Reviewer’s report

Title: BRCA1 and BRCA2 mutation spectrum - an update on mutation distribution in a large cancer genetics clinic in Norway

Version: 0 Date: 23 Oct 2017

Reviewer: Stefan Aretz

Reviewer's report:

General

In this retrospective descriptive study, the authors provide an update on the amount and frequency of BRCA1 and BRCA2 germline mutations in Norway, based on the patient cohort of the largest hereditary cancer clinic, covering around half of the population. Compared to a previous study, much more patients have been included and thus, much more rare and potential founder mutations were identified. The analysis and interpretation of the data is challenged by different mutation screening approaches and techniques over time, the incomplete coverage of the Norwegian population, and the biased number of mutation carriers per family. Although this is a more or less confirmatory study and in the era of NGS panel sequencing, the knowledge of founder mutation frequencies will probably not influence the diagnostic strategy anymore, the authors present a large and carefully analysed data set that allows deeper insights into the origin and distribution of BRCA germline mutations and the number of mutation carriers per index patient who can be reached by cascade genetic screening. The study design is straightforward, the work-up is adequate, the paper is clearly structured, well written and consistent.

Specific comments

1. Throughout the manuscript, different ways of addressing the frequency and spectrum of germline mutations in the study cohort are mixed: the number of unique BRCA mutations (207), the number of families (i.e. the number of apparently unrelated index patients) with BRCA mutations (981), and the overall numbers of mutation carriers (3522). To avoid confusion, I would recommend that the authors clearly mention and differentiate between these three categories. The number of mutation carriers for a given (founder) mutation might be heavily biased through the methods applied and the fact that in former times only founder mutation screening was performed which makes it more likely to have identified more mutation carriers by predictive testing in those old families with founder mutations (see results), as stated in the discussion. Thus, the number of carriers might be less meaningful than the number of affected families to describe mutation frequencies. Based on this considerations it might be important to always describe the frequency of the founder
mutations related to the number of families (index patients). E.g., in the abstract it seems more relevant to mention the fraction of families rather than the fraction of carriers (86%) with frequent mutations.

2. Are there any attempts being made to re-analyse the old cases, where only targeted founder mutation screening was performed, with up-to-date methods (sequencing of the whole coding region and MLPA) to uncover more BRCA1/2 germline mutations in the unexplained old families?

3. Page 6, Classification: the authors state that all identified variants were re-evaluated but they don´t describe, how this was done. I would suggest to describe the procedure in more detail since this is essential to assess the quality of variant interpretation.

4. Page 20, Table 4: it should be indicated that the 17 assumed missense mutations all are regarded as pathogenic (class 4 and 5), if this is true. Overall, the number of missense mutations is quite low (8% of all BRCA1/2 mutations). Do the authors have any explanation for this? How many VUS were identified in the cohort as a whole?

Minor issues

1. Page 7, last sentence: It is not clear to me in which cases "more than one mutation is suspected"? Do the authors refer to index patients with more than one pathogenic BRCA1/2 germline mutation? How many index patients / families met this criterion? …

2. Page 8, Results: to describe it more clearly: "There were 120 unique (or different) BRCA1 variants and 87 unique (or different) BRCA2 variants …" …

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