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Variant: NM_000059.4(BRCA2):c.9374T>A (p.Leu3125His)

Version: 1.0

CA026120

52823 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: afeda980-e6c3-4626-a1d8-2167faef48be
Approved on: 2026/1/5
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HGVS expressions

NM_000059.4(BRCA2):c.9374T>A (p.Leu3125His)
NM_000059.4:c.9374T>A
NC_000013.11:g.32394806T>A
CM000675.2:g.32394806T>A
NC_000013.10:g.32968943T>A
CM000675.1:g.32968943T>A
NC_000013.9:g.31866943T>A
NG_012772.3:g.84327T>A
ENST00000470094.2:c.9374T>A
ENST00000528762.2:c.*741T>A
ENST00000530893.7:c.9005T>A
ENST00000665585.2:c.*936T>A
ENST00000666593.2:c.*219T>A
ENST00000700202.2:c.9323T>A
ENST00000700202.1:c.1790T>A
ENST00000700203.1:n.1501T>A
ENST00000380152.8:c.9374T>A
ENST00000544455.6:c.9374T>A
ENST00000614259.2:c.9382T>A
ENST00000665585.1:c.2252T>A
ENST00000666593.1:c.396T>A
ENST00000680887.1:c.9374T>A
ENST00000380152.7:c.9374T>A
ENST00000470094.1:c.331T>A
ENST00000544455.5:c.9374T>A
NM_000059.3:c.9374T>A

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PS3 PP4

Not Met criteria codes 4

BP7 BP4 BP1 PP3

Evidence Links 0

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 BRCA2 Version 1.1.0*

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.9374T>A variant in BRCA2 is a missense variant predicted to cause substitution of Leucine by Histidine at amino acid 3125 (p.(Leu3125His)). 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:38417439, 39779857, 39779848) (PS3 met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.21, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3.6 (based on Cosegregation LR=0.89; Pathology LR=4.04), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor). In summary, this variant meets the criteria to be classified as a Likely pathogenic variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PS3, PP4).

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:38417439, 39779857, 39779848) (PS3 met).
PP4	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3.6 (based on Cosegregation LR=0.89; Pathology LR=4.04), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor).

Not Met criteria codes

BP7	✖	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.21, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).
BP4	✖	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.21, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).
BP1	✖	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.21, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).
PP3	✖	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.21, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A

SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).

Curation History

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