Reviewer’s report

Title: HFE H63D mutation frequency shows an increase in Turkish women with breast cancer.

Version: Date: 3 November 2005

Reviewer: Ernest Beutler

Reviewer’s report:

General

In this study, genotyping for HFE mutations was done in 88 Turkish women with breast cancer and 100 control women. A significantly greater frequency of H63D heterozygotes was found among the cases (n=39 or 44%) compared with controls (n=28 or 28%) (p=0.02). None of the subgroup comparisons were statistically significant. Although the study is small and the p value is not overwhelming, the results have merit.

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

1. In the second sentence of the Discussion it is stated “The results of this case-control study showed an increased risk for sporadic breast cancer in Turkish women who were carriers for the HFE H63D mutation.” However, the statistically significant comparison that was reported seemed to be between all breast cancer cases (familial + sporadic) and controls. This should be clarified.

2. The statement in the last paragraph of the Discussion that “Most population studies, however, failed to show any effect even in homozygotes for H63D [in regard to iron homeostasis]” is not true. Significant increases in both transferrin saturation and serum ferritin levels in H63D heterozygotes vs. HFE wildtype controls have been demonstrated in all large population studies (Beutler E, et al.: Penetrance of the 845G->A (C282Y) HFE hereditary haemochromatosis mutation in the USA. Lancet 2002, 359: 211-18; Jackson HA, et al.: HFE mutations, iron deficiency and overload in 10 500 blood donors. Br J Haematol 2001, 114: 474-484.)

3. The opening discussion in the Background section on iron-related generation of free radicals as the mechanism for an association of HFE mutations with cancer should be removed as this is highly speculative (and even inconsistent with the authors own statements in the Discussion that most studies have failed to show an effect of the H63D mutation on iron homeostasis). That this is one possible mechanism for an association between the mutation and cancer could more appropriately be mentioned in a sentence in the last paragraph of the introduction instead.


5. The discussion in the Discussion section re: possible association of H63D with HLA in contributing to increased cancer risk is good. Another possibility, that of stratification—particularly
within a population that likely has a mix of European and non-European ancestries—should also be considered and discussed, the idea being that H63D mutations and other, unrelated breast cancer susceptibility gene mutations, may both occur at higher frequencies in a specific subgroup of the population.

6. The authors should also be referred to a recent article making the same comparisons of H63D mutation frequency between Russian women with breast cancer and controls (Kondrashova TV, et al.: Frequency of hemochromatosis gene (HFE) mutations in Russian healthy women and patients with estrogen-dependent cancers. Biochim Biophys Acta 2005). In that study, age was found to be an important confounder of the association, wherein a positive association of H63D with breast cancer was only found among women >57 years old. It would be useful if the similarities and differences between that paper and the current study were discussed.

7. The issue of multiple comparisons, particularly in a small study of this size, should be addressed. If adjustments were made for the premenopausal vs. postmenopausal, familial breast cancer vs. controls, and the familial breast cancer vs. sporadic breast cancer comparisons cited in the paper, the p value for the comparison between all breast cancer cases and controls (0.02) would be changed by a factor of 4 (0.08).

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

1. In the results section, the actual data for the comparisons described in the text (familial breast cancer vs. sporadic and familial breast cancer vs. controls) should be given in Table 2, similar to the premenopausal vs. postmenopausal data.

2. Table 3 is hard to read. The Variable column should be left-justified rather than centered and the last 2 rows should be in the “N=” format as in the preceding rows.

3. A new table, Table 4, is introduced in the Discussion. The data in this table could easily be summarized in the text. The table is not necessary and is actually a bit distracting.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.