Reviewer’s report

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

Version: 1

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Reviewer: Florentine Hilbers

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Larsen and colleagues analyzed the RNA profiles of the tumors of 70 non-BRCA1/2 familial breast cancer cases. This study population includes 11 families for which the tumors of two or more individuals we analyzed. They show that Basal-like, HER2-enriched, Luminal A, Luminal B and Normal-like tumors are found in non-BRCA1/2 familial tumors with a distribution similar to that found in sporadic tumors. In addition they show that in 8 out of 11 families in which two or more samples were available, the tumors of the family members are of the same molecular subtype.

Although the number of families with multiple samples is small, the clustering of molecular subtypes within families is an interesting observation. The authors argue that selection of families based on the clustering a specific subtype could aid the discovery of new high risk breast cancer genes in for example next generation sequencing studies.

However, the high number of non-BRCA1/2 families (8 out of 11) in which a specific subtype seems to cluster suggests that within these groups of families, there is still a considerable amount of etiological heterogeneity. Multiple segregation studies show that mutations in additional high penetrance genes are likely to be very rare and explain only a small proportion of non-BRCA1/2 families, while most familial clustering is likely caused by a polygenic risk. Do the authors think moderate or low risk variants can be responsible for the observed clustering of molecular subtypes? Or do they have another explanation for the difference in suggested frequency of high penetrance mutations in non-BRCA1/2 families suggested by their study and that of most segregation studies (Antoniou et al., Cui et al.)

1. Discussing this might give some depth to the Discussion section which currently contains maybe too many details from the results.

Another argument against the usefulness of this approach to select more genetically homogeneous non-BRCA1/2 families is the fact that tumor RNA of sufficient quality can rarely be collected for more than one individual per family. It will therefore be very hard to collect enough families with the same clustering subtype to gain enough power to detect an association with rare variants within high risk gene.

2. The authors claim that they are the first to “…systematically demonstrate that
members of the same family often share the same tumor subtype…”. However, Didraga et al. (Breast Cancer Research and Treatment 2011) shows that a specific tumor array CGH profile also clusters within a subgroup of non-BRCA1/2 families. (While a follow-up WES study was unable to find mutations in a high penetrance gene in these families).

Minor Essential Revisions

3. In Figure 4 three individual in Family 029 are colored green, suggesting that the tumors of these three individuals have been analyzed and show the same molecular subtype. However, Table 2 includes only two individuals with the same subtype for family 029. Please check if either one contains a mistake or make clear why one individual was not included in Table 2.

4. In general the manuscript could use some editing by a native speaker. Some specific language issues:
   Page 18, last paragraph: “On the contrary, …” a word seems to be missing from this sentence.
   Page 15, first sentence of the last paragraph: also some missing words.

Discretionary Revisions

5. Since the BRCA1, BRCA2, Sporadic and non-BRCA1/2 group differ a lot in size, it would be helpful to add percentages to Table 1.

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

**Quality of written English:** Needs some language corrections before being published

**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