Reviewer's report

Title: Comparing the frequency of common genetic variants and haplotypes between carriers and non-carriers of BRCA1 and BRCA2 deleterious mutations in Australian women diagnosed with breast cancer before 40 years of age

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Reviewer: Tom Scholl

Reviewer’s report:

The authors evaluate an Australian Breast Cancer cohort to understand relationships between common genetic variants and common haplotypes and the incidence of clinically significant mutations. This work is similar to studies produced elsewhere where sometimes conflicting results can be understood in the context of small data sets, some with potentially restricted ethnic backgrounds. This field overall can be difficult to follow due to the use of different SNPs, and other markers, to define the haplotypes and a lack of common designations for haplotypes. BRCA1 can be an interesting model to study haplotypes since it is thought reside at a locus that is somewhat protected from recombination, which reduces complexity at the locus. Also, a series of about 8-14 common polymorphisms spread across the coding regions that appear in clinical sequencing tests can explain virtually all specimens from diverse populations as 9 or 10 prevalent haplotypes.

Major Compulsory Revisions:
None.

Minor Compulsory Revisions:
The authors provide little information regarding the cohort. The potential for bias exists if subsets of the cohort have differential haplotype composition and differential access to the BRCA test. More specifically, a concern could be that specimens in the cohort with Australian Aboriginal ancestry could differ in haplotype composition from those descended from Western Europeans. If selection for testing was also skewed where one group had greater a priori risk of a mutation (for example, where stronger family history is required for one group to receive testing than another), mutation prevalence by haplotype would be affected. Since this type of bias is not unheard of, the authors should address it in the text and if possible, elaborate on the cohort, ethnicity of specimens, and testing selection criteria.

Discretionary Revisions:

Papers in this field attribute value to this research (as on page 3) as a possible way to preclude expensive comprehensive mutation scanning by stratifying patient risk or subdividing the mutations to be tested based on patients’ BRCA
haplotypes. This goal seems very unlikely based on previously published data and the results presented here due to the weak predictive power of haplotypes to explain the presence of mutations. Family history will likely remain the preferred clinical selection criteria for genetic testing in hereditary breast cancer. It would be interesting to address haplotype composition of different ethnic groups. It could also be interesting to describe the genetic variant prevalence and composition that reside on different haplotypes. There are also very practical, though less glamorous, uses of haplotypes that are not addressed by the authors. For example, haplotypes in the BRCA genes have been used to identify patients carrying unbeknownst deletion mutations, and to define the clinical significance of genetic variants. The haplotype composition and localization of genetic variants to particular haplotypes can also be useful quality controls in labs performing clinical testing. The authors might choose to expand their discussion to include any of these topics.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I am a former employee of Myriad Genetics and hold patents, and am prosecuting patent applications, in the field of BRCA genetics.