Reviewer's report

Title: Altered PPP2R2A and Cyclin D1 expression defines a subgroup of aggressive luminal-like breast cancer

Version: 4
Date: 4 January 2015

Reviewer: Ozden Yalcin-Ozuysal

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Summary:
In the manuscript entitled “Altered PPP2R2A and Cyclin D1 expression defines a subgroup of aggressive luminal-like breast cancer” the authors test the hypothesis that PPP2R2A and Cyclin D1 expression levels, evaluated by immunohistochemistry (IHC), could define a subgroup of luminal breast cancer in terms of differential overall and disease free survival (OS and DFS, respectively). Making use of retrospective cohort study design, they analyzed (i) the correlation between PPP2R2A copy number alterations and mRNA expression level/OS, (ii) the association between PPP2R2A expression evaluated by IHC and histological parameters (such as grade, ER, PgR, Her2, Ki67 statuses), (iii) the association between PPP2R2A/Cyclin D1 expression statuses evaluated by IHC and OS/DFS. The reported results support the authors’ conclusion that PPP2R2A(-/low) or PPP2R2A(-/low)/CyclinD1(high) phenotypes evaluated with IHC are associated with poor OS and DFS in luminal like breast cancer. The study contributes to the current knowledge by providing an IHC based PPP2R2A evaluation as a novel criteria to predict OS and DFS.

Major Compulsory Revisions:
The statements about Luminal A- and Luminal B-like subtypes need clarification. More specifically:
1. The histological parameters that are used to classify Luminal A- and Luminal B-like subtypes (grade, Her2 status etc) should be explained.
2. In the “PPP2R2A (B55#)(-/low)/Cyclin D1(high) expression defines a group of luminal BC with worse outcomes” result section, it is stated that 53.3% of the PPP2R2A(-/low)/Cyclin D1(high) phenotype tumors are classifiable as Luminal A-like. However, the data that justifies the statement is not obvious in the given references (Table 1 & Figure 6). The appropriate data should be cited.
3. In the second paragraph of discussion, it is stated that “… approximately half of the cases with the PPP2R2A(-/low)/Cyclin D1(high) phenotype correspond to luminal B-like BC …”. The data that justifies the statement is not obvious and should be cited.
4. In the conclusion, it is stated that “…PPP2R2A(-/low)/Cyclin D1(high) phenotype… allows the identification of a subgroup of luminal BC with reduced
DFS that would be otherwise classified as luminal A-like.” Because of confusions explained in 2nd and 3rd points, the statement lacks the appropriate references in the data.

Minor Essential Revisions:
1. The CNA sample size from TCGA database is stated as 374 (HetDel:334 + HomDel:40) and No CNA (diploid) is stated as 208 in Figure 3. Although, in the second paragraph of the “PPP2R2A CNA status is associated with mRNA expression levels and OS in the TCGA dataset” section, it is written that the same dataset is used, the sample sizes are stated as 208 for CNA and 374 for No CNA both in the text and Figure 4. The consistency of the sample sizes should be checked.

2. In Figure 5, the data size of the validation cohort should be checked. On the figure, it is 374 (PPP2RA high: 258 + PPP2RA -/low: 116), while in the legend it is stated as 274.

3. In Figure 1, in the top boxes “breast cancer” is written twice.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests.