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

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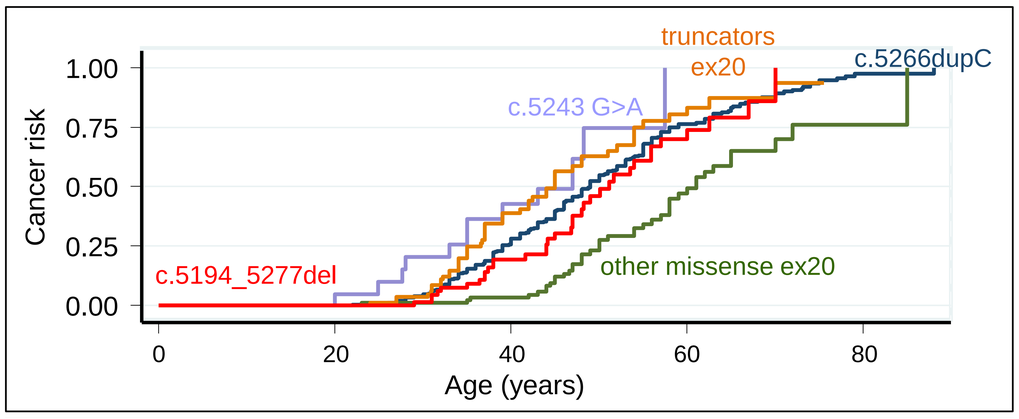
**METHODS**

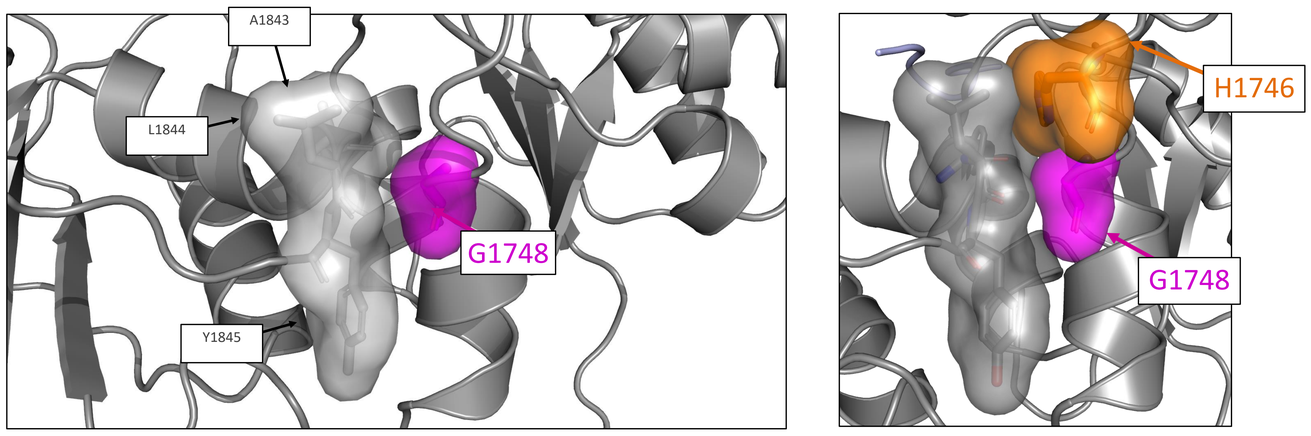
- A family with *BRCA1* c.5243G>A (p.G1748D) harboured 3/7 heterozygous female with breast cancer diagnosed <30y (8 meiosis).
- Clinical data were collected from Ambry Genetics and combined with Manchester clinical data to interrogate the penetrance of BRCA1 p.G1748D as well as other Likely pathogenic (LP) and pathogenic (P) variants originating in exon 20 including c.5243G>A (p.G748D), truncators ex20 (pooled), c.5266dupC (a common founder), c.5194_5277del (in frame del ex20), and other missense ex20 (excluding c.5243G>A) (pooled) The structural implications of p.G1748D in context of other nearby substitutions were assessed to ascertain the potency of this variant.




| ↓variant; →age at censor | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| *BRCA1* c.5243 G>A | 21 | 21 | 9 | 0 | 0 |
| *BRCA1* truncators ex20 | 91 | 91 | 41 | 7 | 0 |
| *BRCA1* c.5266dupC | 471 | 467 | 276 | 57 | 2 |
| *BRCA1* c.5194_5277del | 74 | 74 | 46 | 8 | 0 |
| *BRCA1* other missense ex20 | 103 | 103 | 82 | 23 | 1 |

| Variant 1 | Variant 2 | chi² | p-value |
|---|---|---|---|
| *BRCA1* c.5243G>A (p.G748D) | *BRCA1* truncators ex20 | 0.26 | 0.612 |
| | *BRCA1* c.5266dupC | 3.00 | 0.083 |
| | *BRCA1* c.5194_5277del | 5.35 | 0.021 |
| | *BRCA1* other missense ex20 | 27.01 | <0.0001 |
| *BRCA1* other missense ex20 | *BRCA1* truncators ex20 | 32.72 | <0.0001 |
| | *BRCA1* c.5266dupC | 28.15 | <0.0001 |
| | *BRCA1* c.5194_5277del | 12.01 | 0.001 |

**Figure 1**. Time-to-event Kaplan Meyer curves (left) of females with breast or ovarian cancer for specific variants or pooled variants of a certain category (missense, truncators), each originating in exon 20 using combined Manchester/Ambry data. Curves were compared using chi-square test and p-values are provided in the associated table (right).




| Variant | Class | ΔΔG (kcal/mol) | ΔV (Å³) |
|---|---|---|---|
| G1748S | LB | 8.861 | 28.9 |
| G1748R | LP | 32.065 | 113.3 |
| G1748C | LP | 9.561 | 48.4 |
| G1748D | P | 21.745 | 51.0 |
| H1746D | LP | 2.938 | -42.1 |

**Figure 2**. Structural modeling of residue G1748 and H1746 in the BRCA1 BRCT1 domain (left). The region around G1748 is densely packed and, therefore, geometrically constrained leaving little room to accommodate a larger amino acid, e.g., aspartic acid. H1746 is less densely packed and the H1746D substitution is less disruptive and expected to shrink the residual volume. The change in Gibbs free energy (ΔΔG), the change in volume (ΔV) within three angstroms, and the interpretation of several variants at the same or nearby residues is displayed in the table (right).

**RESULTS & DISCUSSION:**

- Variant-specific penetrance is an emerging topic of study and it could have implications for clinical management.
- *BRCA1* c.5243G>A behaves similarly to other loss of function variants of *BRCA1* ex20.
- In frame del ex20 and some other missense variants in exon 20 may have a milder clinical effect due to partially retained BRCA1 function.
- Increased availability of genetic testing highlights the need for accurate penetrance data, especially for missense and in-frame deletion variants.
- Accurate penetrance data will lead to more accurate risk advice for patients and their families.

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