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Variant: NM_000059.4(BRCA2):c.8168A>C (p.Asp2723Ala)

Version: 2.0

CA025483

52516 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4ba6ceec-f98a-4a5b-8b20-b69a86adda01
Approved on: 2024/6/12
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HGVS expressions

NM_000059.4(BRCA2):c.8168A>C (p.Asp2723Ala)
NM_000059.4:c.8168A>C
NC_000013.11:g.32363370A>C
CM000675.2:g.32363370A>C
NC_000013.10:g.32937507A>C
CM000675.1:g.32937507A>C
NC_000013.9:g.31835507A>C
NG_012772.3:g.52891A>C
ENST00000470094.2:c.8168A>C
ENST00000528762.2:c.8168A>C
ENST00000530893.7:c.7799A>C
ENST00000665585.2:c.8168A>C
ENST00000666593.2:c.8168A>C
ENST00000700202.2:c.8168A>C
ENST00000700202.1:c.635A>C
ENST00000380152.8:c.8168A>C
ENST00000544455.6:c.8168A>C
ENST00000614259.2:c.8176A>C
ENST00000665585.1:c.733A>C
ENST00000680887.1:c.8168A>C
ENST00000380152.7:c.8168A>C
ENST00000544455.5:c.8168A>C
NM_000059.3:c.8168A>C

Pathogenic

Met criteria codes 3

PP3 PP1_Strong PS3

Not Met criteria codes 5

PP4 PM2 BA1 BS1 BP5

Evidence Links 2

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.8168A>C variant in BRCA2 is a missense variant predicted to cause substitution of Aspartic acid by Alanine at amino acid 2723 (p.Asp2723Ala). 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 BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.576, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met). Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 33609447, 33293522) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.557 (based on Pathology LR=0.214; Co-occurrence LR=1.102; Family History LR=2.36), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; 31853058, Internal lab contributors). Cosegregation analysis of family(ies) carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 74321.3, above the thresholds for Very strong pathogenic evidence (LR >350) (PP1_Very strong; Internal lab contributors). In summary, this variant meets the criteria to be classified as a Pathogenic variant variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PP3, PS3, PP1_Very strong).

Met criteria codes

PP3	✔	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.576, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met).
PP1_Strong	✔	Cosegregation analysis of family(ies) carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 74321.3, above the thresholds for Very strong pathogenic evidence (LR >350) (PP1_Very strong; Internal lab contributors).
PS3	✔	Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 33609447, 33293522) (PS3 met). Complete functional impact in homology directed repair assay PubMed:33609447 Complete functional impact in assay measuring viability of knockout mouse embryonic stem cells PubMed:33293522

Not Met criteria codes

PP4	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.557 (based on Pathology LR=0.214; Co-occurrence LR=1.102; Family History LR=2.36), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; Internal lab contributors).
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).

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).
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).
BP5		✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.557 (based on Pathology LR=0.214; Co-occurrence LR=1.102; Family History LR=2.36), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; Internal lab contributors).

Curation History

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