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Variant: NM_007294.4(BRCA1):c.5509T>G (p.Trp1837Gly)

Version: 2.1

CA003681

55607 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 03c35580-6129-4df7-b7b4-8055d39efda1
Approved on: 2026/4/15
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HGVS expressions

NM_007294.4:c.5509T>G
NM_007294.4(BRCA1):c.5509T>G (p.Trp1837Gly)
NC_000017.11:g.43045761A>C
CM000679.2:g.43045761A>C
NC_000017.10:g.41197778A>C
CM000679.1:g.41197778A>C
NC_000017.9:g.38451304A>C
NG_005905.2:g.172223T>G
ENST00000461574.2:c.5506T>G
ENST00000470026.6:c.5509T>G
ENST00000473961.6:c.5383T>G
ENST00000476777.6:c.5503T>G
ENST00000477152.6:c.5431T>G
ENST00000478531.6:c.2197T>G
ENST00000489037.2:c.5431T>G
ENST00000493919.6:c.2059T>G
ENST00000494123.6:c.5509T>G
ENST00000497488.2:c.4621T>G
ENST00000618469.2:c.5509T>G
ENST00000634433.2:c.5386T>G
ENST00000644379.2:c.5575T>G
ENST00000644555.2:c.2059T>G
ENST00000652672.2:c.5368T>G
ENST00000484087.6:c.2071T>G
ENST00000700081.1:n.1392T>G
ENST00000700082.1:n.873T>G
ENST00000357654.9:c.5509T>G
ENST00000471181.7:c.5572T>G
ENST00000644379.1:c.1896T>G
ENST00000352993.7:c.2083T>G
ENST00000357654.7:c.5509T>G
ENST00000461221.5:c.*5292T>G
ENST00000468300.5:c.*23T>G
ENST00000471181.6:c.5572T>G
ENST00000491747.6:c.2197T>G
ENST00000493795.5:c.5368T>G
ENST00000586385.5:c.439T>G

ENST00000591534.5:c.982T>G
ENST00000591849.5:c.208T>G
NM_007294.3:c.5509T>G
NM_007297.3:c.5368T>G
NM_007298.3:c.2197T>G
NM_007299.3:c.*23T>G
NM_007300.3:c.5572T>G
NR_027676.1:n.5645T>G
NM_007297.4:c.5368T>G
NM_007299.4:c.*23T>G
NM_007300.4:c.5572T>G
NR_027676.2:n.5686T>G

Pathogenic

Met criteria codes 3

PP4_Strong | PP3 | PM2_Supporting

Not Met criteria codes 2

BS3 | PS3

Evidence Links 0

Expert Panel

ENIGMA BRCA1 and BRCA2 VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen ENIGMA BRCA1 and BRCA2 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for BRCA1 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.5509T>G variant in BRCA1 is a missense variant predicted to cause substitution of Tryptophan by Glycine at amino acid 1837 (p.Trp1837Gly). 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 0.533, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met). Reported by three calibrated studies with discordant results. Exhibits protein function similar to pathogenic control variants (PMIDs: 30209399, 30765603) and between what was observed for benign and pathogenic control variants (PMID: 30257991) (PS3 and BS3 not met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2004.67 (based on Co-occurrence LR=1.067; Family History LR=1878.3), above the threshold for very strong evidence towards pathogenicity (>350) (PP4_Very strong met; PMID: 31853058, internal data (dataset as per PMID: 17924331)). In summary, this variant meets the criteria to be classified as a Pathogenic variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PP3, PP4_Very strong).

Met criteria codes

PP4_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2004.67 (based on Co-occurrence LR=1.067; Family History LR=1878.3), above the threshold for very strong evidence towards pathogenicity (>350) (PP4_Very strong met; PMID: 31853058, internal data (dataset as per PMID: 17924331)).

PP3		✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.533, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met).
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).

Not Met criteria codes

BS3		✖	Reported by three calibrated studies with discordant results. Exhibits protein function similar to pathogenic control variants (PMIDs: 30209399, 30765603) and between what was observed for benign and pathogenic control variants (PMID: 30257991) (PS3 and BS3 not met).
PS3		✖	Reported by three calibrated studies with discordant results. Exhibits protein function similar to pathogenic control variants (PMIDs: 30209399, 30765603) and between what was observed for benign and pathogenic control variants (PMID: 30257991) (PS3 and BS3 not met).

Curation History

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