Reviewer's report

Title: The risk allele of SNP rs3803662 and the mRNA level of its closest genes TOX3 and LOC643714 predict adverse outcome for breast cancer patients

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Reviewer: Marc Tischkowitz

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Gudmundsdottir et al The risk allele of SNP rs3803662 and the mRNA level of its closest genes TOX3 and LOC643714 predict adverse outcome for breast cancer patients

Major comments

1. This manuscript describes a detailed study of TOX3 and LOC643714 expression in relation to the SNP rs3803662 in a cohort of Icelandic breast cancer cases. It builds on previous studies that show an association of this SNP and breast cancer risk. Although the study numbers are small, the results imply that this risk can be further refined to breast cancer subtypes. However the manuscript is hard to follow in places and sometimes the observations appear to be contradictory. For example the authors found that rs3803662 with lower TOX3 expression was confirmed in oestrogen receptor positive tumours. Yet they also found that low TOX3 and LOC643714 expression correlated with the basal subtype which is typically ER-. Then later in the results section they show that expression levels of TOX3 and LOC643714 were significantly higher in ER positive tumours than in ER negative tumours. These observations appear to be contradictory – can the authors clarify? In fact the manuscript would be greatly enhanced if the authors could provide a schematic figure, outlining the associations they have identified between TOX3 and LOC643714 expression in relation to the SNP rs3803662 in the different breast cancer subtypes.

2. It would also be useful to discuss the possible biological mechanism underlying such associations e.g. are there any known interactions that could connect TOX3, CREB, CBP or CITED1 with ER?

3. Given the previous finding that the minor rs3803662 allele also increased the risk of breast cancer in BRCA1 and BRCA2 carriers, can the authors suggest why this effect does not appear to have been seen for any of the women in this study with the999del5 BRCA2 mutation? Where the numbers too small, or could this be a gene or mutation specific effect.

4. Did the authors verify that high TOX3 levels are a prognostic marker for distant mets and overall survival by allowing for LN status? If not, then this could merely be a proxy for LN status.

Minor comments
1. Abstract methods – please change “normal DNA” to “DNA extracted from blood”

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

**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'