Reviewer's report

Title: Multiplex genetic cancer testing identifies pathogenic mutations in TP53 and CDH1 in a patient with bilateral breast and endometrial adenocarcinoma

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Reviewer: Paolo Aretini

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SUMMARY

The authors demonstrate in this paper the effectiveness of using Next Generations Sequencing technologies instead of traditional screening methods to detect causative mutations in high cancer risk families. In my experience it's very difficult to classify certain families on the basis of family history because of heterogeneity of tumor spectrum. Consequently it's not so easy to choose the genetic test which are performed serially for the most likely genetic causes as reported in the paper.

The authors here present a case of a female with bilateral breast cancer and endometrial carcinoma and a really strong cancer family history. As annotated from the authors, the cancer family history is suggestive for Hereditary Breast and Ovarian Cancer (BRCA1&2 mutations), Li-Fraumeni Syndrome (TP53 mutations) and hereditary diffuse gastric cancer (CDH1 mutations). After non informative test for BRCA1&2 genes, the index case was analysed for 150 genes associated with hereditary cancer or with frequent somatic mutations according to the COSMIC (www.sanger.ac.uk/genetics/CGP/cosmic/) and Cancer Gene Census (www.sanger.ac.uk/genetics/CGP/Census/) databases. This analysis detected heterozygous germline mutations in two genes:

1. a TP53 mutation (c.673-1 G>A) which affects a splicing site (the damaging effect on mRNA splicing of the TP53 mutation were confirmed by cDNA analysis);

2. a CDH1 missense mutation (c.892 G>A), which was reported as pathogenetic in previous work. This mutation can confer a high risk of lobular breast carcinoma (confirmed in index case from histologic revision).

CONCLUSIONS

The paper is well written and all the issues are well elucidated (genetic counselling, genetic analyses, pedigree building, histopahological revision; etc).

I suggest to add the correct nomenclature to describe the amino acid change for the CDH1 mutation (c.892 G>A ---p.A298T).

Optionally I suggest to perform a little bioinformatics analysis to further demonstrate the pathogenetic effect of CDH1 (for example by using Mutation
In my opinion this paper is suitable for the publication.

**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.

**Declaration of competing interests:**

I declare that I have no competing interests