Analysis of hereditary cancer syndromes by use of a panel of genes: more answers than questions.

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Background: Hereditary breast cancer is estimated to account for approximately 10% of all breast cancer cases. In addition, an estimated 15-20% of those affected by breast cancer have a positive family history.
Despite the fact that *BRCA1* and *BRCA2* are the two most significant genes in hereditary breast cancer predisposition, twenty years of analysis has highlighted the fact, that mutations in these two highly penetrant genes, are only present in approximately 20% of high risk families.
Other genes, mutations in which are associated with high risk of breast cancer, were identified because of the strong association with familial cancer syndromes, in which breast cancer is one of the defining components.
Technological advances in molecular biology and especially DNA sequencing, commonly designated as "Next Generation Sequencing – NGS" have aided in the concentrated efforts to identify new genes responsible for the missing heritability, allowing the application of this knowledge in the diagnostic setting.

The scope The aim of this study was to investigate the extent and nature of mutations in 26 genes implicated in hereditary cancer predisposition in families of Romanian descent.

Methods

In total, 297 Romanian families have been analyzed by our group in the past three years.
Genomic DNA was enriched for targeted regions of 26 genes involved in hereditary predisposition to cancer (*ATM, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM (only intron 8, exon 9 and 3'UTR), FAM175A, MEN1, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2*). Sequencing was carried out using the Illumina NGS technology. Reads were aligned to the reference sequence (GRCh38), and sequence changes were identified and interpreted in the context of a single clinically relevant transcript. The presence of large genomic rearrangements was investigated by use of MLPA. All clinically significant observations were confirmed by orthogonal technologies.

Results

In total, a pathogenic mutation was identified in 79 of the 297 families (26.6%) analyzed. Clinically significant mutations were identified in 17 of the genes included in the panel. The most commonly mutated genes in the Romanian population were *BRCA1* and *BRCA2,* accounting for 50% of the mutations identified, followed by *PALB2* (12%), *CHEK2* (9.4%) and *ATM, NBN* and *RAD50* which accounted for 3.5% of the mutations each. Of note is that 7 of the 79 affected families (8.8%) carried clinically significant mutations in two different genes.

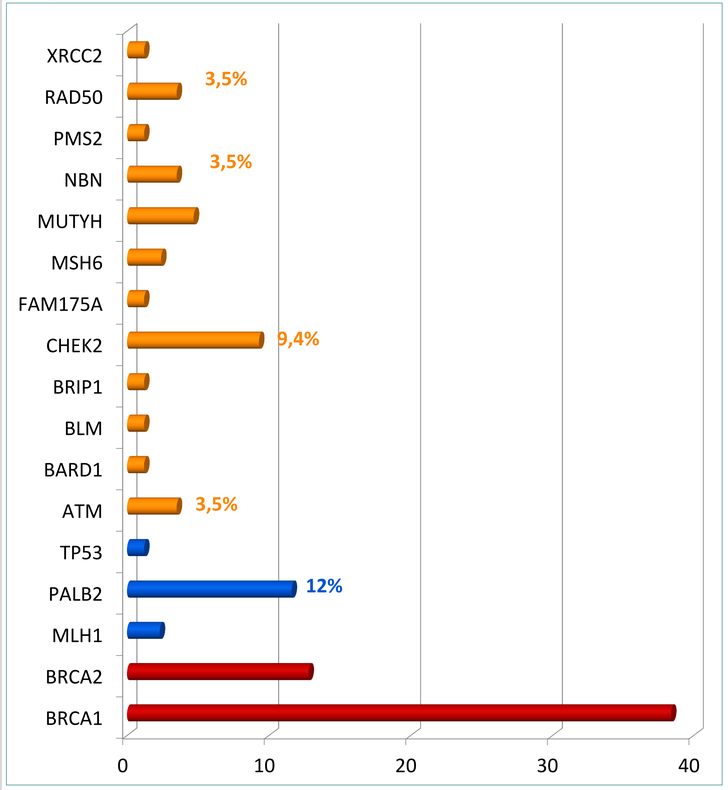

Figure 1. Mutation distribution in genes analyzed

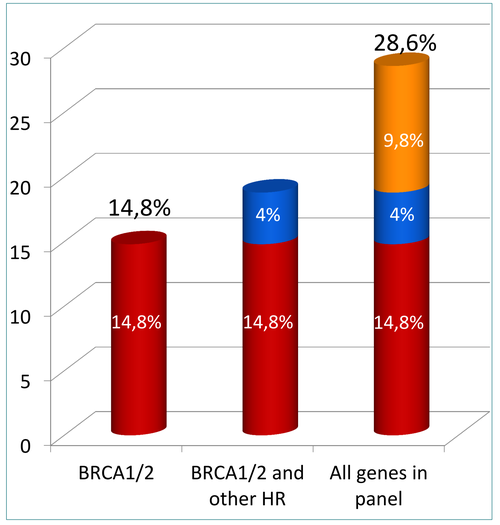

Figure 2. Mutation distribution based on penetrance

Conclusions:

Our results support the use of a panel of genes involved in hereditary cancer predisposition. In this series of patients, analysis of this panel allowed for the identification of 14% additional pathogenic variants. This is especially true in those cases where more than one pathogenic variant was identified.

References:

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