

Variant: *NM_000059.4(BRCA2):c.67G>A (p.Asp23Asn)*

Version: 1.0

CA10576059 [↗](#)

225732 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: acb51610-4f1c-44e1-a593-129bd48b0e1e

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HGVS expressions

NM_000059.4:c.67G>A

NM_000059.4(BRCA2):c.67G>A (p.Asp23Asn)

NC_000013.11:g.32316527G>A

CM000675.2:g.32316527G>A

NC_000013.10:g.32890664G>A

CM000675.1:g.32890664G>A

NC_000013.9:g.31788664G>A

NG_012772.3:g.6048G>A

NG_017006.1:g.428C>T

NG_017006.2:g.3837C>T

ENST00000470094.2:c.67G>A

ENST00000528762.2:c.67G>A

ENST00000530893.7:c.-303+4G>A

ENST00000665585.2:c.67G>A

ENST00000666593.2:c.67G>A

ENST00000700202.2:c.67G>A

ENST00000700199.1:n.191G>A

ENST00000700200.1:n.191G>A

ENST00000700201.1:c.67G>A

ENST00000380152.8:c.67G>A

ENST00000544455.6:c.67G>A

ENST00000614259.2:c.67G>A

ENST00000680887.1:c.67G>A

ENST00000380152.7:c.67G>A

ENST00000530893.6:n.265+4G>A

ENST00000544455.5:c.67G>A

ENST00000614259.1:n.67G>A

NM_000059.3:c.67G>A

Uncertain Significance

Met criteria codes **2**

PM2_Supporting

PVS1_Strong

Not Met criteria codes **1**

PP3

Expert Panel

ENIGMA BRCA1 and BRCA2 VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.67G>A variant in BRCA2 is a missense variant predicted to cause substitution of Aspartic Acid by Asparagine at amino acid 23 (p. (Asp23Asn)). 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 has a SpliceAI score of 0.59, predicting an impact on splicing (score threshold >0.20) (PP3 not applied because a PVS1 code is met). This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by use of a cryptic site 4 nt upstream (PMID: 29750258). The percent reference and aberrant transcripts produced from the variant allele is not stated. A minigene assay demonstrated the variant allele produced 7.7 % reference (full-length, FL) and 89 % aberrant transcript using an allele specific quantitative assessment with Capillary electrophoresis (PMID: 30883759). RT-PCRseq from an Internal lab contributor has also demonstrated that a small number of normally spliced reads contained the variant allele (Ambry internal data). Appropriate code strength determined by comparison of results to PVS1 decision tree and VCEP discussion: PVS1_Strong (RNA). 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 (PM2_Supporting, PVS1_Strong (RNA)).

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).
PVS1_Strong			This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by use of a cryptic site 4 nt upstream (PMID: 29750258). The percent reference and aberrant transcripts produced from the variant allele is not stated. A minigene assay demonstrated the variant allele produced 7.7 % reference (full-length, FL) and 89 % aberrant transcript using an allele specific quantitative assessment with Capillary electrophoresis (PMID: 30883759). RT-PCRseq from an Internal lab contributor has also demonstrated that a small number of normally spliced reads contained the variant allele (Ambry internal data). Appropriate code strength determined by comparison of results to PVS1 decision tree and VCEP discussion: PVS1_Strong (RNA).

Not Met criteria codes

PP3			This BRCA2 missense variant has a SpliceAI score of 0.59, predicting an impact on splicing (score threshold >0.20) (PP3 not applied because a PVS1 code is met).
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