Reviewer's report

Title: BRCA1-mutated and basal-like breast cancers have similar aCGH profiles and a high incidence of protein truncating TP53 mutations

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Reviewer: Nicholas C Turner

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This manuscript reports that BRCA1 related and sporadic BLBC have similar CGH profiles and TP53 mutation status. This is largely a reanalysis of previously published data sets, although new TP53 sequencing is reported. The TP53 mutation data adds to the data of Manie et al Cancer Research 2009, and in contrast to this report finds increased truncating mutations in non-hereditary BLBC. This contrasting finding is important to report.

There are limitations to the CGH analysis as discussed below. Grossly BRCA1 and BLBC are suggested to have similar CGH profiles. Whether this provides evidence for a defect in BRCA1 in sporadic BLBC, or whether this is simply a reflection of the basal-like subtype is unclear.

Minor Essential Revisions

More detail is required on the TP53 sequencing methodology.

I have some concerns with the comparison of BRCA1 mutated profiles (paraffin extracted DNA) with BLBC profiles (frozen extracted DNA). The profiles with paraffin DNA will have increased noise, and the authors attempt to adjust for this by scaling the data. However this may also compress the profiles of highly genomically unstable cancers. In addition there may be chromosomal regions that are differentially affected by noise between paraffin and frozen, and this cannot be accounted for. There is some evidence presented that this has not grossly effected the results, comparison of luminal J and H (Figure 2D), but is unclear if differences between BRCA1 and BLBC could have been missed.

The BAC array used in this work is of low resolution compared to currently used platforms, and this limits the analysis especially with the increased noise of paraffin extracted DNA. This study will therefore be limited to detecting regional chromosomal alterations, and will have limited sensitivity for focal changes.

The authors should discuss these limitations.

TP53 mutations analysis

The Authors reanalyze TP53 mutation data from Holstege et al Cancer Res 2009, but include mutation data of only 13 of the 37 sporadic breast cancers sequences in this paper. It is unclear why the other 24 cancers have been excluded from the mutation analysis in this manuscript.
The authors state that there is no difference in non-truncating mutations between BRCA1 mutated and sporadic luminal cancers. The splitting of the two luminal groups is reducing the power of this analysis. Combining the two luminal groups may lead to significantly increased missense and hotspot TP53 mutations in BRCA1 cancers compared to luminal cancers. This analysis should be presented.

It would be interesting to report the TP53 mutation rate in luminal BRCA1 tumours vs basal, as these cancers are reported to have fewer TP53 mutations Manie et al Cancer Research 2009.

CGH profiles
The authors comment on a significant difference at chromosome 14 between BRCA1 and BLBC, but it is unclear if this is a chance observation.

The analysis of Figure 3B is underpowered. It would be useful to have a fourth panel in this figure comparing Luminal-H and luminal J, to assess whether the comparison of Figure 3C is complicated by DNA type.

Discretionary revisions

Figure 4. The clustering of the data in this figure is to a certain extent self-fulfilling. The authors determine which regions differentiate BRCA1/BLBC from luminal tumours, and then on the same data set show this leads to clustering of the tumours. Demonstration that these regions lead to similar clustering of an independent series would substantially improve the manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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 that I have no competing interests