VALIDATION OF NEXT-GENERATION SEQUENCING FOR THE DIAGNOSIS OF HEREDITARY BREAST AND OVARIAN CANCER

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Introduction: Molecular diagnosis of hereditary breast and ovarian cancer (HBOC) has been mostly based on the identification of germline inactivating mutations in the high-penetrant genes *BRCA1* and *BRCA2*. Although several other HBOC susceptibility genes have been identified, mutations in any of those are rare, rendering sequential genetic testing with standard methodologies time consuming and expensive. Next-generation sequencing (NGS) gene panels allow the simultaneous sequencing of multiple HBOC susceptibility genes at a lower cost. The aim of this work was to validate the use of an NGS cancer susceptibility gene panel for the identification of mutations previously detected by Sanger sequencing in the *BRCA1*, *BRCA2* and *TP53* genes.
Methods: 20 samples from patients with personal/family history of breast cancer were sequenced on a MiSeq using the Trusight Cancer Sequencing Panel (Illumina). Bioinformatic analysis of NGS data included the MiSeq Reporter, VariantStudio and Isaac Enrichment tools (Illumina).
Results: NGS successfully identified all 204 variants (38 unique, including 2 deletions and a splice variant) previously detected by Sanger sequencing in the *BRCA1*, *BRCA2* and *TP53* genes. Until now, no false-negative or false-positive results were obtained.
Discussion: These results demonstrate the high analytical sensitivity and specificity obtained with NGS for the detection of sequence variants in 3 HBOC high-penetrant genes. These validation assays open the way to the definition of a clinically useful multigene panel for HBOC susceptibility based on the Trusight Cancer Sequencing Panel. This will allow a comprehensive and cost-effective molecular diagnosis of HBOC with a shorter turnaround time when compared to standard methodologies. In addition, with appropriate genetic counselling and specialized clinical surveillance, families with HBOC will benefit from these new technologies which have high impact in public health.