Reviewer's report

Title: RNA Profiling Reveals Familial Aggregation of Molecular Subtypes in non-BRCA1/2 Breast Cancer Families

Version: Date: 4 December 2013

Reviewer: Lorenzo Melchor

Reviewer's report:

In this study, Larsen and colleagues analyse a collection of 70 frozen breast tumour biopsies from a total of 58 families by global RNA profiling and promoter methylation analysis. The authors add these results to those shown in a former manuscript, which was focused only on BRCA1- and BRCA2-associated cancers (Larsen et al PLOS One 2013).

The manuscript has a detailed Background section and the Result section is well written and fluid. Overall, this is an article of importance in its field.

First, it provides further reproducibility of the existence of the intrinsic molecular subtypes in hereditary breast cancer in an additional and independent collection of tumour samples. Indeed, the proportions are in agreement with previous studies that showed BRCA1-mutated cancers predominantly displayed basal-like molecular profiles, BRCA2-associated tumours were enriched in luminal B cancers, whereas non-BRCA1/2 tumours resembled the variety and proportions seen in sporadic breast cancer (Melchor et al Oncogene 2008, Waddell et al Breast Cancer Res Treat 2010, Jönsson et al Breast Cancer Res 2010).

Second, the identification of BRCA1 promoter hypermethylation in non-BRCA1/2 tumours that showed a BRCA1-like profile proves the accuracy and potential benefit of their former classifier and is in agreement with other studies that used other techniques (Joosse et al. Breast Cancer Res Treat 2012, Alvarez et al Clin Cancer Res 2005).

Third and more importantly, the authors demonstrate a familial aggregation in eight out of eleven non-BRCA1/2 families with more than 1 tumour where cancer samples shared the same molecular subtype. This association is statistically significant and is further confirmed in a separate sample collection (Hedenfalk et al NEJM 2001). To this referee knowledge, this is the first study reporting such a pattern of familial aggregation. This finding is of importance to further stratify non-BRCA1/2 cancer patients in order to perform better next generation sequencing analysis and mutational screening of new breast cancer susceptibility genes.

It is, therefore, my opinion that this article is suited for the BMC Medical Genomics readership and that the authors could address the following short list of minor revisions.
1. Discussion section titles are repetitive with the Result section ones and may lead to confusion. The authors could take advantage of these section titles in the Discussion to deliver a much clearer message based on their results and conclusions.

2. There are two minor typos to correct in the manuscript:
   a. Discussion p.15. Sentence starting “The aim of this study…” Replace ‘homogenous’ for ‘homogeneous’
   b. Discussion p.18, third paragraph. “On the contrary, a study analysed tumors using noted that different tumors within the same family…” Consider revising the structure or meaning of this sentence.

**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 that I have no competing interests