

Variant: *NM_007294.4(BRCA1):c.5153G>C (p.Trp1718Ser)*

Version: 1.0

CA003305 [↗](#)

55433 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))

Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: aa2d2fb5-7e49-46e0-9022-9bff57071e1c

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HGVS expressions

NM_007294.4:c.5153G>C

NM_007294.4(BRCA1):c.5153G>C (p.Trp1718Ser)

NC_000017.11:g.43063373C>G

CM000679.2:g.43063373C>G

NC_000017.10:g.41215390C>G

CM000679.1:g.41215390C>G

NC_000017.9:g.38468916C>G

NG_005905.2:g.154611G>C

ENST00000461574.2:c.5150G>C

ENST00000470026.6:c.5153G>C

ENST00000473961.6:c.5027G>C

ENST00000476777.6:c.5147G>C

ENST00000477152.6:c.5075G>C

ENST00000478531.6:c.1841G>C

ENST00000489037.2:c.5075G>C

ENST00000493919.6:c.1703G>C

ENST00000494123.6:c.5153G>C

ENST00000497488.2:c.4265G>C

ENST00000618469.2:c.5153G>C

ENST00000634433.2:c.5030G>C

ENST00000644379.2:c.5219G>C

ENST00000644555.2:c.1703G>C

ENST00000652672.2:c.5012G>C

ENST00000484087.6:c.1715G>C

ENST00000357654.9:c.5153G>C

ENST00000471181.7:c.5216G>C

ENST00000644379.1:c.1540G>C

ENST00000352993.7:c.1727G>C

ENST00000357654.7:c.5153G>C

ENST00000461221.5:c.*4936G>C

ENST00000468300.5:c.1841G>C

ENST00000471181.6:c.5216G>C

ENST00000478531.5:c.1841G>C

ENST00000484087.5:c.1466G>C

ENST00000491747.6:c.1841G>C

ENST00000493795.5:c.5012G>C

ENST00000493919.5:c.1703G>C

ENST00000586385.5:c.83G>C
ENST00000591534.5:c.626G>C
ENST00000591849.5:c.-98-13183G>C
NM_007294.3:c.5153G>C
NM_007297.3:c.5012G>C
NM_007298.3:c.1841G>C
NM_007299.3:c.1841G>C
NM_007300.3:c.5216G>C
NR_027676.1:n.5289G>C
NM_007297.4:c.5012G>C
NM_007299.4:c.1841G>C
NM_007300.4:c.5216G>C
NR_027676.2:n.5330G>C

Uncertain Significance

Met criteria codes 3

PM2_Supporting PP3 PP4

Not Met criteria codes 3

BP7 BS3 PS3

Evidence Links 0

Expert Panel

ENIGMA BRCA1 and BRCA2 VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.5153G>C variant in BRCA1 is a missense variant predicted to cause substitution of Tryptophan by Serine at amino acid 1718 (p.(Trp1718Ser)). This variant is absent from gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥ 25) and gnomAD v3.1 (non-cancer subset, read depth ≥ 25) (PM2_Supporting met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.52, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0.14 indicates an unclear predicted impact on splicing (score threshold 0.10-0.20) (PP3 met). Reported by two or more calibrated studies with discordant results. Functional effect similar to pathogenic control variants (PMID:38709234) and between what was observed for benign and pathogenic control variants (PMID:30209399) (PS3 and BS3 not met). mRNA experimental analysis indicates no impact on splicing (PMID: 25724305) but is not applied as strong evidence against pathogenicity since missense impact has not yet been excluded (BP7_Strong (RNA) not met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3.32 (based on Co-occurrence LR=1.03; Family History LR=3.22), within the thresholds for supporting evidence towards pathogenicity (LR > 2.08 & ≤ 4.3) (PP4 met; Internal lab contributor). In summary, this variant meets the criteria to be classified as a Variant of uncertain significance for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PP3, PP4).

Met criteria codes

PM2_Supporting



This variant is absent from gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥ 25) and gnomAD v3.1 (non-cancer subset, read depth ≥ 25) (PM2_Supporting met).

PP3



This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.52, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via

protein change. A SpliceAI score of 0.14 indicates an unclear predicted impact on splicing (score threshold 0.10-0.20) (PP3 met).

PP4



Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3.32 (based on Co-occurrence LR=1.03; Family History LR=3.22), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor).

Not Met criteria codes

BP7



This is a missense variant inside a key functional domain. Impact via the protein change is unclear (PMIDs: 30765603, 30209399). mRNA experimental analysis indicates no impact on splicing (PMID: 25724305), but is not applied as strong evidence against pathogenicity since missense impact has not yet been excluded (BP7_Strong (RNA) not met).

BS3



Reported by two or more calibrated studies with discordant results. Functional effect similar to pathogenic control variants (PMID:38709234) and between what was observed for benign and pathogenic control variants (PMID:30209399) (PS3 and BS3 not met).

PS3



Reported by two or more calibrated studies with discordant results. Functional effect similar to pathogenic control variants (PMID:38709234) and between what was observed for benign and pathogenic control variants (PMID:30209399) (PS3 and BS3 not met).

Curation History



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