the last sentence should be omitted. If a doctor wants to know the effect hemoglobin levels on heart failure mortality it will be far better to study this connection directly.

Minor Essential Revisions

6 Table 2 Distribution of HFE genotypes. To avoid confusion between cultures who use a comma and those who use a full stop to delineate four figure numbers, I suggest removing the punctuation in the column corresponding to the numbers for Pederson et al. 3.871 can something quite different from 3,871 but I think 3871 is understood by all.

Level of interest: An article of limited interest

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