Author's response to reviews

Title: HFE C282Y and H63D in Adults with Malignancies in a Community Medical Oncology Practice

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re: revision of manuscript “HFE C282Y and H63D in Adults with Malignancies in a Community Medical Oncology Practice” by J.C. Barton, L.F. Bertoli, and R.T. Acton

Dear Dr. Puebla:

Thank you for the prompt and thorough review of our work. Herein we have summarized responses to the criticisms and suggestions of the Reviewers, and offer point-by-point responses. The criticisms and suggestions are displayed in italics, and our responses appear in standard font. We have largely excluded the commentary of the Reviewers that does not contain suggestions for change.

Reviewer: Anna Carla C. Goldberg
Discussion: Minor Point
It strikes us that, for example, in the 6 cases of polycythemia vera, apparently 4 carried one of the mutated alleles. The data are not clear on this point.

The Reviewer is correct. We have inserted these sentences in the footnote of Table 1: “Among the six patients who had polycythemia rubra vera, two were heterozygous for C282Y, one was a compound C282Y/H63D heterozygote, one was homozygous for H63D, and two did not have C282Y or H63D. The one patient with Ph-positive chronic myelogenous leukemia was heterozygous for H63D.”

We inserted this parenthetic phrase in the Discussion, third paragraph: “(six of whom had polycythemia rubra vera).”

Major Points
In another part of the Discussion, low frequency of H63D mutation is associated to B-lymphoma but p = n.s. In other cases, no difference is seen when compared to normal controls. As the authors themselves propose:

“The allele frequencies of C282Y and H63D in the central Alabama whites are relatively great (0.0896 and 0.1447, respectively) [15, 16]. Thus, a positive or negative association of malignancy with HFE genotype in a population in which the frequency of HFE mutations is relatively high may be due to chance association with other genetic or environmental factors. Contrariwise, a significantly increased relative risk of malignancy may be more readily demonstrated in populations in which C282Y or H63D frequencies are lower [7, 27].”

Thus, in spite of a very well written and detailed Discussion, the general impression conveyed is that HFE gene might indeed have a role in development of malignancies, which cannot be concluded from the data. The authors regard the OR values that are >2.0 or < 0.5 as having relevant biological value, or in other words, that they represent a trend (Results and
Discussion. However, in no instance are the results statistically significant which compromises the first sentence of conclusions as stated in the Abstract.

We have revised the Conclusions section of the Abstract thusly: “In 100 consecutive adults with malignancy evaluated in a community medical oncology practice, frequencies of HFE C282Y or H63D were similar to those in the general population. This suggests that C282Y or H63D is not associated with an overall increase in cancer risk. However, odds ratios computed in the present study suggest that increased (or decreased) risk for developing specific types of malignancy may be associated with the inheritance of HFE C282Y or H63D. Study of more patients with these specific types of malignancies is needed to determine if trends described herein would remain and yield significant differences.”

Thus, discussion and conclusions should be changed accordingly as they are indicative that even in an extended cohort of 100 patients HFE gene is not conducive or associated to cancer development.

The first paragraph of the Discussion indicates that we agree in principle with the Reviewer. Further, we have made re-written this paragraph to agree with changes made above in the Abstract: “The present 100 patients with malignancy were 12 years older than the 318 control subjects, on average, yet the corresponding frequencies of HFE C282Y and H63D in the patients and controls were similar, and the occurrence of C282Y or H63D was not associated with an increased (or decreased) OR for malignancy. Because the present cohort of patients consisted of consecutive patients with malignancy who were evaluated in a community medical oncology practice, there was no bias that favored selection of adult patients of a certain age or with a specific type of malignancy. Consistent with the present observations, there was no significant relationship of C282Y frequency to age in primary care patients in California [22]. This is in contrast with the postulate that there is age-related susceptibility to malignancy in persons with C282Y [8]. Nonetheless, the present observations do not exclude the possibility that an increased (or decreased) risk of developing specific types of malignancy may be associated with common HFE mutations.”

The concluding sentences of the Abstract (see previous revision above) and the final sentences of the Discussion have been revised thusly: “In 100 consecutive adults with malignancy evaluated in a community medical oncology practice, frequencies of HFE C282Y or H63D were similar to those in the general population. This suggests that C282Y or H63D is not associated with an overall increase in cancer risk. However, odds ratios computed in the present study suggest that increased (or decreased) risk for developing specific types of malignancy may be associated with the inheritance of HFE C282Y or H63D. Study of more patients with these specific types of malignancies is needed to determine if trends described herein would remain and yield significant differences.”

Reviewer: Seppo Parkkila
Minor Compulsory Revisions
1. The authors mention that: 318 apparently healthy white persons from the general population were used as controls. In the Results section, the controls include 148 men and 160 women that makes only 308 controls. I think that there has to be errors in some numbers.

There was a typographical error. “148” should be “158.” This has been corrected.

2. Based on the Results section, “24 patients had myeloid malignancies” (24 patients had myeloid malignancies (myelodysplasia, myeloproliferative disorders, or acute non-lymphoblastic leukemia). If I counted those patients in Table 1, I get a different number (23).

Data in Table 1 are correct (13 patients with myelodysplasia, 5 with myeloproliferative disorders, and 3 with acute non-lymphoblastic leukemia). Thus we have changed the Results section to reflect 23 rather than 24 patients.

3. It is not appropriate to provide values of p or OR’s when n < 5 (e.g., see Table 2).

We respectfully disagree. We did not use chi-square approximations when any number in a cell was less than five. In every case when a number in a cell was less than five, we used Fisher’s exact test. This is consistent with standard statistical methodology and with the underlying assumptions of the Fisher’s exact test. In Statistical Considerations, we have inserted the phrase “when a number in a cell was < 5” and removed the original phrase “as appropriate.”

We believe that these changes have significantly improved the manuscript. Each author has reviewed the manuscript and agrees with the changes. We have also reviewed the manuscript to be certain that formatting is correct in accordance with the on-line checklist. Thanks in advance for your further review of our work.

Yours truly,

Ronald T. Acton, Ph.D.

cc: J.C. Barton, L.F. Bertoli