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Variant: NM_007294.4(BRCA1):c.191G>A (p.Cys64Tyr)

Version: 2.0

CA001262

54400 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: aed4706a-e502-48b4-8417-bb5c3aa01461
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HGVS expressions

NM_007294.4:c.191G>A
NM_007294.4(BRCA1):c.191G>A (p.Cys64Tyr)
NC_000017.11:g.43106477C>T
CM000679.2:g.43106477C>T
NC_000017.10:g.41258494C>T
CM000679.1:g.41258494C>T
NC_000017.9:g.38512020C>T
NG_005905.2:g.111507G>A
ENST00000354071.8:n.255G>A
ENST00000461574.2:c.191G>A
ENST00000470026.6:c.191G>A
ENST00000473961.6:c.191G>A
ENST00000476777.6:c.191G>A
ENST00000477152.6:c.135-1521G>A
ENST00000478531.6:c.191G>A
ENST00000489037.2:c.135-1521G>A
ENST00000493919.6:c.50G>A
ENST00000494123.6:c.191G>A
ENST00000497488.2:c.-218-11617G>A
ENST00000618469.2:c.191G>A
ENST00000634433.2:c.191G>A
ENST00000644379.2:c.191G>A
ENST00000644555.2:c.50G>A
ENST00000652672.2:c.50G>A
ENST00000484087.6:c.191G>A
ENST00000700182.1:c.135-1521G>A
ENST00000700183.1:c.*126+1G>A
ENST00000700184.1:n.434G>A
ENST00000357654.9:c.191G>A
ENST00000471181.7:c.191G>A
ENST00000642945.1:c.*65G>A
ENST00000644555.1:c.50G>A
ENST00000652672.1:c.50G>A
ENST00000352993.7:c.191G>A
ENST00000354071.7:c.191G>A
ENST00000357654.7:c.191G>A
ENST00000461221.5:c.190+1G>A

ENST00000461798.5:c.190+1G>A
ENST00000468300.5:c.191G>A
ENST00000470026.5:c.191G>A
ENST00000471181.6:c.191G>A
ENST00000476777.5:c.191G>A
ENST00000477152.5:c.135-1521G>A
ENST00000478531.5:c.191G>A
ENST00000489037.1:c.135-1521G>A
ENST00000491747.6:c.191G>A
ENST00000492859.5:c.*127G>A
ENST00000493795.5:c.50G>A
ENST00000493919.5:c.50G>A
ENST00000494123.5:c.191G>A
ENST00000497488.1:c.-218-11617G>A
ENST00000586385.5:c.4+18705G>A
ENST00000591534.5:c.-44+18794G>A
ENST00000591849.5:c.-99+18794G>A
ENST00000634433.1:c.191G>A
NM_007294.3:c.191G>A
NM_007297.3:c.50G>A
NM_007298.3:c.191G>A
NM_007299.3:c.191G>A
NM_007300.3:c.191G>A
NR_027676.1:n.351+1G>A
NM_007297.4:c.50G>A
NM_007299.4:c.191G>A
NM_007300.4:c.191G>A
NR_027676.2:n.392+1G>A

Pathogenic

Met criteria codes 4

PS3 PP4_Strong PP3 PM2_Supporting

Evidence Links 1

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 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.191G>A variant in BRCA1 is a missense variant predicted to cause substitution of Cysteine by Tyrosine at amino acid 64 (p.Cys64Tyr). 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 0.557, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met). Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 30209399) (PS3 met). Multifactorial

likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 17239845573264 (based on Cosegregation LR=5300394; Pathology LR=189; Family History LR=17201), above the threshold for Very strong evidence towards pathogenicity (>350) (PP4_Very strong met; PMID: 31131967, 31853058). In summary, this variant meets the criteria to be classified as a Pathogenic variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PP3, PS3, PP4_Very strong).

Met criteria codes

PS3	✔	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 30209399) (PS3 met). Deleterious PubMed:30209399
PP4_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 17239845573264 (based on Cosegregation LR=5300394; Pathology LR=189; Family History LR=17201), above the threshold for Very strong evidence towards pathogenicity (>350) (PP4_Very strong met; PMID: 31131967).
PP3	✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.557, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. SpliceAI predictor score of 0.00 suggests that the variant has 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).

Curation History

Showing 1 to 3 of 3 rows