Author's response to reviews

Title: Hepatocellular carcinoma and the penetrance of HFE C282Y mutations: a cross sectional study.

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Response to Reviewers:

We are grateful for the time and attention given by the three reviewers who have raised 12 questions. As a result we have made 11 modifications to the paper and believe that the standard of the paper has been significantly improved.

Changes in response to Reviewer 1:
1. We agree that the diagnosis and management (or otherwise) of haemochromatosis is an important consideration. We have therefore explicitly discussed this in relation to our data in the discussion (page 10), adding an additional reference.
2. We have also altered the legend to table 3, clarifying the source of our venesection data. Being a retrospective analysis we have very limited data for this.
3. We agree that we should have used an odds ratio to express the risk of developing HCC. The abstract (page 2), results (page7) and discussion (page 9) have been altered accordingly.
4. We have qualified our comment about the association between HFE genotype and HCC on pages 9 and 10 of the discussion.
5. Our reference to the tables (3 not 2) in the Results (histology) section (page 9) is now correct.
6. The histological stage of fibrosis is now explained in the header of table 3 as is the grade of siderosis (liver iron). The grading method is described in the Ishak reference in the Results; Histology section.

Changes in response to Reviewer 2:
1. We have now cited our work on arthritis in the introduction (page 4) with the addition of another reference.
2. We have clarified that the Norwich cases were cross-referenced with the Cambridge cases to exclude overlap by modifying the Methods section (page 5).
3. We have modified the methods section (pages 5 and 6) to give a more detailed description of the unpublished method.
4. The standard ABI Taqman protocol used required optimisation; determining the optimal primer and probe concentrations by empirical titration using controls. The newer taqman protocols with minor groove binders can be used with standard concentrations of all reagents. We have not made any alterations to the manuscript in reference to this point.

Changes in response to reviewer 3:
1. We have added and discussed the Boige reference suggested by the reviewers and altered page 12 accordingly. We highlight that this group used a different case ascertainment strategy for their study in comparison to ours.
2. The retrospective nature of this study precluded collection of comprehensive data about environmental risk factors. We recognise this as a limitation and we have modified the end of the discussion on page 12 to indicate this. We hope that this study will encourage a similar prospective study (including data on environmental modifiers) in a large tertiary hepatology referral centre.