

Variant: *NM\_000059.4(BRCA2):c.316G>A (p.Gly106Arg)*

Version: 1.0

CA017418 [↗](#)

185084 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal dominant inheritance

**UUID:** 6371fabd-245a-4c40-87b6-dbf1d91d6416

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## HGVS expressions

**NM\_000059.4(BRCA2):c.316G>A (p.Gly106Arg)**

**NM\_000059.4:c.316G>A**

NC\_000013.11:g.32319325G>A

CM000675.2:g.32319325G>A

NC\_000013.10:g.32893462G>A

CM000675.1:g.32893462G>A

NC\_000013.9:g.31791462G>A

NG\_012772.3:g.8846G>A

NG\_017006.2:g.1039C>T

ENST00000470094.2:c.316G>A

ENST00000528762.2:c.316G>A

ENST00000530893.7:c.-54G>A

ENST00000665585.2:c.316G>A

ENST00000666593.2:c.316G>A

ENST00000700202.2:c.316G>A

ENST00000700200.1:n.191+2798G>A

ENST00000700201.1:c.316G>A

ENST00000380152.8:c.316G>A

ENST00000544455.6:c.316G>A

ENST00000614259.2:c.316G>A

ENST00000680887.1:c.316G>A

ENST00000380152.7:c.316G>A

ENST00000530893.6:n.514G>A

ENST00000544455.5:c.316G>A

ENST00000614259.1:n.316G>A

NM\_000059.3:c.316G>A

Uncertain Significance

Met criteria codes **2**

PP3

PM3

Not Met criteria codes **8**

BA1

BS1

BS3

BP5

BP7

PS3

PP4

PM2

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

Evidence submitted by expert panel

**ENIGMA BRCA1 and BRCA2 VCEP**

The c.316G>A variant in BRCA2 is a missense variant predicted to cause substitution of Glycine by Arginine at amino acid 106 (p. (Gly106Arg)). 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). Missense variant shown to alter splicing (see PVS1 or BP7 for description), functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study to exhibit a partial impact on protein function, between what was observed for benign and pathogenic control variants (PMID:32641407) (PS3 and BS3 not met). This BRCA2 missense variant has a SpliceAI score of 0.29, predicting an impact on splicing (score threshold >0.20) (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.54 (based on Family History LR=1.54), 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). This is a missense variant outside a key functional domain, and mRNA experimental analysis indicates production of a sufficient amount of wildtype transcript (PMID: 32641407), however the VCEP decided to currently not apply BP7\_Strong (RNA) due to the results being close to the threshold (~30% WT or assumed functional transcript). This variant has been detected in an individual with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least two clinical features of FA (physical features, pathology findings and cancer diagnosis ≤5yr) and confirmed chromosome breakage are seen in this individual. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant (BRCA2:c.2808\_2811del), confirmed to be in trans. Total points equated to 2 (PM3 met; PMIDs: 32641407, 36721989). 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 (PP3, PM3).

Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3 |  |  | This BRCA2 missense variant has a SpliceAI score of 0.29, predicting an impact on splicing (score threshold >0.20) (PP3 met).                                                                                                                                                                                                                                                                                                                                                                   |
| PM3 |  |  | This variant has been detected in an individual with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least two clinical features of FA (physical features, pathology findings and cancer diagnosis ≤5yr) and confirmed chromosome breakage are seen in this individual. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant (BRCA2:c.2808_2811del), confirmed to be in trans. Total points equated to 2 (PM3 met; PMIDs: 32641407, 36721989). |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                                                                                                                                   |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BA1 |  |  | 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). |
| BS1 |  |  | 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). |
| BS3 |  |  |                                                                                                                                                                                                                                   |

Missense variant shown to alter splicing (see PVS1 or BP7 for description), functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study to exhibit a partial impact on protein function, between what was observed for benign and pathogenic control variants (PMID:32641407) (PS3 and BS3 not met).

|     |                                                                                   |                                                                                    |                                                                                                                                                                                                                                                                                                                                                                 |
|-----|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BP5 |  |   | Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.54 (based on Family History LR=1.54), 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).                                                                      |
| BP7 |  |   | This is a missense variant outside a key functional domain, and mRNA experimental analysis indicates production of a sufficient amount of wildtype transcript (PMID: 32641407), however the VCEP decided to currently not apply BP7_Strong (RNA) due to the results being close to the threshold (~30% WT or assumed functional transcript).                    |
| PS3 |  |   | Missense variant shown to alter splicing (see PVS1 or BP7 for description), functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study to exhibit a partial impact on protein function, between what was observed for benign and pathogenic control variants (PMID:32641407) (PS3 and BS3 not met). |
| PP4 |  |   | Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.54 (based on Family History LR=1.54), 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).                                                                      |
| 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).                                                                                                                               |

Curation History 



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