Author's response to reviews

Title: The R337H Mutation in TP53 and Breast Cancer in Brazil

Authors:

Magda C.B. Gomes (maggomes@superig.com.br)
Joanne Kotsopoulos (joanne.kotsopoulos@wchospital.ca)
Gutemberg Leão de Almeida (gute.almeida@uol.com.br)
Mauricio M Costa (mamcosta@yahoo.com)
Roberto Vieira (rvieira@iff.fiocruz.br)
Firmino de A G Filho (firminoag@ig.com.br)
Marcos B Pitombo (MPITOMBO@URBI.COM.BR)
Paulo Roberto F Leal (prfalcao@globo.com)
Robert Royer (robert.royer@wchospital.ca)
Phil Zhang (phil.zhang@utoronto.ca)
Steven A Narod (steven.narod@wchospital.ca)

Version: 2 Date: 8 March 2012

Author's response to reviews: see over
Dear Dr. Lubinski,

Thank you for reviewing our manuscript. We enclose the revised manuscript which we would like you to consider for publication as a Research Article in Hereditary Cancer in Clinical Practice. Our manuscript has been modified to incorporate the reviewer comments that are outlined below.

We would like to respond to the reviewers in turn:

**Reviewer 1:**

**Comments**

**Results:**

Please draw family trees for the two mutation positive families.

We have included pedigrees for the two mutation positive families.

**Discussion:**

The authors conclude that the frequency of R337H founder mutation (0.5%) in their study is lower than in two previous studies in other regions of Brasil (Sao Paolo and Porto Alegre) which reported frequency of 2.4% (San Paolo) and 11% (Porto Alegre), and they suggest that there may be regional differences in the mutation frequency as Sao Paolo and Porto Alegre are 442 km and 1546 km from Rio de Janeiro. This conclusion is wrong as it is derived from comparison of different series of cases - in Rio de Janeiro unselected cases of breast cancer were studied, in Sao Paolo a mix of high risk families with multiple breast cancer cases (n=45) and sporadic cases of breast cancer (n=78) was analyzed, and in Porto Alegre, Li-Fraumeni and LFS-like families (only some presented with breast cancer) were genotyped. It is not surprising that the frequencies in these series are different. You cannot compare apples to pineapples because they sound similar.

The authors appreciate this comment and have revised the manuscript to include additional information on the different study populations utilized in the aforementioned studies on page 8.

**Reviewer 2:**
Major Compulsory Revision:
There are a few points that require clarification. In the two patients identified with the R337H polymorphism their family histories are described. It would be valuable to know if the polymorphism segregated with the other family members who presented with a malignancy.

Although the authors appreciate this comment and agree that it would be valuable to know if this polymorphism segregated with other family members with a malignancy, we do not have information on the cancer or mutation status of family members and cannot accurately address this concern.

Minor Essential Revision:
A minor point is in the Abstract, the authors should change the last sentence of the background statement from "....low-penetrance breast cancer susceptibility gene." to "low-penetrance breast cancer susceptibility polymorphism." - we know that P53 is a breast cancer susceptibility gene.

The authors appreciate this comment and have made the suggested change.

We hope that you find these changes satisfactory.

Yours truly,

Steven A. Narod