Characterization of a novel large deletion and single point mutations in the BRCA1 gene in a Greek cohort of families with suspected hereditary breast cancer.

Belogianni I, Apessos A, Mihalatos M, Razi E, Labropoulos S, Petounis A, Gaki V, Keramopoulos A, Pandis N, Kyriacou K, Hadjisavvas A, Kosmidis P, Yannoukakos D, Nasioulas G.

Source

Molecular Biology Research Center HYGEIA "Antonis Papayiannia", DTCA HYGEIA, 15123 Maroussi, Athens, Greece. Iolia.Beloyianni@hygeia.gr

Abstract

BACKGROUND:

Germline mutations in BRCA1 and BRCA2 predispose to breast and ovarian cancer. A multitude of mutations have been described and are found to be scattered throughout these two large genes. We describe analysis of BRCA1 in 25 individuals from 18 families from a Greek cohort.

METHODS:

The approach used is based on dHPLC mutation screening of the BRCA1 gene, followed by sequencing of fragments suspected to carry a mutation including intron--exon boundaries. In patients with a strong family history but for whom no mutations were detected, analysis was extended to exons 10 and 11 of the BRCA2 gene, followed by MLPA analysis for screening for large genomic rearrangements.

RESULTS:

A pathogenic mutation in BRCA1 was identified in 5/18 (27.7 %) families, where four distinct mutations have been observed. Single base putative pathogenic mutations were identified by dHPLC and confirmed by sequence analysis in 4 families: 5382insC (in two families), G1738R, and 5586G > A (in one family each). In addition, 18 unclassified variants and silent polymorphisms were detected including a novel silent polymorphism in exon 11 of the BRCA1 gene. Finally, MLPA revealed deletion of exon 20 of the BRCA1 gene in one family, a deletion that encompasses 3.2 kb of the gene starting 21 bases into exon 20 and extending 3.2 kb into intron 20 and leads to skipping of the entire exon 20. The 3' breakpoint lies within an AluSp repeat but there are no recognizable repeat motifs at the 5' breakpoint implicating a mechanism different to Alu-mediated recombination, responsible for the majority of rearrangements in the BRCA1 gene.

CONCLUSIONS:

We conclude that a combination of techniques capable of detecting both single base mutations and small insertions/deletions and large genomic rearrangements is necessary in order to accurately analyze the BRCA1 gene in patients at high risk of carrying a germline mutation as determined by their family history. Furthermore, our results suggest that in those families with strong evidence of linkage to the BRCA1 locus in whom no point mutation has been identified re-examination should be carried out searching specifically for genomic rearrangements.