Reviewer’s report

Title: Expanding the genetic basis of copy number variation in familial breast cancer

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Reviewer: kay huebner

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This is a well-written (with small necessary edits listed above) and well-illustrated MS exploring germ line copy number variations (CNVs) in DNA of 129 young women wit apparent familial breast cancer (fBC) not caused by the known fBC genes. Authors fond 275 rearrangements not in controls, some of which were previously reported as BC susceptibility genes. IN particular, authors discuss WWOX CNVs in 2 patients and partial FHIT deletion in 1.

Overall comments

1. This is a larger study than the 2 previous similar studies but with only 40 control cases. What all of the studies lack is a demonstration of CNVs tracking with disease AND any evidence of function of the gains or losses in contributing to disease development. This study is no exception. Evidently the study was not designed to include BC cases from the same family to see if a specific CNV tracked with disease. Authors seem to believe that because many of the losses and gains include or are very near to previously identified cancer-associated genes, that this is evidence for functionality in causing BC.

2. Since several of the genes involved in CNVs, including FHIT, have been reported to be involved in genome stability or impaired DNA break repair, one wonders if sequencing of the germ line DNA, perhaps in the youngest patient of 22 years, carrying the FHIT partial deletion might reveal increased mutations (since loss of FHIT causes genome instability and FHIT is haploinsufficient for some functions). If indeed this patient’s germ line DNA exhibits enhanced mutation frequency this would be strong evidence for functionality of loss of a portion of one FHIT allele and would also provide a rationale for how this might lead to further mutations and cancer development.

3. the authors also call for larger studies and hopefully the enlarger studies will be designed to include multiple BC cases within individual families to allow tracking of specific CNVs with disease.

Specific comments

1. Authors imply that FHIT CNVS have not been exported but the DGV database lists many of them. Also, there is a paper by Lucito et al, 2007, that describes FHIT CNVs in two pancreatic family individuals’ germline DNA.

2. In Fig 3, the FHIT locus deletion seems to include exon 5; is this the case?

3. Are tumors of any of these cases available?
(for the above overall and specific comments, alterations to the MS could include comments on these issues)

Minor but necessary edits:
p2, line 11 from bottom—“resolution … has increased”
p3, CNV and Stat analysis, line 1—“comprehensive analyses”
p5, line 3, versus
p5, ‘occurrence and distribution…’—line 1, …of which 35 also occurred …
p5, 6 lines from bottom— have recently been …
p6, line 4 from bottom—the FHIT gene …
p7, ‘small but substantial;…’—maybe say small but significant?
p7, paragraph 4, last sentence—‘combination of …’
p8, line 8—a fraction of fBCs

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare I have no competing interests