Author's response to reviews

Title: Contribution of germline BRCA1 and BRCA2 sequence alterations to breast cancer in Northern India.

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Author’s response to reviews: see over
Dear Dr. Simpson,

We have carefully corrected grammatical errors and formatted the manuscript to conform to journal style guidelines.

Concerning the comment of Reviewer 2 which suggests that insufficient numbers of control samples had been analyzed to determine relative risk of mutations that do not cause premature protein truncation:

We have taken care in the manuscript to classify these mutations as “unclassified variants” and to provide a thorough discussion about the difficulties associated with assigning disease causality to such mutations. We do not include these variants in our calculations of disease-associated mutation frequencies in the North Indian population. In addition, we have made the effort to screen an additional 20 control samples for the presence of these unclassified variants (total of 140 samples) to determine population carrier frequencies, with the expectation that an appreciable carrier frequency would identify neutral polymorphisms. Generally accepted standards for this type of validation are 100 chromosomes, or 50 unaffected population controls. We have nearly tripled the number of patient samples analysed and show that none of the variants identified in our patient samples occur at an appreciable frequency in the general population. Overall, we have presented all available data that might aid in interpreting the nature of these mutations, but include the appropriate caveats in our discussion. We have also modified Table 4 (previously uploaded as table 6). Since the uploading is not possible because of its big size, the table is divided into two parts. The nomenclatures issue is not insignificant, and while the second round review may not have commented on it, it makes the manuscript nicer if we pay attention to these details. It also allowed a more comprehensive data summary of the number of times each mutation has been identified in the Indian population, and in what type of cases (familial, early-onset, etc.).

The additional mutation screening we have undertaken in response to the reviewer’s comment has added a fair bit of time to the revision of our manuscript. We thank you for your patience.

Sincere regards,