Reviewer’s report

Title: Genetic variants of prospectively demonstrated phenocopies in BRCA1/2 kindreds

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Reviewer: Jacek Gronwald

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It was observed that women form families with pathogenic BRCA1/2 mutation, who are negative for this mutation develop breast or ovarian cancer with higher frequency than would result population risk. The authors consider the presence of additional genetic variants, which may increase the cancer risk. The study is well designed. Molecular methods of evaluation are proper. Number of cases is satisfactory.

The authors found additional pathogenic mutations in about 10% of cases. They found also 26 variants of unknown significance and 3 of them were predicted to affect RNA splicing.

Conclusion, that all women with breast cancer or breast/ovarian cancer kindreds would benefit from being offered genetic testing for BRCA1/2, ATM and possibly MMR genes irrespective of which causative genetic variants have been demonstrated in their relatives is justified.

Minor comments

1. Cases from MU were from BRCA2 families only. Were they selected or only families with BECA2 mutation were available.

2. Pedigree in figure 1 was chosen not very fortunately. Patient with CC and LC / father of patients with ovarian cancer (all of them are carriers of the BRCA1 mutation), is not a relative of a patient with EC - a carrier of the MSH6 mutation. Therefore, the term that the pedigree of a patient with EC corresponds with Lynch syndrome is exaggerated (he is not a relative of a patient with CC, relationship with patients with OC, is far - III degree), unless MSH6 carrier would be confirmed in a DNA sample of one of the patients with OC. MSH6 testing in OC patients should be performed or suggestion about LS should be withdrawn.

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