

Variant: *NM_007294.4(BRCA1):c.132C>T (p.Cys44=)*

Version: 1.0

CA10580710 [↗](#)

230061 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))

Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: f4b09e6f-931d-4187-98a3-106e39e2f87c

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HGVS expressions

NM_007294.4:c.132C>T

NM_007294.4(BRCA1):c.132C>T (p.Cys44=)

NC_000017.11:g.43115728G>A

CM000679.2:g.43115728G>A

NC_000017.10:g.41267745G>A

CM000679.1:g.41267745G>A

NC_000017.9:g.38521271G>A

NG_005905.2:g.102256C>T

ENST00000354071.8:n.196C>T

ENST00000461574.2:c.132C>T

ENST00000470026.6:c.132C>T

ENST00000473961.6:c.132C>T

ENST00000476777.6:c.132C>T

ENST00000477152.6:c.132C>T

ENST00000478531.6:c.132C>T

ENST00000489037.2:c.132C>T

ENST00000493919.6:c.-8+8289C>T

ENST00000494123.6:c.132C>T

ENST00000497488.2:c.-219+9543C>T

ENST00000618469.2:c.132C>T

ENST00000634433.2:c.132C>T

ENST00000644379.2:c.132C>T

ENST00000644555.2:c.-10C>T

ENST00000652672.2:c.-10C>T

ENST00000484087.6:c.132C>T

ENST00000700182.1:c.132C>T

ENST00000700183.1:c.132C>T

ENST00000700184.1:n.375C>T

ENST00000700185.1:n.251C>T

ENST00000357654.9:c.132C>T

ENST00000471181.7:c.132C>T

ENST00000642945.1:c.132C>T

ENST00000644555.1:c.-10C>T

ENST00000652672.1:c.-10C>T

ENST00000352993.7:c.132C>T

ENST00000354071.7:c.132C>T

ENST00000357654.7:c.132C>T

ENST00000461221.5:c.132C>T
ENST00000468300.5:c.132C>T
ENST00000470026.5:c.132C>T
ENST00000471181.6:c.132C>T
ENST00000476777.5:c.132C>T
ENST00000477152.5:c.132C>T
ENST00000478531.5:c.132C>T
ENST00000489037.1:c.132C>T
ENST00000491747.6:c.132C>T
ENST00000492859.5:c.132C>T
ENST00000493795.5:c.-8+8289C>T
ENST00000493919.5:c.-8+8289C>T
ENST00000494123.5:c.132C>T
ENST00000497488.1:c.-219+9543C>T
ENST00000586385.5:c.4+9454C>T
ENST00000591534.5:c.-44+9543C>T
ENST00000591849.5:c.-99+9543C>T
ENST00000634433.1:c.132C>T
NM_007294.3:c.132C>T
NM_007297.3:c.-8+8289C>T
NM_007298.3:c.132C>T
NM_007299.3:c.132C>T
NM_007300.3:c.132C>T
NR_027676.1:n.293C>T
NM_007297.4:c.-8+8289C>T
NM_007299.4:c.132C>T
NM_007300.4:c.132C>T
NR_027676.2:n.334C>T

Pathogenic

Met criteria codes 3

PVS1 PS3 PM2_Supporting

Not Met criteria codes 1

PP3

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.132C>T variant in BRCA1 is a synonymous variant (p.(Cys44=)). This variant is absent from gnomAD v4.1 (read depth $\geq 25x$ in >90% samples, PM2_Supporting met). Silent variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study incorporating mRNA splicing effects to exhibit function similar to pathogenic control variants (PMID:30209399) (PS3 met). This variant has a SpliceAI score of 0.92, predicting an impact on splicing (score threshold ≥ 0.2) (PP3 not applied because a PVS1 code is met). This variant is reported to result in aberrant mRNA splicing. Mini-gene demonstrated that the variant impacts splicing by usage of a cryptic splice donor site 4 bp within exon 3 resulting in a truncated protein. Sequencing of the gel bands showed the variant allele produced only the aberrant transcript (PMID: 24667779). A different Mini-gene assay confirmed the complete

aberrant splicing. Non-allele specific RT-PCR on patient-derived mRNA (blood) also showed the aberrant splicing (skipping of 4 nucleotides) (PMID: 35087763). An additional assay in tumour tissue containing this variant produced the same aberrant transcript (PMID: 34120093). Appropriate code strength determined by comparison of results to PVS1 decision tree and Rubric of weighing mRNA data (Appendix Table 9): PVS1 (RNA). In summary, this variant meets the criteria to be classified as a Pathogenic variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PS3, PVS1 (RNA)).

Met criteria codes

PVS1			This variant is reported to result in aberrant mRNA splicing. Mini-gene demonstrated that the variant impacts splicing by usage of a cryptic splice donor site 4 bp within exon 3 resulting in a truncated protein. Sequencing of the gel bands showed the variant allele produced only the aberrant transcript (PMID: 24667779). A different Mini-gene assay confirmed the complete aberrant splicing. Non-allele specific RT-PCR on patient-derived mRNA (blood) also showed the aberrant splicing (skipping of 4 nucleotides) (PMID: 35087763). An additional assay in tumour tissue containing this variant produced the same aberrant transcript (PMID: 34120093). Appropriate code strength determined by comparison of results to PVS1 decision tree and Rubric of weighing mRNA data (Appendix Table 9): PVS1 (RNA).
PS3			Silent variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study incorporating mRNA splicing effects to exhibit function similar to pathogenic control variants (PMID:30209399) (PS3 met).
PM2_Supporting			This variant is absent from gnomAD v4.1 (read depth $\geq 25\times$ in $>90\%$ samples, PM2_Supporting met).

Not Met criteria codes

PP3			This variant has a SpliceAI score of 0.92, predicting an impact on splicing (score threshold ≥ 0.2) (PP3 not applied because a PVS1 code is met).
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Curation History



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