

Variant: NM_007294.4(BRCA1):c.5242G>T (p.Gly1748Cys)

Version: 1.0

CA003383 [↗](#)

37650 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))
Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 39ed444e-1f32-4a44-9cb5-df3eda0c7333
Approved on: 2025/8/18
Published on: 2025/8/18

HGVS expressions

NM_007294.4:c.5242G>T
NM_007294.4(BRCA1):c.5242G>T (p.Gly1748Cys)
NC_000017.11:g.43057087C>A
CM000679.2:g.43057087C>A
NC_000017.10:g.41209104C>A
CM000679.1:g.41209104C>A
NC_000017.9:g.38462630C>A
NG_005905.2:g.160897G>T
ENST00000461574.2:c.5239G>T
ENST00000470026.6:c.5242G>T
ENST00000473961.6:c.5116G>T
ENST00000476777.6:c.5236G>T
ENST00000477152.6:c.5164G>T
ENST00000478531.6:c.1930G>T
ENST00000489037.2:c.5164G>T
ENST00000493919.6:c.1792G>T
ENST00000494123.6:c.5242G>T
ENST00000497488.2:c.4354G>T
ENST00000618469.2:c.5242G>T
ENST00000634433.2:c.5119G>T
ENST00000644379.2:c.5308G>T
ENST00000644555.2:c.1792G>T
ENST00000652672.2:c.5101G>T
ENST00000484087.6:c.1804G>T
ENST00000357654.9:c.5242G>T
ENST00000471181.7:c.5305G>T
ENST00000644379.1:c.1629G>T
ENST00000352993.7:c.1816G>T
ENST00000357654.7:c.5242G>T
ENST00000461221.5:c.*5025G>T
ENST00000468300.5:c.1930G>T
ENST00000471181.6:c.5305G>T
ENST00000491747.6:c.1930G>T
ENST00000493795.5:c.5101G>T
ENST00000586385.5:c.172G>T
ENST00000591534.5:c.715G>T
ENST00000591849.5:c.-98-6897G>T

NM_007294.3:c.5242G>T
NM_007297.3:c.5101G>T
NM_007298.3:c.1930G>T
NM_007299.3:c.1930G>T
NM_007300.3:c.5305G>T
NR_027676.1:n.5378G>T
NM_007297.4:c.5101G>T
NM_007299.4:c.1930G>T
NM_007300.4:c.5305G>T
NR_027676.2:n.5419G>T

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PS3 PP3

PM2_Supporting

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 1.2.0
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.5242G>T variant in BRCA1 is a missense variant predicted to cause substitution of Glycine by Cysteine at amino acid 1748 (p. (Gly1748Cys)). 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). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 38709234, 35196514) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.3, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 4.36 (based on Family History LR=4.36), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID: 31853058). In summary, this variant meets the criteria to be classified as a Likely pathogenic variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PS3, PP4_Moderate, PP3).

Met criteria codes

PP4_Moderate			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 4.36 (based on Family History LR=4.36), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID: 31853058).
PS3			Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 38709234, 35196514) (PS3 met).
PP3			

This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.3, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0 predicts 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).

Curation History



 

 

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