Partially functional (hypomorphic) missense variants in *BRCA2* are reduced penetrance pathogenic variants

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Background: *BRCA2* variants with partially aberrant RNA splicing have been associated with a relatively lower breast cancer risk (reduced penetrance) relative to canonical pathogenic variants. However, the existence of partial loss of function (hypomorphic) missense variants, conferring reduced penetrance, is less certain. Identification and assessment of the clinical relevance of such reduced penetrance pathogenic variants (RPPVs) is needed to provide accurate risk estimates.

Methods: Comprehensive functional characterization of hypomorphic missense variants (n=70) in the BRCA2 DNA-binding domain, initially identified through homology-directed DNA repair (HDR) assays, was conducted through multiple independent functional assays, including HDR, CRISPR/Cas9-based endogenous targeting, RAD51 foci formation assay, and Poly(ADP-ribose) polymerase (PARP) inhibitor response assay. Risk estimates were obtained using two large datasets from patients referred for hereditary cancer testing. A ClinGen/ACMG/AMP model was used for clinical classification.

Results: The variants consistently demonstrated hypomorphic HDR activity and endogenous survival in HAP1 targeted cells, decreased RAD51 foci formation, and increased sensitivity to PARP inhibitors. These variants were associated with a moderate increase in breast cancer risk, as shown in two independent studies: one using multivariable logistic analysis adjusted for age, ancestry and family history (OR=2.41, 95%CI=1.51-3.85) and another comparing frequencies of variants in breast cancer cases to public reference controls adjusted for ancestry (OR=2.09, 95% CI=1.16-4.08). The mean age of breast cancer diagnosis for carriers of hypomorphic variants was 57 years, which was significantly older than the mean age of diagnosis of 51 years for carriers of protein truncating variants. Functional data were combined with other evidence sources in a ClinGen/ACMG/AMP model to classify 14 variants as “likely pathogenic”.

Conclusions: We identified partially functional, hypomorphic missense variants associated with reduced penetrance for breast cancer. Cancer risk management guidelines for this new category of variants should be revisited given that the associated breast cancer risks warrant

high risk screening but do not meet the threshold at which risk reducing mastectomy is offered. This study supports a shift in paradigm to considering variant-based risks on a continuum, with implications for risk-appropriate cancer risk management.