

Variant: *NM_000059.4(BRCA2):c.7970A>C (p.Lys2657Thr)*

Version: 1.0

CA387747333 [↗](#)

441298 (ClinVar) [↗](#)

Gene: BRCA2 ([HGNC:675](#))

Condition: BRCA2-related cancer predisposition ([MONDO:0700269](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 5ed6fe62-d047-4d91-a3e3-20b2a64286fd

Approved on: 2025-05-23

Published on: 2025-05-23

HGVS expressions

NM_000059.4:c.7970A>C

NM_000059.4(BRCA2):c.7970A>C (p.Lys2657Thr)

NC_000013.11:g.32362687A>C

CM000675.2:g.32362687A>C

NC_000013.10:g.32936824A>C

CM000675.1:g.32936824A>C

NC_000013.9:g.31834824A>C

NG_012772.3:g.52208A>C

ENST00000470094.2:c.7970A>C

ENST00000528762.2:c.7970A>C

ENST00000530893.7:c.7601A>C

ENST00000665585.2:c.7970A>C

ENST00000666593.2:c.7970A>C

ENST00000700202.2:c.7970A>C

ENST00000700202.1:c.437A>C

ENST00000380152.8:c.7970A>C

ENST00000544455.6:c.7970A>C

ENST00000614259.2:c.7978A>C

ENST00000665585.1:c.535A>C

ENST00000680887.1:c.7970A>C

ENST00000380152.7:c.7970A>C

ENST00000544455.5:c.7970A>C

NM_000059.3:c.7970A>C

Uncertain Significance

Met criteria codes **1**

PS3

Not Met criteria codes **4**

PP4

PP3

PM2

BP5

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**

ENIGMA BRCA1 and BRCA2 VCEP

The c.7970A>C variant in BRCA2 is a missense variant predicted to cause substitution of lysine by threonine at amino acid 2657 (p. (Lys2657Thr)). This BRCA2 missense variant is within a key functional domain. The computational predictor BayesDel (noAF) gives a score of 0.27, indicating that impact on BRCA2 function via protein change is unclear (score range 0.18-0.30) and the SpliceAI score of 0.00 predicts no impact on splicing (score threshold ≤ 0.1) (no bioinformatic code is applied). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMID: 38417439, 39779857, 39779848). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.49 (based on Family History LR=1.49), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (PMID: 31853058). This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). In summary, this variant meets the criteria to be classified as a Variant of uncertain significance for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PS3).

Met criteria codes

PS3			Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMID: 38417439, 39779857, 39779848).
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Not Met criteria codes

PP4			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.49 (based on Family History LR=1.49), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).
PP3			This BRCA2 missense variant is within a key functional domain. The computational predictor BayesDel (noAF) gives a score of 0.27, indicating that impact on BRCA2 function via protein change is unclear (score range 0.18-0.30) and the SpliceAI score of 0.00 predicts no impact on splicing (score threshold ≤ 0.1) (no bioinformatic code is applied).
PM2			This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
BP5			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.49 (based on Family History LR=1.49), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).

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