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Variant: NM_007294.4(BRCA1):c.5202T>G (p.Phe1734Leu)

Version: 1.0

CA10576081

225711 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: f9ff3fc0-3211-4cb4-a369-43bd609c1aa4
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HGVS expressions

NM_007294.4:c.5202T>G
NM_007294.4(BRCA1):c.5202T>G (p.Phe1734Leu)
NC_000017.11:g.43057127A>C
CM000679.2:g.43057127A>C
NC_000017.10:g.41209144A>C
CM000679.1:g.41209144A>C
NC_000017.9:g.38462670A>C
NG_005905.2:g.160857T>G
ENST00000461574.2:c.5199T>G
ENST00000470026.6:c.5202T>G
ENST00000473961.6:c.5076T>G
ENST00000476777.6:c.5196T>G
ENST00000477152.6:c.5124T>G
ENST00000478531.6:c.1890T>G
ENST00000489037.2:c.5124T>G
ENST00000493919.6:c.1752T>G
ENST00000494123.6:c.5202T>G
ENST00000497488.2:c.4314T>G
ENST00000618469.2:c.5202T>G
ENST00000634433.2:c.5079T>G
ENST00000644379.2:c.5268T>G
ENST00000644555.2:c.1752T>G
ENST00000652672.2:c.5061T>G
ENST00000484087.6:c.1764T>G
ENST00000357654.9:c.5202T>G
ENST00000471181.7:c.5265T>G
ENST00000644379.1:c.1589T>G
ENST00000352993.7:c.1776T>G
ENST00000357654.7:c.5202T>G
ENST00000461221.5:c.*4985T>G
ENST00000468300.5:c.1890T>G
ENST00000471181.6:c.5265T>G
ENST00000491747.6:c.1890T>G
ENST00000493795.5:c.5061T>G
ENST00000586385.5:c.132T>G
ENST00000591534.5:c.675T>G
ENST00000591849.5:c.-98-6937T>G

NM_007294.3:c.5202T>G
NM_007297.3:c.5061T>G
NM_007298.3:c.1890T>G
NM_007299.3:c.1890T>G
NM_007300.3:c.5265T>G
NR_027676.1:n.5338T>G
NM_007297.4:c.5061T>G
NM_007299.4:c.1890T>G
NM_007300.4:c.5265T>G
NR_027676.2:n.5379T>G

Likely Pathogenic

Met criteria codes 3

PS1_Moderate PM2_Supporting PS3

Not Met criteria codes 3

BP4 BP1 PP3

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.5202T>G variant in BRCA1 is a missense variant predicted to cause substitution of Phenylalanine by Leucine at amino acid 1734 (p.(Phe1734Leu)). 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 two calibrated studies to exhibit protein function similar to pathogenic control variants (PMID:30209399, 35196514) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.27, indicating impact on BRCA1 function via protein change is unclear (score range 0.15-0.28). A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied). A different nucleotide change leading to the same amino acid change (c.5200T>C p.Phe1734Leu, ClinVar Variation ID 125806) is classified as likely pathogenic by the ENIGMA BRCA1/2 VCEP. Splicing prediction revealed no effects on splicing due to either variant. These results suggest that the variant has an impact on protein consistent with pathogenicity (PS1_Moderate (Missense) met). 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, PS1_Moderate (Missense)).

Met criteria codes

PS1_Moderate	✔	A different nucleotide change leading to the same amino acid change (c.5200T>C p.Phe1734Leu, ClinVar Variation ID 125806) is classified as likely pathogenic by the ENIGMA BRCA1/2 VCEP. Splicing prediction revealed no effects on splicing due to either variant. These results suggest that the variant has an impact on protein consistent with pathogenicity (PS1_Moderate (Missense) 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).
PS3	✔	

Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMID:30209399, 35196514) (PS3 met).

Not Met criteria codes

BP4	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.27, indicating impact on BRCA1 function via protein change is unclear (score range 0.15-0.28). A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).
BP1	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.27, indicating impact on BRCA1 function via protein change is unclear (score range 0.15-0.28). A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).
PP3	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.27, indicating impact on BRCA1 function via protein change is unclear (score range 0.15-0.28). A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).

Curation History

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