

Variant: *NM_000059.4(BRCA2):c.9052A>G (p.Ser3018Gly)*

Version: 1.0

CA025943 [↗](#)

96877 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 1dbcd3fb-b72d-45cf-b03f-e67f4a11d3bf

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HGVS expressions

NM_000059.4:c.9052A>G

NM_000059.4(BRCA2):c.9052A>G (p.Ser3018Gly)

NC_000013.11:g.32379848A>G

CM000675.2:g.32379848A>G

NC_000013.10:g.32953985A>G

CM000675.1:g.32953985A>G

NC_000013.9:g.31851985A>G

NG_012772.3:g.69369A>G

ENST00000470094.2:c.9052A>G

ENST00000528762.2:c.*419A>G

ENST00000530893.7:c.8683A>G

ENST00000665585.2:c.*614A>G

ENST00000666593.2:c.9052A>G

ENST00000700202.2:c.9001A>G

ENST00000700202.1:c.1468A>G

ENST00000700203.1:n.1179A>G

ENST00000380152.8:c.9052A>G

ENST00000544455.6:c.9052A>G

ENST00000614259.2:c.9060A>G

ENST00000665585.1:c.1930A>G

ENST00000680887.1:c.9052A>G

ENST00000380152.7:c.9052A>G

ENST00000470094.1:c.9A>G

ENST00000544455.5:c.9052A>G

NM_000059.3:c.9052A>G

Pathogenic

Met criteria codes **4**

PM2_Supporting

PVS1

PS3

PP4

Not Met criteria codes **1**

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**

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.9052A>G variant in BRCA2 is a missense variant predicted to cause substitution of Serine by Glycine at amino acid 3018 (p. (Ser3018Gly)). This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met). This BRCA2 missense variant has a SpliceAI score of 0.83, predicting an impact on splicing by creating a donor site at the position of the variant (score threshold >0.20) (PP3 not applied because a PVS1 code is met). This variant is reported to result in aberrant mRNA splicing, confirming the prediction. RT-PCRseq demonstrated that the variant impacts splicing by skipping part of exon 23 (r.9053_9117del65 p.K3019Ffs*3). The percent of aberrant transcripts produced by the variant allele was estimated to be 90-95% using an allele specific semi-quantitative assessment with sequence analysis (Ambry internal data). We estimate up to 10% full-length transcript is produced by the variant allele. Appropriate code strength determined by comparison of results to PVS1 decision tree and Rubric of weighing mRNA data (Appendix Table 9): PVS1 (RNA) met. Missense variant predicted to alter splicing, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study incorporating mRNA splicing effects to exhibit function similar to pathogenic control variants (PMID: 39779857) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.4 (based on Co-occurrence LR=1.08; Family History LR=2.24), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; PMID: 31853058, Internal lab contributor). In summary, this variant meets the criteria to be classified as a Pathogenic variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PVS1 (RNA), PM2_Supporting, PP4, PS3).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met).
PVS1			This variant is reported to result in aberrant mRNA splicing, confirming the prediction. RT-PCRseq demonstrated that the variant impacts splicing by skipping part of exon 23 (r.9053_9117del65 p.K3019Ffs*3). The percent of aberrant transcripts produced by the variant allele was estimated to be 90-95% using an allele specific semi-quantitative assessment with sequence analysis (Ambry internal data). We estimate up to 10% full-length transcript is produced by the variant allele. Appropriate code strength determined by comparison of results to PVS1 decision tree and Rubric of weighing mRNA data (Appendix Table 9): PVS1 (RNA) met.
PS3			Missense variant predicted to alter splicing, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study incorporating mRNA splicing effects to exhibit function similar to pathogenic control variants (PMID: 39779857) (PS3 met).
PP4			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.4 (based on Co-occurrence LR=1.08; Family History LR=2.24), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; PMID: 31853058, Internal lab contributor).

Not Met criteria codes

PP3			This BRCA2 missense variant has a SpliceAI score of 0.83, predicting an impact on splicing by creating a donor site at the position of the variant (score threshold >0.20) (PP3 not applied because a PVS1 code is met).
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