Breast Cancer Res Treat (2009) 116:621–622
DOI 10.1007/s10549-008-0188-x

LETTER TO THE EDITOR

About the c.156_157insAlu BRCA2 breast cancer predisposing mutation

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Received: 4 September 2008 / Accepted: 4 September 2008 / Published online: 21 September 2008
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We followed with interest the articles and commentary notes about the screening of the BRCA2 c.156_157insAlu mutation, a mutation that we have detected for the first in a Portuguese patient residing in Belgium [1]. Machado et al. recently described this mutation in 20 Portuguese families [2], while Peixoto et al. reported a little bit later this same mutation in 14 Portuguese families [3]. All authors agree that this highly recurrent mutation initially occurred in a single patient (founder effect), but with some disagreement about which method to use for the molecular identification of the high breast cancer risk mutation carriers. In a letter to the editor of this journal, Machado and Vaz proposed a three step PCR assay for which they have a patent pending [4]. The mutant BRCA2 allele is unable to generate wild type full length mRNA, but a shorter messenger missing exon 3 (the target exon for the Alu repeat insertion). A shorter BRCA2 mRNA form missing exon 3 can also be generated by the wt allele, but in (much) smaller amounts when compared to the full length form. The biological significance of the BRCA2 alternative messenger missing exon 3 is actually unknown. According to Machado et al. [5] the alternative and mutant transcripts missing exon 3 are not identical, but differ at the level of the exon 10 coding sequence, a property that these authors want to exploit in their proprietary assay to detect the c.156_157insAlu associated mutant transcript.

We want to comment shortly on two points.

First, because of the frequent occurrence of the c.156_157insAlu mutation in Portuguese breast cancer families (while absent in a corresponding control population) and a clear genotype/phenotype correlation, we are convinced that performing the molecular diagnosis on RNA material in addition to genomic DNA is without significant use and much more cumbersome. Moreover, results obtained on RNA from leucocytes are not necessarily representative for what would occur in the breast epithelial cells. A well designed mutation specific single step gDNA PCR/sequence analysis should be sufficient for the correct characterization of high risk patients or families.

Second, the mutation was first reported by us in a publication dating from 2005. As we mentioned in that article, we collected a large number of blood samples from family members residing in Portugal. Then, the team in Lisbon (Dr Vaz and colleagues) accepted to perform for us the genetic counseling for the interested family members living in Portugal. In July 2002 we provided them the clinical phenotypes and genotypes of 24 family members, eight being mutation carriers. We communicated that the mutation corresponded to an insertion of about 300 bp within exon 3 of BRCA2, resulting in the synthesis of mRNA molecules that lack exon 3. This information made it possible to easily characterize the mutation.

For these reasons and aside from ethical considerations, we question the patentability of the assay for specific identification of the c.156_157insAlu mutation.

We hope this specific mutation, together with all other BRCA1/2 mutations, will remain ‘public domain’ in the interest of all families concerned.

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