Functional Analysis of BRCA1 Missense Mutations

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The breast cancer is the second most frequent type of cancer in the world and the first between women. Two genes had been associated with hereditary predisposition to breast cancer: *BRCA1* and *BRCA2*. BRCA1 is directly associated with DNA damage repair mechanisms and its C-terminus region is essential for this function. Germline mutations in *BRCA1* confer a 56%–80% lifetime risk for breast cancer and a 15%–60% lifetime risk for ovarian cancer in women. Today, more than 1200 polymorphisms in *BRCA1* are registered. However, the relevance of the many missense changes in the gene for which the effect on protein function is unknown remains unclear. Determination of which variants are causally associated with cancer is important for assessment of individual risk. In this study we investigate functional correlations between missense mutations in the BRCA1 C-terminus region and the predisposition to breast cancer. A set of naturals (chosen in the database of the Breast Cancer Information Core) and non-naturals (putative phosphorilation and ubiquitination residues) variants were examined using a functional assay that measures the transactivation activity of BRCA1. Preliminary data suggest that M1411T, C1697F, D1739G, D1739V, H1746N, G1748D, R1751P and A1752T natural variants have a deleterious behavior. Analysis of protein modeling based on the structure of BRCA1 BRCT domains will be used in combination with available genetic data to determine or not a putative cancer association.

Keywords: BRCA1; cancer; polymorphism; transcriptional transactivation