Reviewer's report

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

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Reviewer: Ana Osorio

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The manuscript by Larsen et al. describes an expression profiling study of a relatively large series of hereditary breast tumours (BRCA1/BRCA2/BRCAX). The study is well designed and involves an acceptable number of samples given the difficulty to obtain the frozen tumours required. The authors confirm previous observations about the distribution of BRCAX tumours along the intrinsic molecular subtypes and association of BRCA1 and BRCA2 tumours with the basal and luminal B subtype respectively. The most interesting finding is perhaps the observation that affected members of the same family tend to share the same molecular subtype, suggesting a link between the genetic defect and the subtype, which could be very useful in the search for new susceptibility genes.

Minor essential revision:

My only concern to this study is the heterogeneous and somehow incomplete way in which the patients have been tested for mutations in BRCA1 and BRCA2. The authors mention a mixture of techniques used for the screening that include the Protein Truncation Test which could have lead to some false negatives. It is necessary to specify the percentage of cases tested with each of the techniques to be sure about the reliability of the results. A table showing the distribution of the different families with respect to the inclusion criteria should be also added.

Regarding the non-BRCA1/2 tumours that the authors find to be BRCA1 or BRCA2-like, using the BRCA1 and BRCA2-signatures prediction, they should specify how this cases were tested (which was the technique used) to be sure that they don’t harbour a mutation that could have been missed.

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.