

Identification of Genetic Alterations in Hereditary Breast and Colorectal Cancer in Greece

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Approximately 30-50% of the FAP patients harbor truncating germ-line mutations in the APC tumor suppressor gene (Adenomatous Polyposis Coli). Germ line mutations in genes encoding proteins involved in DNA mismatch repair are responsible for the autosomal dominantly inherited cancer predisposition syndrome HNPCC in colorectal cancer. Mutations in the *BRCA1/2* genes predispose individuals to breast and ovarian cancer. The lifetime risk of breast cancer in female carriers of a *BRCA1* mutation is 60-80% while that of ovarian cancer is 20-40%. The median age of diagnosis of breast cancer is 42 years.

Results and discussion

FAP: To date we have tested 90 members from 18 families. Pathogenic mutations were identified in 14 families (32 out of 37 patients 86,5%) including three novel truncating mutations - 2601delGA, A2767T, 1577insT, as well as three families (17%) with *de-novo* mutations and one family with a large deletion (*APC*del exons 6-15).

HNPCC: Here we describe the combination of different molecular biology techniques for the detection of mutations and large genomic rearrangements of the APC and MMR genes in familial CRC in Greek patients. A unique disease-causing mutation has been identified in 7/9 (78%) families. The types of mutations identified are nonsense (5/7) (*hMLH1*: E557X, R226X; *hMSH2*: Q158X, R359X and R711X), a 2 bp deletion (*hMSH2* 1704_1705delAG) and a 2.2 kb *Alu*-mediated deletion encompassing exon 3 of the *hMSH2* gene.

BRCA: We describe analysis of *BRCA1/2* in families from a Greek cohort. A pathogenic mutation in *BRCA1* was identified in 27.7 % of the families, where four distinct mutations have been observed. In one family MLPA revealed deletion of exon 20 of the *BRCA1* gene. Finally in one family the *BRCA2* gene was mutated. Here we describe the combination of different molecular biology techniques for the detection of mutations.

In conclusion, our results document and extend previous work, suggesting that genomic rearrangements account for a large proportion of identified mutations. This

therefore warrants use of a combination of techniques capable of identifying both single base mutations in addition to large genomic rearrangements. In this respect, we have found that use of dHPLC for single base mutations and MLPA for large genomic rearrangements is a reliable and cost-effective combination for use as an initial screening step followed by sequencing for characterization of the mutations identified.

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