Substantially different penetrance of different pathogenic variants in *BRCA1* exon 20 (18): Not all pathogenic variants are equal

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Introduction: Studies suggest pathogenic missense variants confer lower risks than truncating variants. Identification of missense variant exceptions is critical in providing accurate risk assessment/management recommendations.

Methods: We initially investigated a Manchester family with the *BRCA1* c.5243G>A p.G1748D missense variant. 3/7 heterozygous females developed breast cancer <30 years (24,27,28) despite being separated by 8 meioses. Using combined Ambry/Manchester data, we assessed penetrance for breast/ovarian cancer in women with *BRCA1* c.5243G>A (n=21) and compared this with other likely pathogenic/pathogenic (LP/P) exon 20 variants including missense (n=103), truncating (excluding the common founder, c.5266dupC), (n=91) and the in-frame exon20 deletion, *BRCA1* c.5194_5277del p.His1732_Lys1759del, (n=74). Individuals were censored at: first *BRCA1* related diagnosis; death; risk-reducing mastectomy or date of last follow-up (Manchester); or testing date if unaffected (Ambry). Kaplan-Meier incidence curves were generated.

Results: *BRCA1* c.5243G>A had similar penetrance to truncating variants [50y:74%-(95%CI=46-95%) versus 62.7%-(95%CI=51-75%), p=NS]. Penetrance was significantly higher than for other missense LP/P variants in exon 20 [50y: 27.6% (95%CI=19-39%), p<0.001] or the exon 20 deletion [50y:46%-(95%CI=33-63%), p=0.02]. All inter-group p-values were significant, except *BRCA1* c.5243G>A versus truncating. Notably, the exon 20 deletion had significantly lower penetrance than truncating variants, and higher penetrance than non-codon 1748 missense LP/P variants (p<0.001). While penetrance estimates are not adjusted for ascertainment bias, resulting in potential over-estimation, inter-group comparisons are still valid due to identical ascertainment.

Conclusion: These data suggest that *BRCA1* c.5194_5277del and at least some of the exon 20 LP/P missense variants retain partial BRCA1 function and that *BRCA1* c.5243G>A is at least a complete loss-of-function variant and may even act as a dominant negative. Further data is needed on all in-frame exon deletions and missense variants so that women can receive more accurate risk estimates for these attenuated phenotypes.