Reviewer’s report

Title: Elevated C1orf63 expression is correlated with CDK10 and predicts better outcome for advanced breast cancers: a retrospective study

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Reviewer: Daniel Cohen

Reviewer’s report:

Review of “Elevated C1orf63 expression is correlated with CDK10 and predicts better outcome for advanced breast cancers: a retrospective study.” Submitted to BMC Cancer.

The authors provide exciting data suggested to demonstrate that chromosome 1 open reading frame 63 (C1orf63) protein expression is a valuable biomarker for breast cancer. The authors show evidence from microarray data of 128 tumors and conclude that 1) C1orf63 expression is associated with better outcome (increased overall survival) in patients with stage III-IV breast cancer and 2) that CDK10 expression and C1orf63 expression are correlated.

Data Sources:
1) 8 patients with tumor and normal tissue
2) 4 breast cancer cell lines (MCF-7, BT549, MDA-MB-231, SK-BR-3)
3) 128 breast cancer tumors with clinical parameters including overall survival (OS)
4) mRNA expression microarray data of 4 cohorts in public domain (E-GEOD-49922, E-GEOD-5847, E-GEOD-23988, E-TABM-158)

Analysis:
1) C1orf63 expression by IHC in normal vs tumor
2) C1orf63 expression by western blot in cell lines
3) C1orf63 and CDK10 expression patterns by IHC in 182 patients
4) C1orf63 and CDK10 mRNA expression in 4 tumors.

The methods for comparing C1orf63 expression in 8 tumor and normal samples, C1orf63 and CDK10 expression in 128 breast tumors with clinical parameters and mRNA levels from 4 tumors with available microarray data were described and written adequately. The figure presentation of data appear sound. However, the writing of the paper is presently unacceptable. This deficiency makes the written presentation of the data, discussion of implications and comprehension of the authors’ conclusions very difficult to understand.

The number of controls (8 normal tissue/tumor pairs) are somewhat limited should be increased. Additional breast cancer vs normal tissue should be
evaluated for C1orf63 expression. Consideration of examination of C1orf63 expression in other tumors (colorectal and lung adenocarcinoma) available microarray data would strengthen the study. Further discussion of the candidate functions of the protein should be included in the discussion. This may help clarify the possible dual tumor promoter and suppressor actions proposed by the authors. C1orf63 is also known as Arginine/serine-rich protein 1 (RSRP1, NCBI gene ID: 57035) but was not referenced by the authors.

Therefore, I find this study very intriguing with potential impact on the diagnosis and prognosis of breast cancer. I would consider this manuscript of interest to the scientific and pathology community and potentially worthy of publication, however the manuscript in its present state is unacceptable for publication in BMC Cancer. Thorough editing and revision of the manuscript by a native English speaker is essential.

Major Compulsory Revisions:
1) Seek editorial revision by a native English language speaker or comparable expert.
2) Controls: 8 tumors served as controls with adjacent normal tissue. Only 4 of these showed C1orf63 staining. The authors should obtain at least two (2) more control breast cancer tumor tissue samples with normal adjacent tissue to demonstrate that C1orf63 is not expressed in non-tumor tissue.

Minor Essential Revisions:
1) Confirm adherence to journal format requirements.
2) Verify that references properly correlate with in-text citation.
3) Verify that figure references properly correlate with the in-text citations.
4) In the introduction note that C1orf63 is also known as Arginine/serine-rich protein 1 (RSRP1, NCBI gene ID: 57035)
5) “Comparable to adjacent non-cancerous tissues, there was a higher positive rate of C1orf63 expression in tumors, which demonstrated the early stage of breast cancer, C1orf63 might serve as a tumor promoter….Thus, C1orf63 expression in breast might not involve ER, PR, HER-2 expression. In the advanced stage of breast cancer however, C1orf63 might act as a tumor suppressor.” p.12
   a. This is confusing. What were the criteria used to designate the “early stage of breast cancer”? Clarify in methods the histopathological definitions of “early cancer” and revise discussion.
   b. How may C1orf63 function as a tumor promoter and subsequently a tumor suppressor? Provide proposal of a mechanism supported by the literature of similar protein arginine/serine rich proteins functions.

Discretionary Revisions:
1) Examination of C1orf63 expression in other tumors (colorectal and lung adenocarcinoma) available microarray data would strengthen the manuscript and
should be added.

2) Consider these as sources for C1orf63 functions and discussion:

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**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.