The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2024/6/12
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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

PVS1 PP4_Strong

Not Met criteria codes 3

BA1 PM2 BS1

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

Evidence submitted by expert panel

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

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).
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).

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).
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).

Curation History

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