Reviewer's report

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

Version: 1 Date: 14 March 2005

Reviewer: Ernest Beutler

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General
This manuscript reports the frequency of HFE genotypes among the 144 cases of hepatocellular carcinoma (HCC) collected from two hospitals in East Anglia over a 30 year span. The frequency of C282Y homozygotes among these cases is then applied to data on annual incidence of HCC and frequency of C282Y homozygosity among the overall population to calculate the lifetime risk of HCC among C282Y homozygotes, which is estimated to be 1.31% (0.52%-3.32%). The calculations were limited to males as none of the 8 C282Y homozygotes among the 144 HCC cases were female. The manuscript addresses a very important question, ie. what is the penetrance of the C282Y homozygous genotype. The approach they have used is a more robust than most, given that the phenotype is well-defined, allowing a relatively unbiased estimate of penetrance. However, the low incidence of HCC makes collection of these data difficult. Because the numbers are by necessity small, the variance of their estimate is large.

This is the third paper by this group reporting similar data on hepatocellular carcinoma in C282Y homozygotes. As noted by the authors, the current manuscript includes some cases included in the prior publications. In the first of these, published in Lancet in 1997, a penetrance of 0.4% based on 2/28 homozygotes found and extrapolated to the 49 HCC cases in the series was reported. In the second, published in Gut in 2000, the penetrance was estimated to be 1.1% based on 3 homozygotes found among 34 HCC cases.

Although the current paper reports on a larger number of cases, the numbers are still quite small and the confidence interval around the percentage of homozygotes (8/102 male HCC cases or 7.8%) is therefore of necessity still very large. Compounding the problem is that fact that the calculation of lifetime risk for homozygotes is dependent on several other estimates, the variances of which do not appear to be taken into account: the 1.26/100,000 annual incidence among males in the total population, the 0.6% frequency of C282Y homozygotes in the population, and the number of subjects in the total population reaching the age of 54 annually (1260/100,000). Taking the variance of all the estimates used in the final calculation would make the variance of the overall estimate even larger.

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

The authors cite two papers finding a similar percentage of C282Y homozygotes among HCC cases, one reporting 2 homozygotes/35 HCC cases in France (Blanc JF, et al. J Hepatol 2000) and the other reporting 5 homozygotes/162 HCC cases in Austria (Cauza E, et al. Am J Gastroenterol 2003), but do not cite another French study reporting 0 homozygotes/133 HCC cases (Boige V, et al. Lack of association between HFE gene mutations and hepatocellular carcinoma in patients with cirrhosis. Gut 2003;52:1178-1181). This report should be cited, and discussed. Three other Italian and Spanish studies reporting no homozygotes among HCC cases are dismissed as having small populations with low HFE C282Y prevalence.

Given the major risk of HCC associated with viral hepatitis, it is surprising that the authors did not test for these factors to analyze their interaction with C282Y homozygosity in this population.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
none

The review of this manuscript for was a joint effort of Jill Waalen MD MPH and Prof Ernest Beutler

**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:**

We declare that we have no competing interests