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Variant: NM_007294.4(BRCA1):c.5200T>A (p.Phe1734Ile)

Version: 1.0

CA10580495

232047 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 991d394d-e48d-44f8-80b4-bc3ce767d949
Approved on: 2025/8/18
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HGVS expressions

NM_007294.4(BRCA1):c.5200T>A (p.Phe1734Ile)
NM_007294.4:c.5200T>A
NC_000017.11:g.43057129A>T
CM000679.2:g.43057129A>T
NC_000017.10:g.41209146A>T
CM000679.1:g.41209146A>T
NC_000017.9:g.38462672A>T
NG_005905.2:g.160855T>A
ENST00000461574.2:c.5197T>A
ENST00000470026.6:c.5200T>A
ENST00000473961.6:c.5074T>A
ENST00000476777.6:c.5194T>A
ENST00000477152.6:c.5122T>A
ENST00000478531.6:c.1888T>A
ENST00000489037.2:c.5122T>A
ENST00000493919.6:c.1750T>A
ENST00000494123.6:c.5200T>A
ENST00000497488.2:c.4312T>A
ENST00000618469.2:c.5200T>A
ENST00000634433.2:c.5077T>A
ENST00000644379.2:c.5266T>A
ENST00000644555.2:c.1750T>A
ENST00000652672.2:c.5059T>A
ENST00000484087.6:c.1762T>A
ENST00000357654.9:c.5200T>A
ENST00000471181.7:c.5263T>A
ENST00000644379.1:c.1587T>A
ENST00000352993.7:c.1774T>A
ENST00000357654.7:c.5200T>A
ENST00000461221.5:c.*4983T>A
ENST00000468300.5:c.1888T>A
ENST00000471181.6:c.5263T>A
ENST00000491747.6:c.1888T>A
ENST00000493795.5:c.5059T>A
ENST00000586385.5:c.130T>A
ENST00000591534.5:c.673T>A
ENST00000591849.5:c.-98-6939T>A

NM_007294.3:c.5200T>A
NM_007297.3:c.5059T>A
NM_007298.3:c.1888T>A
NM_007299.3:c.1888T>A
NM_007300.3:c.5263T>A
NR_027676.1:n.5336T>A
NM_007297.4:c.5059T>A
NM_007299.4:c.1888T>A
NM_007300.4:c.5263T>A
NR_027676.2:n.5377T>A

Likely Pathogenic

Met criteria codes 3

PS3 PP4 PM2_Supporting

Not Met criteria codes 3

PP3 BP4 BP1

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.5200T>A variant in BRCA1 is a missense variant predicted to cause substitution of Phenylalanine by Isoleucine at amino acid 1734 (p.(Phe1734Ile)). 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 0.24, 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). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3.9 (based on Family History LR=3.9), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 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).

Met criteria codes

PS3	✔	Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMID:30209399, 35196514) (PS3 met).
PP4	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3.9 (based on Family History LR=3.9), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; PMID: 31853058).
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

PP3	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.24, 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).
BP4	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.24, 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 0.24, 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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