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Variant: NM_007294.4(BRCA1):c.5522G>A (p.Ser1841Asn)

Version: 2.0

CA003696

55613 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 97edbb9e-9abc-4eb4-acb8-8c2d6be224e2
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HGVS expressions

NM_007294.4(BRCA1):c.5522G>A (p.Ser1841Asn)
NM_007294.4:c.5522G>A
NC_000017.11:g.43045748C>T
CM000679.2:g.43045748C>T
NC_000017.10:g.41197765C>T
CM000679.1:g.41197765C>T
NC_000017.9:g.38451291C>T
NG_005905.2:g.172236G>A
ENST00000461574.2:c.5519G>A
ENST00000470026.6:c.5522G>A
ENST00000473961.6:c.5396G>A
ENST00000476777.6:c.5516G>A
ENST00000477152.6:c.5444G>A
ENST00000478531.6:c.2210G>A
ENST00000489037.2:c.5444G>A
ENST00000493919.6:c.2072G>A
ENST00000494123.6:c.5522G>A
ENST00000497488.2:c.4634G>A
ENST00000618469.2:c.5522G>A
ENST00000634433.2:c.5399G>A
ENST00000644379.2:c.5588G>A
ENST00000644555.2:c.2072G>A
ENST00000652672.2:c.5381G>A
ENST00000484087.6:c.2084G>A
ENST00000700081.1:n.1405G>A
ENST00000700082.1:n.886G>A
ENST00000357654.9:c.5522G>A
ENST00000471181.7:c.5585G>A
ENST00000644379.1:c.1909G>A
ENST00000352993.7:c.2096G>A
ENST00000357654.7:c.5522G>A
ENST00000461221.5:c.*5305G>A
ENST00000468300.5:c.*36G>A
ENST00000471181.6:c.5585G>A
ENST00000491747.6:c.2210G>A
ENST00000493795.5:c.5381G>A
ENST00000586385.5:c.452G>A

ENST00000591534.5:c.995G>A
ENST00000591849.5:c.221G>A
NM_007294.3:c.5522G>A
NM_007297.3:c.5381G>A
NM_007298.3:c.2210G>A
NM_007299.3:c.*36G>A
NM_007300.3:c.5585G>A
NR_027676.1:n.5658G>A
NM_007297.4:c.5381G>A
NM_007299.4:c.*36G>A
NM_007300.4:c.5585G>A
NR_027676.2:n.5699G>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate BP4 PM2_Supporting PS3

Evidence Links 0

Expert Panel

ENIGMA BRCA1 and BRCA2 VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.5522G>A variant in BRCA1 is a missense variant predicted to cause substitution of Serine by Asparagine at amino acid 1841 (p.(Ser1841Asn)). 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). Reported by two or more calibrated studies with discordant results. Reported by three calibrated studies with discordant results. Functional effect similar to pathogenic control variants (PMIDs:30209399, 38709234) and between what was observed for benign and pathogenic control variants (PMID:30257991), however due to the number of concordant assays and only one discrepancy, the VCEP decided to apply PS3 (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.14, which is below the recommended threshold of 0.15 for predicting no impact on BRCA1 via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (BP4 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 8.42 (based on Cosegregation LR=14.79; Pathology LR=0.09; Co-occurrence LR=1.07; Family History LR=5.98), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID: 31131967, Internal lab contributor). In summary, this variant meets the criteria to be classified as a Likely pathogenic variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, BP4, PP4_Moderate, PS3).

Met criteria codes

PP4_Moderate	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 8.42 (based on Cosegregation LR=14.79; Pathology LR=0.09; Co-occurrence LR=1.07; Family History LR=5.98), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID: 31131967, Internal lab contributor).
BP4	✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.14, which is below the recommended threshold of 0.15 for predicting no impact on BRCA1 via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (BP4 met).

PM2_Supporting	ℹ	✔	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).
PS3	ℹ	✔	Reported by three calibrated studies with discordant results. Functional effect similar to pathogenic control variants (PMIDs:30209399, 38709234) and between what was observed for benign and pathogenic control variants (PMID:30257991), however due to the number of concordant assays and only one discrepancy, the VCEP decided to apply PS3 (PS3 met).

Curation History

Showing 1 to 2 of 2 rows

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