Functional and clinical characterization of BRCA2 hypomorphic missense variants

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Many inherited missense variants (>4000) have been detected in *BRCA2* by clinical genetic testing. Of these <30 have been established as pathogenic variants that inactivate BRCA2 function and confer high risks of breast and ovarian cancer, similar to protein truncating variants. In addition, several hundred missense variants that have no influence on BRCA2 function have been classified as benign. Here we report on the identification of 70 missense variants in the DNA binding domain (DBD) of BRCA2 that have partial effects on the homologous recombination DNA repair activity of BRCA2. Based on a homology directed DNA repair cell-based assay that evaluates the influence of variants on the homologous recombination DNA repair activity of BRCA2 we have shown that these variants retain 30-50% of BRCA2 activity. These hypomorphic variants also had partial effects on survival of haploid human HAP1 cells targeted by CRISPR/cas9 knockin approaches and on response of these cells to the Olaparib PARP inhibitor. Sequence alignment analysis found that the variants were highly conserved across species from pufferfish to human. Structural analysis showed that these variants are located predominantly in unstructured regions of the DBD. Case-control association studies of large datasets from clinically tested breast cancer cases and public reference unaffected controls, demonstrated that these hypomorphs confer moderate risks of breast cancer (OR: 2.58; 95%CI: 1.41-4.73) compared to protein truncating variants (OR:8.83; 95%CI:5.32-14.67). Thus, this study identifies a novel group of variants in *BRCA2* that confer moderate risks of breast cancer similar to *ATM* and *CHEK2* variants. These findings suggest that patients carrying these variants should receive modified clinical management relative to carriers of BRCA2 protein truncating variants.