

Variant: NM_007294.4(BRCA1):c.5003T>C (p.Phe1668Ser)

Version: 1.0

CA10591513 [↗](#)

629251 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))
Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 87589b30-a23f-4f4c-99fd-4ec81ed242e8
Approved on: 2025/8/18
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HGVS expressions

NM_007294.4:c.5003T>C
NM_007294.4(BRCA1):c.5003T>C (p.Phe1668Ser)
NC_000017.11:g.43067679A>G
CM000679.2:g.43067679A>G
NC_000017.10:g.41219696A>G
CM000679.1:g.41219696A>G
NC_000017.9:g.38473222A>G
NG_005905.2:g.150305T>C
ENST00000461574.2:c.5000T>C
ENST00000470026.6:c.5003T>C
ENST00000473961.6:c.4877T>C
ENST00000476777.6:c.4997T>C
ENST00000477152.6:c.4925T>C
ENST00000478531.6:c.1691T>C
ENST00000489037.2:c.4925T>C
ENST00000493919.6:c.1553T>C
ENST00000494123.6:c.5003T>C
ENST00000497488.2:c.4115T>C
ENST00000618469.2:c.5003T>C
ENST00000634433.2:c.4880T>C
ENST00000644379.2:c.5069T>C
ENST00000644555.2:c.1553T>C
ENST00000652672.2:c.4862T>C
ENST00000484087.6:c.1565T>C
ENST00000357654.9:c.5003T>C
ENST00000471181.7:c.5066T>C
ENST00000644379.1:c.1390T>C
ENST00000352993.7:c.1577T>C
ENST00000357654.7:c.5003T>C
ENST00000461221.5:c.*4786T>C
ENST00000468300.5:c.1691T>C
ENST00000471181.6:c.5066T>C
ENST00000472490.1:n.156T>C
ENST00000478531.5:c.1691T>C
ENST00000484087.5:c.1316T>C
ENST00000491747.6:c.1691T>C
ENST00000493795.5:c.4862T>C

ENST00000493919.5:c.1553T>C
ENST00000586385.5:c.5-3728T>C
ENST00000591534.5:c.476T>C
ENST00000591849.5:c.-98-17489T>C
NM_007294.3:c.5003T>C
NM_007297.3:c.4862T>C
NM_007298.3:c.1691T>C
NM_007299.3:c.1691T>C
NM_007300.3:c.5066T>C
NR_027676.1:n.5139T>C
NM_007297.4:c.4862T>C
NM_007299.4:c.1691T>C
NM_007300.4:c.5066T>C
NR_027676.2:n.5180T>C

Uncertain Significance

Met criteria codes 2

PS3 PM2_Supporting

Not Met criteria codes 3

BP4 BP1 PP3

Evidence Links 2

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.5003T>C variant in BRCA1 is a missense variant predicted to cause substitution of phenylalanine by serine at amino acid 1668 (p.Phe1668Ser). 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 0.24, indicating impact on BRCA1 function via protein change is unclear (score range 0.15-0.28). A SpliceAI score of 0.04 predicts no impact on splicing (score threshold ≤0.1) (no bioinformatic code is applied). Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 38709234) (PS3 met). 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, PS3).

Met criteria codes

PS3



Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 38709234) (PS3 met).

Per table S1 - variant has functional score mean of -1.76 = LOF. PubMed:30209399

Per table S3 - fClass 5 = Pathogenic Per fig 4 - reduced transcription activation compared to WT

PubMed:30765603

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			
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 0.04 predicts no impact on splicing (score threshold ≤ 0.1) (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 0.04 predicts no impact on splicing (score threshold ≤ 0.1) (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 0.24, indicating impact on BRCA1 function via protein change is unclear (score range 0.15-0.28). A SpliceAI score of 0.04 predicts no impact on splicing (score threshold ≤ 0.1) (no bioinformatic code is applied).

Curation History 	
	
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