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BRCA1-BRCT cancer-related point mutations alter sub-cellular localization of BRCA1 *in vitro*

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Mutations of the breast cancer susceptibility genes *brca1* and *brca2* account for 30–50% of hereditary breast and ovarian cancer cases reported worldwide. The *brca1* gene is the most extensively studied and a large number of mis-sense mutations are located in BRCT tandem repeats of the BRCA1 protein while only few of them are detrimental for the function as well as the interaction of BRCA1 with partner molecules. Mutations at the two C-terminal tandem (BRCT) repeats of BRCA1 detected in breast tumor patients have identified either to lower the stability of the BRCT domain and/or disrupt the interaction of BRCT with synthetic phosphopeptides. Such mutations, especially in the BRCT domain, may also result in the BRCA1 mis-localization due to modifications of BRCA1 binding to interacting proteins. Based on these data we sought to determine whether the M1775K and the V1809F destabilizing mutants of the BRCT domain do alter BRCA1 function *in vitro*, as shown by cell compartmentalization. The effects of these mutations on sub-cellular localization of BRCA1 protein were studied by following the expression of BRCA1wt and mutants fused to EGFP, in MCF-7 cells. The cytoplasmic mis-localization of M1775K and V1809F mutations which disrupt BRCA1 C-terminal folding, in contrast to the EGFP-BRCA1wt and the less affected variant M1652I, indicate that the functional changes might be crucial for BRCA1 nuclear transport. Additionally, the results compared with computational docking analysis in order to extract more information's about the impact of the mutation to protein interactions. These data suggest that the impact of the integrity of the BRCA1-BRCT domain in structural level is crucial for proper function of the protein as shown by the modifications in its sub-cellular localization and may contribute to the deficiency of DNA repair procedure and cell cycle control observed in breast cancer cells.

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Identification of novel genetic variations in oral squamous cell carcinoma using exome sequencing

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Oral squamous cell carcinoma (OSCC) is the most common cancer of the oral cavity representing 90% of malignancy. The exact mechanism involved in this oral carcinogenesis remains unknown. Therefore, a detailed study to identify targeted specific gene changes in oral cancer is essential to provide a better understanding on the molecular events that underlies the progression and development of OSCC. Our research focuses on the identification of novel genetic variations in OSCC through the use of Whole Exome Sequencing (WES) on a cohort of ethnically diverse OSCC population. WES was performed on pairs of tumor and normal adjacent tissue from 10 OSCC patients (84.6% female; average age of 57.0±11.7 years) using Agilent Sure Select Human All Exome 71M for enrichment and sequenced through high throughput sequencing using Illumina HiSeq 2000 platform. This was followed by variant alignment to the NCBI human genome build 37 (Hg19) and annotation/classification using ANNOVAR. Through bioinformatics analysis, a total of 4,348 potential novel sequence variation/mutations were identified, of which 1,071 were non-synonymous. In addition to the previously identified HNSCC and OSCC genes (TP53, NOTHC1, FAT1 and CASP8), the annotation of our data to COSMIC and Oral Cancer Gene Database revealed additional novel gene variations that has not been previously implicated in OSCC. The identified genes were further compared with the protein profile obtained through Label Free LC-MS. Our results had successfully identified novel genetic variants in OSCC, which could provide critical insights into OSCC carcinogenesis and the mechanisms involved in the cancer therapies.

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