

Variant: NM_007294.4(BRCA1):c.74C>T (p.Pro25Leu)

Version: 1.0

CA10580713 [↗](#)

232955 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))

Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 5d3554ab-d031-4a42-a748-2b8efadd75a8

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HGVS expressions

NM_007294.4(BRCA1):c.74C>T (p.Pro25Leu)

NM_007294.4:c.74C>T

NC_000017.11:g.43124023G>A

CM000679.2:g.43124023G>A

NC_000017.10:g.41276040G>A

CM000679.1:g.41276040G>A

NC_000017.9:g.38529566G>A

NG_005905.2:g.93961C>T

ENST00000354071.8:n.138C>T

ENST00000461574.2:c.74C>T

ENST00000470026.6:c.74C>T

ENST00000473961.6:c.74C>T

ENST00000476777.6:c.74C>T

ENST00000477152.6:c.74C>T

ENST00000478531.6:c.74C>T

ENST00000489037.2:c.74C>T

ENST00000493919.6:c.-14C>T

ENST00000494123.6:c.74C>T

ENST00000497488.2:c.-219+1248C>T

ENST00000618469.2:c.74C>T

ENST00000634433.2:c.74C>T

ENST00000644379.2:c.74C>T

ENST00000644555.2:c.-213C>T

ENST00000652672.2:c.-187C>T

ENST00000484087.6:c.74C>T

ENST00000700182.1:c.74C>T

ENST00000700183.1:c.74C>T

ENST00000700184.1:n.317C>T

ENST00000700185.1:n.193C>T

ENST00000700186.1:n.193C>T

ENST00000357654.9:c.74C>T

ENST00000471181.7:c.74C>T

ENST00000642945.1:c.74C>T

ENST00000644555.1:c.-213C>T

ENST00000652672.1:c.-187C>T

ENST00000352993.7:c.74C>T

ENST00000354071.7:c.74C>T

ENST00000357654.7:c.74C>T
ENST00000461221.5:c.74C>T
ENST00000461798.5:c.74C>T
ENST00000468300.5:c.74C>T
ENST00000470026.5:c.74C>T
ENST00000471181.6:c.74C>T
ENST00000476777.5:c.74C>T
ENST00000477152.5:c.74C>T
ENST00000478531.5:c.74C>T
ENST00000489037.1:c.74C>T
ENST00000491747.6:c.74C>T
ENST00000492859.5:c.74C>T
ENST00000493795.5:c.-14C>T
ENST00000493919.5:c.-14C>T
ENST00000494123.5:c.74C>T
ENST00000497488.1:c.-219+1248C>T
ENST00000586385.5:c.4+1159C>T
ENST00000591534.5:c.-44+1248C>T
ENST00000591849.5:c.-99+1248C>T
ENST00000634433.1:c.74C>T
NM_007294.3:c.74C>T
NM_007297.3:c.-14C>T
NM_007298.3:c.74C>T
NM_007299.3:c.74C>T
NM_007300.3:c.74C>T
NR_027676.1:n.235C>T
NM_007297.4:c.-14C>T
NM_007299.4:c.74C>T
NM_007300.4:c.74C>T
NR_027676.2:n.276C>T

Likely Pathogenic

Met criteria codes 3

PS3 PP3 PM2_Supporting

Evidence Links 1

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.74C>T variant in BRCA1 is a missense variant predicted to cause substitution of proline by leucine at amino acid 25 (p.Pro25Leu). 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 0.35, 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 ≤0.1) (PP3 met). Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 35659930) (PS3 met). 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, PP3, PS3).

Met criteria codes

PS3			Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 35659930) (PS3 met).
Per table S1, function.score.mean = -1.66083571915168 (LOF) PubMed:30209399 			
PP3			This BRCA1 missense variant is within a key functional domain and 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. A SpliceAI score of 0.02 predicts no impact on splicing (score threshold ≤ 0.1) (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

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