

Variant: NM_007294.4(BRCA1):c.5143A>T (p.Ser1715Cys)

Version: 1.0

CA003265 [↗](#)

55415 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))
Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 50a3a90a-c1a9-4ddc-8872-407c8b987b5d
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HGVS expressions

NM_007294.4(BRCA1):c.5143A>T (p.Ser1715Cys)
NM_007294.4:c.5143A>T
NC_000017.11:g.43063883T>A
CM000679.2:g.43063883T>A
NC_000017.10:g.41215900T>A
CM000679.1:g.41215900T>A
NC_000017.9:g.38469426T>A
NG_005905.2:g.154101A>T
ENST00000461574.2:c.5140A>T
ENST00000470026.6:c.5143A>T
ENST00000473961.6:c.5017A>T
ENST00000476777.6:c.5137A>T
ENST00000477152.6:c.5065A>T
ENST00000478531.6:c.1831A>T
ENST00000489037.2:c.5065A>T
ENST00000493919.6:c.1693A>T
ENST00000494123.6:c.5143A>T
ENST00000497488.2:c.4255A>T
ENST00000618469.2:c.5143A>T
ENST00000634433.2:c.5020A>T
ENST00000644379.2:c.5209A>T
ENST00000644555.2:c.1693A>T
ENST00000652672.2:c.5002A>T
ENST00000484087.6:c.1705A>T
ENST00000357654.9:c.5143A>T
ENST00000471181.7:c.5206A>T
ENST00000644379.1:c.1530A>T
ENST00000352993.7:c.1717A>T
ENST00000357654.7:c.5143A>T
ENST00000461221.5:c.*4926A>T
ENST00000468300.5:c.1831A>T
ENST00000471181.6:c.5206A>T
ENST00000478531.5:c.1831A>T
ENST00000484087.5:c.1456A>T
ENST00000491747.6:c.1831A>T
ENST00000493795.5:c.5002A>T
ENST00000493919.5:c.1693A>T

ENST00000586385.5:c.73A>T
ENST00000591534.5:c.616A>T
ENST00000591849.5:c.-98-13693A>T
NM_007294.3:c.5143A>T
NM_007297.3:c.5002A>T
NM_007298.3:c.1831A>T
NM_007299.3:c.1831A>T
NM_007300.3:c.5206A>T
NR_027676.1:n.5279A>T
NM_007297.4:c.5002A>T
NM_007299.4:c.1831A>T
NM_007300.4:c.5206A>T
NR_027676.2:n.5320A>T

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PS3 PP3

Not Met criteria codes 2

BP5 PP4

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.5143A>T variant in BRCA1 is a missense variant predicted to cause substitution of Serine by Cysteine at amino acid 1715 (p.(Ser1715Cys)). 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, 37168384) (PS3 met). This BRCA1 missense variant is within a key functional domain and a SpliceAI score of 0 predicts no impact on splicing (score threshold ≤0.1). The computational predictor BayesDel (noAF) gives a score of 0.35, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.91 (based on Co-occurrence LR=1.03; Family History LR=1.85), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058, Internal lab contributor). 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, PP3).

Met criteria codes

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 three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 38709234, 37168384) (PS3 met).
PP3		✓	

This BRCA1 missense variant is within a key functional domain and a SpliceAI score of 0 predicts no impact on splicing (score threshold ≤ 0.1). The computational predictor BayesDel (noAF) gives a score of 0.35, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change (PP3 met).

Not Met criteria codes

BP5			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.91 (based on Co-occurrence LR=1.03; Family History LR=1.85), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058, Internal lab contributor).
PP4			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.91 (based on Co-occurrence LR=1.03; Family History LR=1.85), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058, Internal lab contributor).

Curation History

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