Reviewer's report

Title: Founder mutations in BRCA1/2 are not found at higher frequency in Canadian Ashkenazi Jewish men with prostate cancer

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Reviewer: David Goldgar

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after discretionary revisions

This paper examines the frequency of three specific founder mutations in the BRCA1 and BRCA2 genes in a series of 150 unselected Ashkenazi Jewish prostate cancer cases. In addition to their own data, the authors perform a pooled analysis of other published data on similar series. Although the study is straightforward and competently executed, and the article is generally well-written, I have a few suggestions for improvement.

1. The introduction should be expanded, perhaps adding more background on the reasons for the founder effect in this population.
2. The authors cite reference 7 in the context of showing an increased risk of prostate cancer in BRCA1 carriers. I believe that in this paper, there was only a very slight (<2x) increased risk for early onset cases, while in those older than age 65 (similar to the cases in the present study, there was no effect at all. For this reason, it might be more relevant to focus only on the BRCA2 6174 del T mutation.
3. Surprisingly the authors do not reference the recent paper by Edwards et al. published in January in the American Journal of Human Genetics, although they somewhat cryptically refer to this paper in their discussion. The authors state that their series is the largest series of prostate cancer studied for these mutations to date. Presumably the larger Edwards series does not count, since it examined all mutations in BRCA2?
4. The authors should provide more details on the definition of Ashkenazi Jewish used in their study. Given that this was defined through self-report, what sort of question was asked? Was a distinction made between Ashkenazi and Sephardic? Was there a requirement on the number of Jewish grandparents or something like this?
5. In the discussion on the OCCR region in BRCA2 on page ? (please put page numbers on your manuscript next time), it should be emphasised that the 6174delT falls within this region.
6. The heading on table 1 should say prostate cancer cases and controls.
7. I am not sure, but I vaguely remember that the Struwing et al. Washington DC study included breast cancer cases among the 'controls'. If so this may give higher frequencies. It is not clear to me why the Roa et al. and Oddoux et al. data on controls (refs 9&10) was not used in table 1.

Of these comments, i would say that 1,3,4,5 and 6 are compulsory, while the other two comments are more discretionary (though i hope that they would be considered)
Competing interests:

None declared.