The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000059.4(BRCA2):c.7874G>T (p.Arg2625Ile)

Version: 1.0

CA16619772

419217 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: ea913484-ec79-4f9a-a76b-f8b38ed49a21
Approved on: 2025/12/3
Published on: 2025/12/2

HGVS expressions

NM_000059.4(BRCA2):c.7874G>T (p.Arg2625Ile)
NM_000059.4:c.7874G>T
NC_000013.11:g.32362591G>T
CM000675.2:g.32362591G>T
NC_000013.10:g.32936728G>T
CM000675.1:g.32936728G>T
NC_000013.9:g.31834728G>T
NG_012772.3:g.52112G>T
ENST00000470094.2:c.7874G>T
ENST00000528762.2:c.7874G>T
ENST00000530893.7:c.7505G>T
ENST00000665585.2:c.7874G>T
ENST00000666593.2:c.7874G>T
ENST00000700202.2:c.7874G>T
ENST00000700202.1:c.341G>T
ENST00000380152.8:c.7874G>T
ENST00000544455.6:c.7874G>T
ENST00000614259.2:c.7882G>T
ENST00000665585.1:c.439G>T
ENST00000680887.1:c.7874G>T
ENST00000380152.7:c.7874G>T
ENST00000544455.5:c.7874G>T
ENST00000614259.1:n.7882G>T
NM_000059.3:c.7874G>T

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PP4_Moderate PS3

Not Met criteria codes 3

PP3 BP4 BP1

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.7874G>T variant in BRCA2 is a missense variant predicted to cause substitution of Arginine by Isoleucine at amino acid 2625 (p.(Arg2625Ile)). 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 0.2, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.01 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 5.33 (based on Case-Control LR=5.33), within the thresholds for moderate evidence towards pathogenicity (LR ≥4.3 & <18.7) (PP4_Moderate met; PMID: 40413188). 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_Moderate).

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).
PP4_Moderate	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 5.33 (based on Case-Control LR=5.33), within the thresholds for moderate evidence towards pathogenicity (LR ≥4.3 & <18.7) (PP4_Moderate met; PMID: 40413188).
PS3	✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met).

Not Met criteria codes

PP3	✖	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.2, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.01 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 0.2, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.01 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 0.2, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.01 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).

Curation History

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