Author's response to reviews

Title: The frequent BRCA1 mutation 1135insA has multiple origins: a haplotype study in different populations

Authors:

Teresa M Rudkin (teresa@mrs.mni.mcgill.ca)
Nancy Hamel (nancy.hamel@mail.mcgill.ca)
Maria Galvez (maria.galvez@mail.mcgill.ca)
Frans Hogervorst (f.hogervorst@nki.nl)
Johan JP Gille (jjg.gille@vumc.nl)
Pål Moller (pal.moller@medisin.uio.no)
Jaran Apold (jaran.apold@helse-bergen.no)
William D Foulkes (william.foulkes@staff.mcgill.ca)

Version: 3 Date: 12 November 2005

Author's response to reviews:

November 11, 2005

Thank you for considering our submission entitled: "The frequent BRCA1 mutation 1135insA has multiple origins: a haplotype study in different populations". Enclosed are the changes made to the manuscript in response to the reviewers.

Reviewer 1 (Bohdan Gorski)
* Minor comment 1
  Added findings from work by Xudong Liu et al (1999) - Discussion, paragraph 2
* Minor comment 2
  To try to respond to the question regarding the frequency within the Norwegian population of the 1135insA haplotype, we supplemented our text with data from P Moller's lab. Although the overall frequency of the 1135insA haplotype is not known, we can report the following with respect to the mutation itself (page 3; paragraph 1): "... it is responsible for ~20% of all BRCA1/2 mutations in Norway (Moller, unpublished data). This mutation occurs on an ancient haplotype, and the age of the 1135insA mutation has not yet been determined. All tested Norwegian individuals with the 1135insA mutation carry the same flanking markers (Moller, unpublished data)."

Reviewer 2 (Heli Nevablina)
* Minor essential revision 1
  Removed the noncontributory clinical information from the Results section.
* Minor essential revision 2
  Page 5: Toned down the assertion that "...that the mutation occurred independently in other populations" by rephrasing to "...the mutation likely occurred independently...".
* Minor essential revision 3
  This was addressed already as part of "Reviewer 1, general comment 1".
* Minor essential revision 4
  This was addressed already as part of "Reviewer 1, discretionary revision 3".
* Minor essential revision 5
  The title was changed from "...ethnically diverse populations" to "...different populations"

Reviewer 3 (J. Struwing)
* General comment 1:
  We addressed the question of the use of targeted analysis before full sequencing in several ways:
1. The last sentence of the Abstract was rephrased to emphasize the particular relevance of our study to those genetic centres that use targeted mutation as a screening test prior to gene sequencing.
2. A sentence was added to the Conclusion that targeted mutation analysis can be and is currently used in clinical contexts in which founder mutation panels are known.
* Minor essential revision 1:
* Minor essential revision 2:
Italized "ins1135A" was reformatted to standardized nomenclature.

* Discretionary revision 1:
Page 3 (paragraph 1) - "frequent mutations that occur on a common haplotype..." was changed to: "Mutations that are seen repeatedly on a common haplotype ...."

* Discretionary revision 2:
Page 5 (paragraph 2) - Muted the tone of the sentence: “The data from the Montreal and Amsterdam centres, described above, confirm that this mutation is highly penetrant for breast and ovarian cancer”, by changing it to: “Although not discussed above, the family histories of these cases are consistent with this mutation being highly penetrant for both breast and ovarian cancer.”

* Discretionary revision 3
Page 7 (paragraph 2) Modified the terminology to replace "hot spot" with "homopolymer tract". This addresses concerns from reviewers 1 and 2.

We hope that these changes are satisfactory.

Yours sincerely,
William D Foulkes MB PhD

On behalf of all the authors
Room L10-116
Montreal General Hospital
1650 Cedar Ave
McGill University
Montreal, QC, Canada
H3G 1A4
Fax: 514 934 8273
Email: William.Foulkes@mcgill.ca