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# *Variant: NM_000059.4(BRCA2):c.9364G>C (p.Ala3122Pro)*

Version: 1.0

*CA387761167*

*439019 (ClinVar)*

**Gene**: BRCA2 (HGNC:675)
**Condition**: BRCA2-related cancer predisposition (MONDO:0700269)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** aafb9cc9-786a-4252-81fe-768288673f09
**Approved on**: 2025/12/3
**Published on**: 2025/12/2

## *HGVS expressions*

**NM_000059.4(BRCA2):c.9364G>C (p.Ala3122Pro)**
**NM_000059.4:c.9364G>C**
NC_000013.11:g.32394796G>C
CM000675.2:g.32394796G>C
NC_000013.10:g.32968933G>C
CM000675.1:g.32968933G>C
NC_000013.9:g.31866933G>C
NG_012772.3:g.84317G>C
ENST00000470094.2:c.9364G>C
ENST00000528762.2:c.*731G>C
ENST00000530893.7:c.8995G>C
ENST00000665585.2:c.*926G>C
ENST00000666593.2:c.*209G>C
ENST00000700202.2:c.9313G>C
ENST00000700202.1:c.1780G>C
ENST00000700203.1:n.1491G>C
ENST00000380152.8:c.9364G>C
ENST00000544455.6:c.9364G>C
ENST00000614259.2:c.9372G>C
ENST00000665585.1:c.2242G>C
ENST00000666593.1:c.386G>C
ENST00000680887.1:c.9364G>C
ENST00000380152.7:c.9364G>C
ENST00000470094.1:c.321G>C
ENST00000544455.5:c.9364G>C
NM_000059.3:c.9364G>C

**Likely Pathogenic**

**Met criteria codes** 3

PP1_Moderate PS3 PM2_Supporting

**Not Met criteria codes** 3

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 1.2.0*

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

***ENIGMA BRCA1 and BRCA2 VCEP***

**The c.9364G>C variant in BRCA2 is a missense variant predicted to cause substitution of alanine by proline at amino acid 3122 (p.Ala3122Pro). 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 BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.22, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A 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 (PMIDs:38417439, 39779857, 39779848) (PS3 met). Cosegregation analysis of two families carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 16.96 (applied as LR), within the thresholds for moderate pathogenic evidence (LR ≥4.3 & <18.7) (PP1_Moderate met; Internal lab contributors). 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, PP1_Moderate).**

**Met criteria codes**

| | | |
|---|---|---|
| **PP1_Moderate** | ✔ | Cosegregation analysis of two families carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 16.96 (applied as LR), within the thresholds for moderate pathogenic evidence (LR ≥4.3 & <18.7) (PP1_Moderate met; Internal lab contributors). |
| **PS3** | ✔ | Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 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). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **BP4** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BP1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PP3** | ✖ | This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.22, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.00 predicts no impact on splicing (score threshold ≤0.1) (no bioinformatic code is applied). |

## Curation History

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| See Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
|---|---|---|---|---|---|---|---|
| View | NM_000059.4(BRCA2):c.9364G>C (p.Al... | Likely Pathogenic | BRCA2-Related Cancer Predisposition | 2025-12-02 | 1.0 | ClinGen ENIGMA BRCA1 and BRCA2 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for BRCA2 Version 1.2.0 | BRCA2 |

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