Reduced penetrance *BRCA1* and *BRCA2* pathogenic variants in clinical germline genetic testing

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Despite the current binary clinical classification of variants (pathogenic versus benign), it is widely recognized that risk is a continuum. Prior studies have suggested the existence of reduced penetrance pathogenic variants (RPPVs), which pose challenges for identification, reporting, patient counseling and care. Through the current study, we sought to establish RPPVs as a new category of variants, with efforts focused specifically on *BRCA1* and *BRCA2* (*BRCA*).

We compiled, compared, and assessed data for *BRCA* RPPVs from two large clinical diagnostic laboratories to establish an initial set of reduced penetrance pathogenic variants. Specifically, candidate *BRCA* RPPVs provided by clinical diagnostic laboratories were compiled to identify those with the highest prior likelihood of being a RPPV, based on concordant interpretations. Evidence of reduced penetrance included: 1) the identification of biallelic Fanconi Anemia-affected carriers; 2) splicing, missense, and nonsense-mediated RNA decay (NMD)-escaping variants; 3) laboratory-validated cancer history weighting models; 4) published variant-specific risk estimation data; 5) extrapolation of a reduced-risk interpretation onto close match variants that are expected to have the same effect; and 6) functional data.

Sixteen candidate *BRCA* RPPV present in both lists from both laboratories were systematically assessed. For *BRCA1,* variants included c.5096G>A p.(Arg1699Gln) and variants impacting the canonical c.671 splice acceptor site. For *BRCA2,* variants included three frameshift (c.658_658delGT, c.9672dupA, c.9699_9702delTATG), two spliceogenic (c.8488-1G>A and c.8488-1G>T), and three missense (c.7878G>C, T, p.(Trp2626Cys); and c.9302T>G p.(Leu3101Arg)) variants.

Our study is the first to clearly evaluate and establish *BRCA* RPPVs as a new class of variants, based on consistency in results across 16 variants using different interpretation strategies between laboratories. These variants impart a moderately increased risk of breast cancer, often considered to be between 2-4 fold, which should be considered when determining risk-informed cancer prevention strategies. Furthermore, our study establishes a framework to harmonize interpretation and standardize reporting of *BRCA* RPPV, by providing evidence to support this new classification for 16 variants. Further work to define clinically meaningful risk thresholds and categories for reporting *BRCA* RPPV are needed to personalize cancer risks in conjunction with other risk factors.