

Variant: NM_007294.4(BRCA1):c.5165C>A (p.Ser1722Tyr)

Version: 1.0

CA10591215 [↗](#)

491098 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))
Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 64381fa9-c857-4871-b5ee-7835aa4a39bd
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HGVS expressions

NM_007294.4(BRCA1):c.5165C>A (p.Ser1722Tyr)
NM_007294.4:c.5165C>A
NC_000017.11:g.43063361G>T
CM000679.2:g.43063361G>T
NC_000017.10:g.41215378G>T
CM000679.1:g.41215378G>T
NC_000017.9:g.38468904G>T
NG_005905.2:g.154623C>A
ENST00000461574.2:c.5162C>A
ENST00000470026.6:c.5165C>A
ENST00000473961.6:c.5039C>A
ENST00000476777.6:c.5159C>A
ENST00000477152.6:c.5087C>A
ENST00000478531.6:c.1853C>A
ENST00000489037.2:c.5087C>A
ENST00000493919.6:c.1715C>A
ENST00000494123.6:c.5165C>A
ENST00000497488.2:c.4277C>A
ENST00000618469.2:c.5165C>A
ENST00000634433.2:c.5042C>A
ENST00000644379.2:c.5231C>A
ENST00000644555.2:c.1715C>A
ENST00000652672.2:c.5024C>A
ENST00000484087.6:c.1727C>A
ENST00000357654.9:c.5165C>A
ENST00000471181.7:c.5228C>A
ENST00000644379.1:c.1552C>A
ENST00000352993.7:c.1739C>A
ENST00000357654.7:c.5165C>A
ENST00000461221.5:c.*4948C>A
ENST00000468300.5:c.1853C>A
ENST00000471181.6:c.5228C>A
ENST00000478531.5:c.1853C>A
ENST00000484087.5:c.1478C>A
ENST00000491747.6:c.1853C>A
ENST00000493795.5:c.5024C>A
ENST00000493919.5:c.1715C>A

ENST00000586385.5:c.95C>A
ENST00000591534.5:c.638C>A
ENST00000591849.5:c.-98-13171C>A
NM_007294.3:c.5165C>A
NM_007297.3:c.5024C>A
NM_007298.3:c.1853C>A
NM_007299.3:c.1853C>A
NM_007300.3:c.5228C>A
NR_027676.1:n.5301C>A
NM_007297.4:c.5024C>A
NM_007299.4:c.1853C>A
NM_007300.4:c.5228C>A
NR_027676.2:n.5342C>A

Uncertain Significance

Met criteria codes 3

PP4_Moderate

PP3

PM2_Supporting

Not Met criteria codes 2

PS3

BS3

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.5165C>A variant in BRCA1 is a missense variant predicted to cause substitution of Serine by Tyrosine at amino acid 1722 (p. (Ser1722Tyr)). 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 a partial impact on protein function, between what was observed for benign and pathogenic control variants (PMIDs:30209399, 30257991) (PS3 and BS3 not met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.43, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0.02 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 6.04 (based on Cosegregation LR=37.75; Pathology LR=0.16), within the thresholds for moderate evidence towards pathogenicity (LR > 4.3 & ≤ 18.7) (PP4_Moderate met; Internal lab contributors). 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, PP3, PP4_Moderate).

Met criteria codes

PP4_Moderate



Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 6.04 (based on Cosegregation LR=37.75; Pathology LR=0.16), within the thresholds for moderate evidence towards pathogenicity (LR > 4.3 & ≤ 18.7) (PP4_Moderate met; Internal lab contributors).

PP3



This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.43, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0.02 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).
Not Met criteria codes			
PS3			Reported by two calibrated studies to exhibit a partial impact on protein function, between what was observed for benign and pathogenic control variants (PMIDs:30209399, 30257991) (PS3 and BS3 not met).
BS3			Reported by two calibrated studies to exhibit a partial impact on protein function, between what was observed for benign and pathogenic control variants (PMIDs:30209399, 30257991) (PS3 and BS3 not met).

Curation History 			
			
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