G1738R is a BRCA1 founder mutation in Greek breast/ovarian cancer patients: evaluation of its pathogenicity and inferences on its genealogical history.

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Source

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Abstract

We have performed screening in 287 breast/ovarian cancer families in Greece which has revealed that approximately 12% (8/65) of all index patients-carriers of a deleterious mutation in BRCA1 and BRCA2 genes, contain the base substitution G to A at position 5331 of BRCA1 gene. This generates the amino acid change G1738R for which based on a combination of genetic, in silico and histopathological analysis there are strong suggestions that it is a causative mutation. In this paper, we present further evidence suggesting the pathogenicity of this variant. Forty breast/ovarian cancer patients were reported in 11 Greek families: the above eight living in Greece, two living in Australia and one in USA, all containing G1738R. Twenty of these patients were screened and were all found to be carriers of the same base substitution. In addition, we have detected the same base change in five breast/ovarian cancer patients after screening 475 unselected patient samples with no apparent family history. The mean age of onset for all the above patients was 39.4 and 53.6 years for breast and ovarian cancer cases, respectively. A multi-factorial likelihood model for classification of unclassified variants in BRCA1 and BRCA2 developed previously was applied on G1738R and the odds of it being a deleterious mutation was estimated to be 11470:1. In order to explain the prevalence of this mutation mainly in the Greek population, its genealogical history was examined. DNA samples were collected from 11 carrier families living in Greece, Australia and USA. Screening of eight intragenic SNPs, three intragenic and seven extragenic microsatellite markers and comparison with control individuals, suggested a common origin for the mutation while the time to its most recent common ancestor was estimated to be 11 generations (about 275 years assuming a generational interval of 25 years) with a 1-lod support interval of 4-24 generations (100-600 years). Considering the large degree of genetic heterogeneity in the Greek population, the identification of a frequent founder mutation greatly facilitates genetic screening.