Author's response to reviews

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

Authors:

Natalia V Bogdanova (bogdanova.natalia@mh-hannover.de)
Sonja Helbig (helbig.sonja@mh-hannover.de)
Thilo Dork (doerk.thilo@mh-hannover.de)

Version: 2 Date: 19 August 2013

Author's response to reviews: see over
Reply to the Reviewers:

Reviewer 1:

We thank the Reviewer for his time and his helpful comments and suggestions. We fully agree with all his points and have addressed them in the revised version as follows:

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).

These names have now been included in brackets.

- 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 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.

This is an excellent point. Both genes have now been included in an extra paragraph on pages 4-5 and in Table 1, and references have been added accordingly. The new para reads as follows:

“- UIMC1/ FAM175A/ BABAM1: The binding of BRCA1 to ubiquitylated and sumoylated histones at the site of double strand breaks is mediated by the ubiquitin-interaction motif containing protein UIMC1 (better known as RAP80) through binding the FAM175A gene product ABRAXAS (also known as ABRA1 or CCDC98) that interacts with BRCA1 in a complex stabilised by MERIT40, the product of the BABAM1 gene [44]. Only few studies have addressed the role of UIMC1 or FAM175A mutations in breast cancer susceptibility. Familial breast cancer screening has revealed a rare alteration in the RAP80 UIM domain that impairs DNA damage response function [45], and an ABRAXAS mutation that disrupts nuclear localisation has been observed in breast cancer patients with mainly lobular tumour histology [46]. In addition, BABAM1 has emerged as a significant low-penetrance risk locus for triple-negative breast cancer in genome-wide association studies as will be discussed further below.”
- 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.

We have added this sentence on page 7.

- throughout the paper the authors should be consistent 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.).

We have opted for capital letters throughout the text, in view that the widely used abbreviations such as A-T, FA, or BS are always written in capital letters.

- 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).

We have opted for the British version and thus write “counselling”, “signalling” and “germ-line”.

- 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.

The sentence has been modified accordingly.

- page 3, para 2, third sentence would be better as: …polygenic trait and also that several more susceptibility genes exist.

The sentence has been modified accordingly.

- page 4, last sentence: proto-oncogenes

We have now written proto-oncogene (just referring to RAD51)
Reviewer 2:

This is an interesting review on the role of several susceptibility genes with a varied risk on hereditary breast cancer risk. These genes are well represented in different categories from high to low penetrance risk and described efficiently. Since GWAS are more popular and efficient technology trusted to detect risk alleles in different cancer, the coverage from the big consortium studies is very meaningful and helpful in further research.

I would suggest discussing the population risk of these breast cancer susceptibility genes with different ethnic groups and races. It would provide stronger evidence to perform gene based experiments in different populations.

We thank the Reviewer for his time and helpful comments and suggestion. We agree that population stratification is an important issue and have incorporated a new paragraph into the revised version on page 9 that addresses ethnic diversity as follows:

“Population diversity needs to be taken into account for breast cancer susceptibility at all levels of penetrance. Due to founder effects, single mutations can contribute significantly to the breast cancer burden in founder populations and intermediate-risk alleles in some genes have almost exclusively been found in certain population groups, such as for FAM175A and RAD50 in the Finnish population or NBN in Slavic populations [46, 73-75,77]. In fact, much of the present knowledge about those genes relies on particular founder mutations, and in regard of allelic heterogeneity one must be cautious to extrapolate and generalise these observations to other less common alleles. Similarly, common polymorphisms at breast cancer susceptibility loci will differentially impact on breast cancer risk in different ethnic groups, if they display different frequencies or different linkage disequilibrium patterns across populations, such as CASP8*D302H that is virtually absent in Asians [152], or the ESR1 locus at which different risk alleles SNPs have emerged in Asians and Europeans [100,103,154-156]. Gene-based strategies for an improved risk prediction will therefore need to be elaborated in a population-specific way.”