Reviewer’s report

Title: Hereditary breast cancer: Ever more pieces to the polygenic puzzle

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Reviewer: Robert Winqvist

Reviewer’s report:

This review on hereditary breast cancer predisposition is very well and consisely written, and also the overall structure of the paper is nice. The field is rapidly evolving (during 2013 alone, altogether over 50 new susceptibility factors have been reported) and therefore a timely literature review like the current one, encompassing also the latest discoveries as well as a critical assessment of their clinical impact, is highly important for various kinds of readers with an interest in this exciting topic.

Minor essential comments:
- for completeness and also for clarification on page 5, para 2, lines 5-6, the authors should add the corresponding Fanconi anemia gene name for BRCA2 (the FANCD1 gene), PALB2 (the FANCN gene) and RAD51C (the FANCO gene).
- in section I. Rare mutations with a high to intermediate penetrance, and also in Table 1, it would be appropriate also to include the FAM175A gene (also known as ABRAXAS/ABRA1/CCDC98), the rare mutations of which that appear to associate with genetic predisposition to predominantly breast cancer of the lobular subtype [Solyom S et al. Breast cancer-associated Abraxas mutation disrupts nuclear localization and DNA damage response functions. Sci Transl Med. 2012 Feb 22;4(122):122ra23]. Also, rare germline mutations in UIMC1 (also known as RAP80) appear to be associated with predisposition to both breast and some other types of cancer [Nikkilä J et al. Familial breast cancer screening reveals an alteration in the RAP80 UIM domain that impairs DNA damage response function. Oncogene. 2009 Apr 23;28(16):1843-52]. The products of both of these genes are important regulators of BRCA1 function.
- in section II. Polymorphic variants with low penetrance, it would be very helpful for the reader if the authors could add a brief clarifying statement saying that the observed intronic and intergenic variants may affect genomic regions important for the regulation of gene expression and/or gene function.
- throughout the paper the authors should be cosistent in the way they use the names for various cancer related syndromes (eg. Cowden Disease should be Cowden disease, Ataxia-telangiectasia should be ataxia-telangiectasia, Fanconi Anemia should be Fanconi anemia, etc.).
- care should also be taken with the usage of either UK engl. or US engl., not a mix of both as is currently the case (eg. germ-line vs. germline).
- page 3, para 1, last sentence would be better as: …monoallelic occurrence of mutations predisposes heterozygous carriers outside of syndrome families to cancer, as will be described in more detail below.
- page 3, para 2, third sentence would be better as: … polygenic trait and also that several more susceptibility genes exist.
- page 4, last sentence: proto-oncogenes

**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