Reviewer's report

Title: First evidence of a CHEK2 duplication involved in cancer predisposition in an Italian family with hereditary breast cancer

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Reviewer: Quinten Waisfisz

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The paper by Tedaddi et al., describes the identification of a novel duplication in the CHEK2 gene in a family with multiple cancer cases. They conclude that this finding suggests that CHEK2 mutations are heterogeneous and confer susceptibility to different types of tumours. In addition, they conclude that the data demonstrate the importance of screening for such rare mutations.

Although the mutation is indeed novel and the first duplication to be described, the authors overinterpret their results.

Major Compulsory Revisions:

1. Authors should be much more modest in their suggested causal relationship between the observed CHEK2 mutation in the family and the cancer cases within the family that have not been tested. These individuals may or may not carry the mutation. Even if they are able to show that additional cancer cases in the family indeed carry the mutation a causal relationship between the mutation and the observed phenotype is not proven. Therefore, throughout the manuscript, i.e. title, abstract and the rest of the manuscript.

   In this respect the discussion related to Li-Fraumeni should also be removed or rephrased. Several studies have studied the contribution of CHEK2 germline mutations to LFS and LFL syndrome but the suggested role of CHEK2 as a major gene involved in LFS could not be confirmed. (See e.g. Evans DG, Birch JM, Narod SA: Is CHEK2 a cause of the Li-Fraumeni syndrome? J Med Genet 2008, 45:63-64)

2. Include in figure 2C all available family members (II-3, II-5, II-7, III-4, and III-5).

3. Include the predicted effect of the duplication. Is it an in frame or out of frame duplication?

4. We have described autosomal recessive inheritance of CHEK2 mutations, i.e. homozygous CHEK2*1100delC, in several families (Adank et al., 2011). These families are characterized by multiple breast cancer cases in a single generation and cases are frequently affected by multiple primary tumours including bilateral breast cancer. Authors should sequence all coding exons (including splice sites) of the CHEK2 gene in patient II-3 to test for compound heterozygous mutations in CHEK2.

Minor Essential Revisions:
1. The first paragraph of the Background section lacks references, please include these.

2. The CHEK2*1100delC mutation is present at nucleotide 1100 in a transcript that is consists of 15 exons while the transcript used in figure 2B has 16 exons. Please indicate refseq numbers (NM#'s) to make this clear.

3. Replace in figure 1 the asterisks by + or – symbol indicated that the individual has been tested and was either carrier for the mutation or wt.

4. There are ways to combine the figures in 2A in one plot by shifting one of the plots by a few nucleotides (and change the color of one of the plots). In this way it is much easier for the reader to see what probes are changed in their relative height. Alternatively scale the plots in such a way that the absolute height of the reference peaks is similar in both plots. I also suggest starting the plots with the first reference peak at 133 bp and remove the first peaks.

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