

Variant: NM_000059.4(BRCA2):c.8023A>G (p.Ile2675Val)

Version: 2.0

CA025410 [↗](#)

52475 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: a635e51b-a3d1-4c44-b83f-c8e9bad4ccaf

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HGVS expressions

NM_000059.4:c.8023A>G

NM_000059.4(BRCA2):c.8023A>G (p.Ile2675Val)

NC_000013.11:g.32363225A>G

CM000675.2:g.32363225A>G

NC_000013.10:g.32937362A>G

CM000675.1:g.32937362A>G

NC_000013.9:g.31835362A>G

NG_012772.3:g.52746A>G

ENST00000470094.2:c.8023A>G

ENST00000528762.2:c.8023A>G

ENST00000530893.7:c.7654A>G

ENST00000665585.2:c.8023A>G

ENST00000666593.2:c.8023A>G

ENST00000700202.2:c.8023A>G

ENST00000700202.1:c.490A>G

ENST00000380152.8:c.8023A>G

ENST00000544455.6:c.8023A>G

ENST00000614259.2:c.8031A>G

ENST00000665585.1:c.588A>G

ENST00000680887.1:c.8023A>G

ENST00000380152.7:c.8023A>G

ENST00000544455.5:c.8023A>G

NM_000059.3:c.8023A>G

Pathogenic

Met criteria codes **2**

PP4_Strong

PVS1

Not Met criteria codes **3**

PM2

BS1

BA1

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 1.0.0

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

[↗](#) **Criteria Specifications for this VCEP**

ENIGMA BRCA1 and BRCA2 VCEP

The c.8023A>G variant in BRCA2 is a missense variant predicted to cause substitution of Isoleucine by Valine at amino acid 2675 (p.Ile2675Val). 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). This variant is reported to result in aberrant mRNA splicing. RT-PCR and mini-gene assays demonstrated that the variant impacts splicing by creation of a donor site, resulting in skipping of 309nt of exon 18 (PMIDs: 18424508, 22505045, 28339459). All studies report no wild-type transcript from the variant allele. Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1 (RNA) met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1612 (based on Cosegregation LR=605.1; Pathology LR=0.88; Co-occurrence LR=1.05; Family History LR=2.88), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 31131967). 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), PP4_Very strong).

Met criteria codes

PP4_Strong			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1612 (based on Cosegregation LR=605.1; Pathology LR=0.88; Co-occurrence LR=1.05; Family History LR=2.88), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 31131976).
PVS1			This variant is reported to result in aberrant mRNA splicing. RT-PCR and mini-gene assays demonstrated that the variant impacts splicing by creation of a donor site, resulting in skipping of 309nt of exon 18 (PMIDs: 18424508, 22505045, 28339459). All studies report no wild-type transcript from the variant allele. Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1 (RNA) met).

Not Met criteria codes

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).
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).
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).

