

Variant: *NM\_000059.4(BRCA2):c.631+4A>G*

Version: 1.0

CA023861 [↗](#)

52056 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal dominant inheritance

**UUID:** c606ba33-bde7-4122-bd73-7cd241b13573

**Approved on:** 2025/8/18

**Published on:** 2025/8/18

### *HGVS expressions*

**NM\_000059.4(BRCA2):c.631+4A>G**

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NC\_000013.11:g.32326617A>G

CM000675.2:g.32326617A>G

NC\_000013.10:g.32900754A>G

CM000675.1:g.32900754A>G

NC\_000013.9:g.31798754A>G

NG\_012772.3:g.16138A>G

ENST00000470094.2:c.631+4A>G

ENST00000528762.2:c.631+4A>G

ENST00000530893.7:c.262+4A>G

ENST00000665585.2:c.631+4A>G

ENST00000666593.2:c.631+4A>G

ENST00000700202.2:c.631+4A>G

ENST00000700200.1:n.506A>G

ENST00000700201.1:c.\*410+4A>G

ENST00000380152.8:c.631+4A>G

ENST00000544455.6:c.631+4A>G

ENST00000614259.2:c.631+4A>G

ENST00000680887.1:c.631+4A>G

ENST00000380152.7:c.631+4A>G

ENST00000530893.6:n.829+4A>G

ENST00000544455.5:c.631+4A>G

ENST00000614259.1:n.631+4A>G

NM\_000059.3:c.631+4A>G

**Likely Pathogenic**

**Met criteria codes** **2**

**PM2** **PVS1**

**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 1.2.0

[↗](#) **Criteria Specification Approval History**

Evidence submitted by expert panel

*ENIGMA BRCA1 and BRCA2 VCEP*

The c.631+4A>G variant is an intronic variant occurring in intron 7 of the BRCA2 gene. This variant is absent from gnomAD v2.1 (exomes only, non-cancer subset, read depth  $\geq 25$ ) and gnomAD v3.1 (non-cancer subset, read depth  $\geq 25$ ) (PM2\_Supporting met). This BRCA2 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.71, predicting an impact on splicing (score threshold  $\geq 0.2$ ) (PP3 not applied because a PVS1 code is met). This variant is reported to result in aberrant mRNA splicing. RNAseq, minigene and RT-PCR demonstrated that the variant impacts splicing by exon skipping (PMIDs: 20455026, 31143303). Preliminary code strength determined by comparison of results to PVS1 decision tree and assessment of mRNA splicing data (PVS1 (RNA) met). The percent reference (full-length, FL) and aberrant transcripts produced from the variant allele using allele specific quantitative assessment with Capillary electrophoresis was determined to be full-length (0%) / exon skipping (100%). Final code strength determined by the rubric: PVS1 (RNA). 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, PVS1 (RNA)).

Met criteria codes

|      |                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM2  |                                                                                      | This variant is absent from gnomAD v2.1 (exomes only, non-cancer subset, read depth $\geq 25$ ) and gnomAD v3.1 (non-cancer subset, read depth $\geq 25$ ) (PM2_Supporting met).                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PVS1 |   | This variant is reported to result in aberrant mRNA splicing. RNAseq, minigene and RT-PCR demonstrated that the variant impacts splicing by exon skipping (PMIDs: 20455026, 31143303). Preliminary code strength determined by comparison of results to PVS1 decision tree and assessment of mRNA splicing data (PVS1 (RNA) met). The percent reference (full-length, FL) and aberrant transcripts produced from the variant allele using allele specific quantitative assessment with Capillary electrophoresis was determined to be full-length (0%) / exon skipping (100%). Final code strength determined by the rubric: PVS1 (RNA). |

Not Met criteria codes

|     |                                                                                                                                                                         |                                                                                                                                                                                                                                                  |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3 |   | This BRCA2 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.71, predicting an impact on splicing (score threshold $\geq 0.2$ ) (PP3 not applied because a PVS1 code is met). |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Curation History [↗](#)

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