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.7879A>T (p.Ile2627Phe)

Version: 2.0

CA025321

52430 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: fba08ba8-3664-4d8a-ba08-13e7495a93a0
Approved on: 2024/6/12
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HGVS expressions

NM_000059.4:c.7879A>T
NM_000059.4(BRCA2):c.7879A>T (p.Ile2627Phe)
NC_000013.11:g.32362596A>T
CM000675.2:g.32362596A>T
NC_000013.10:g.32936733A>T
CM000675.1:g.32936733A>T
NC_000013.9:g.31834733A>T
NG_012772.3:g.52117A>T
ENST00000470094.2:c.7879A>T
ENST00000528762.2:c.7879A>T
ENST00000530893.7:c.7510A>T
ENST00000665585.2:c.7879A>T
ENST00000666593.2:c.7879A>T
ENST00000700202.2:c.7879A>T
ENST00000700202.1:c.346A>T
ENST00000380152.8:c.7879A>T
ENST00000544455.6:c.7879A>T
ENST00000614259.2:c.7887A>T
ENST00000665585.1:c.444A>T
ENST00000680887.1:c.7879A>T
ENST00000380152.7:c.7879A>T
ENST00000544455.5:c.7879A>T
ENST00000614259.1:n.7887A>T
NM_000059.3:c.7879A>T

Pathogenic

Met criteria codes 3

PP4_Strong PS3 PM2_Supporting

Not Met criteria codes 3

BP4 BP1 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 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.7879A>T variant in BRCA2 is a missense variant predicted to cause substitution of Isoleucine by Phenylalanine at amino acid 2627 (p.Ile2627Phe). 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 is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.25 indicating that impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (no bioinformatic code is applied). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 29988080, 33609447, 32444794) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 406 (based on Cosegregation LR=1.88; Co-occurrence LR=1.28; Family History LR=168.6), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 17924331, 31853058). 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 (PM2_Supporting, PP4_Very strong, PS3).

Met criteria codes

PP4_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 406 (based on Cosegregation LR=1.88; Co-occurrence LR=1.28; Family History LR=168.6), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 17924331).
PS3	✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 29988080, 33609447, 32444794) (PS3 met).
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).

Not Met criteria codes

BP4	✖	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.25 indicating that impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).
BP1	✖	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.25 indicating that impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).
PP3	✖	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.25 indicating that impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).

Curation History

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