

MOLECULAR ANALYSIS OF BRCA1/2 GENES AND MULTIGENE-PANEL TESTING IN SICILIAN TRIPLE NEGATIVE BREAST CANCER

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Background. Triple-negative breast cancers (TNBC) define a heterogeneous subgroup (15-20%) of all breast cancers associated with poor prognosis and characterized by the lack of ER, PR and Her-2 gene expression. The 15-20% of all TNBC showed BRCA1/2 germline mutations. Therefore, other genes, involved in Homologous Recombination repair (HR), has been investigated to predict the hereditary breast cancer risk and to develop novel therapeutic strategies. In this study, we evaluate the frequency of germline mutations in BRCA1/2 genes and in multigene-panel (ATM, CHEK2, NBN, PALB2, RAD50, RAD51C, RAD51D, BRIP1 and BARD1).

Patients and methods. This cohort involved 84 TNBC patients, 9 of these were ≤ 36 years at diagnosis. Germline mutations in BRCA1/2 genes and in multigene-panel testing were identified in peripheral blood samples. The analysis was performed using *BRaCA SCREEN* and *HEVA SCREEN* (4bases) through *IonS5 NGS system* (ThermoFisher Scientific) and confirmed by Sanger Sequencing.

Results. BRCA1/2 pathogenetic variants (PVs) were present in 23% of patients (19/84). Of these, 84% (16/19) were found in BRCA1 gene and 16% (3/19) in BRCA2 gene. The most frequent PVs were c.5266_5267insC, BRCA1 (3/16), c.514delC, BRCA1 (3/16) and c.5851_5854delAGTT, BRCA2 (2/3).

Variant Unknown Significance (VUS) were reported in 10% (8/84) patients, of which 38% (3/8) in BRCA1 gene and 62% (5/8) in BRCA2 gene.

The remaining 67% (56/84) were BRCA1/2 negative; among them 36% (20/56) have been analyzed with multigene-panel testing to evaluate PVs in other genes involved in HR pathway, and a VUS in NBN gene (c.171+4 T>C) was found.

Conclusions. Data obtained show a strong association between TNBC and BRCA1 PVs in Sicilian population with breast cancer. This study confirms that BRCA1/2 are the main genes involved in HR repair in TNBC. However, negative BRCA1/2 patients could have PVs in other genes implicated in HR pathway. Therefore, the analysis with a multigene-panel testing is necessary to improved cancer risk assessment and to identify new therapeutic strategies compared to conventional or PARP inhibitor therapies.