Effect of the novel Moroccan BRCA1 and BRCA2 frameshift mutations

Sir,

Deleterious BReast CAncer susceptibility gene 1 (BRCA1) and BReast CAncer susceptibility gene 2 (BRCA2) mutations have significant clinical implications. Point mutations in essential functional domains and frameshift mutations resulting in early termination of protein translation were associated with high breast and ovarian cancer risk. Indeed, premature stop codons destabilize mRNA and lead to a state of haplo-insufficiency.[1] During our BRCA1/2 mutation screening in Moroccan patients, we have identified four novel germline mutations.[2] The c.2805delA BRCA1 mutation generates a dysfunctional truncated protein as a result of the introduction of a premature stop codon at position 999. This mutation occurs within the largest exon 11 of BRCA1 gene which encodes two putative nuclear localization signals (NLSs)[3,4] for targeting BRCA1 to the nucleus. It also contains a domain that interacts with the DNA repair protein (RAD51).[5-7] Many other proteins interact directly or indirectly with BRCA1 exon 11 including c-Myc, RB, JunB, FANCA, RAD50, p53, and BRCA2.[8,9] On the other hand, the stop codon at position 999 would generate a truncated protein that lack the BRCT domain, a high conserved region which is involved in protein-protein interaction and facilitate the formation of hetero- and homo-oligomers.[10] Consequently, the BRCT motifs of BRCA1 bind to the phosphorylated protein partners involved in the control of the G2/M phase checkpoint and DNA damage repair.[11,12] Truncation and missense mutations in this region correlate with a high-risk for breast and ovarian cancers.[13,14]

Furthermore, three novel BRCA2 frameshift mutations were identified (c.3381delT, c.7110delA and c. 7235insG). They lead to protein truncation at amino acid positions 1150, 2376, and 2413 respectively. The c.7110delA and c.7235insG mutations were located in exon 14 while c.3381delT mutation was detected in exon 11 which codes for a large central region of the protein and houses eight highly conserved BRC repeats reported to have an important ability to bind RAD51 an essential enzyme for homologous DNA recombination. It was shown that deletion of several BRC repeats in mice leads to cancer

development[15] and somatic mutations in these repeats have been found to be associated with breast cancer.[16] Thus, mutations within these repeats are associated with an increased cancer predisposition risk.[17-19] Moreover, these BRCA2 truncated mutations cause loss of C-terminal region that contains DNA-binding domain (DBD) implicated in cell cycle checkpoints[20] and two putative NLSs. Loss of these NLSs, through truncations, makes protein cytoplasmic since it cannot perform a translocation into the nucleus.[21]

Otherwise, the identification of new mutations in the Moroccan population suggests that it still presents a fertile field for advanced research and extensive studies in this area.

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