CanVar-UK
Cancer Predisposition Gene Variant Database

BRCA1:c.5207T>C p.(Val1736Ala)

SUMMARY

Gene	BRCA1
Ensembl transcript	ENST00000357654
RefSeq transcript	NM_007294.3
Chromosome	17
Genomic position (hg19)	41209139
Genomic position (hg38)	43057122
Reference allele	T
Variant allele	C
HGVS cDNA	c.5207T>C
HGVS (protein)	p.Val1736Ala
HGVS (protein, 1-letter)	p.V1736A
Alternative notation	exon20
rsID	rs45553935
Exon/Intron	BRCA1exon19of23
Variant location	exon
Variant type	substitution
Variant coding effect	missense
cDNA position	5207
Intronic position	0
First/Last 3 bases of exon	
HGMD classification (2015)	DM
DMuDB classification (2015)	Unclassified/Not Known/Probably Pathogenic
UMD classification (2015)	
ClinVar interpretation	Pathogenic
ClinVar review status	3 STARS
ClinVar last evaluated	2019/06/25 00:00

CanVar-UK
Cancer Predisposition Gene Variant Database

BRCA1:c.5207T>C p.(Val1736Ala)

IN SILICO

Missense/nonsense predictions

REVEL [0-1]	0.827
BayesDel (no AF)	0.418246
BayesDel (add AF)	0.456703
CADD v1.4 raw score	4.056719
CADD v1.4 scaled score [0-99]	20.8
CADD v1.6 (CADD-Splice) raw score	3.906729
CADD v1.6 (CADD-Splice) scaled score [0-99]	27
Gene-specific AlignGVGD class	C55
Gene-specific AlignGVGD variation (GV)	0
Gene-specific AlignGVGD deviation (GD)	64.43
AlignGVGD class	C65
AlignGVGD variation (GV)	0
AlignGVGD deviation (GD)	65.28
SIFT prediction	Deleterious
SIFT weight	0
SIFT median	2.56
PolyPhen-2 HumVar prediction	benign
PolyPhen-2 HumVar probability of being damaging	0.38
PolyPhen-2 HumVar estimated FDR	0.194
PolyPhen-2 HumDiv prediction	possibly damaging
PolyPhen-2 HumDiv probability of being damaging	0.802
PolyPhen-2 HumDiv estimated FDR	0.104
SuSPect score [0-100]	86
MAPP prediction	bad
MAPP p-value	2.549E-5
MAPP p-value median	0.0001315

SwissProt features

Description	BRCT 1
Type	Domain

Conservation

No. of orthologues in alignment	13
No. of conserved residues in alignment	13
BLOSUM62	0

Splicing predictions

Distance to nearest splice site	14
Nearest splice site	3'
SpliceAI delta score (acceptor gain)	< 0.1
SpliceAI delta score (acceptor loss)	< 0.1
SpliceAI delta score (donor gain)	< 0.1
SpliceAI delta score (donor loss)	< 0.1
Wild-type MaxEntScan Score	9.36102
Variant MaxEntScan Score	9.36102
% change MaxEntScan Score	0
Wild-type SSF Score	90.4999
Variant SSF Score	90.4999
% change SSF Score	0
Wild-type NNS Score	0.729312
Variant NNS Score	0.703226
% change NNS Score	-3.5767956649555

CanVar-UK
Cancer Predisposition Gene Variant Database

BRCA1:c.5207T>C p.(Val1736Ala)

CONTROL FREQUENCY

GNOMAD NON-CANCER POPULATION FREQUENCIES (V2.1.1 - JAN 2019)

	Allele count	Individuals sequenced	WES in dataset
African	0	-	7451
Latino	0	-	17130
Ashkenazi Jewish	0	-	4786
East Asian	0	-	8846
European (Finnish)	0	-	10816
European (Non-Finnish)	0	-	51377
Other	0	-	2810
South Asian	0	-	15263
Total	0	-	118479

UK BIOBANK POPULATION FREQUENCIES (RETRIEVED JAN. 2023)

	Allele count	Individuals sequenced	WES in dataset
White	10	442259	442266
Mixed	0	2695	2695
Asian	0	9081	9081
Black	0	7267	7267
Chinese	0	1452	1452
Other	0	5769	5769
Total	10	468523	468530

CASE FREQUENCY

UK diagnostic labs **Release date: July 2023**

Total proband count	16
Total probands tested	80722
White eth. (use as NFE): total proband count	16
White eth. (use as NFE): total probands tested	62319

CanVar-UK
Cancer Predisposition Gene Variant Database

BRCA1:c.5207T>C p.(Val1736Ala)

GENETIC EPIDEMIOLOGY

EASTON ET AL, AM J HUM GENET. 2007

Family LLR (Easton LLR/ACMG LLR)	-1.50/-2.05
Co-occurrence LLR (Easton LLR/ACMG LLR)	-2.10/-2.87
Segregation LLR (Easton LLR/ACMG LLR)	0.25/0.34
Combined LLR (Easton LLR/ACMG LLR)	-3.35/-4.57
Odds of causality (Easton)	0
Odds of neutrality (Easton)	2219

CanVar-UK
Cancer Predisposition Gene Variant Database

BRCA1:c.5207T>C p.(Val1736Ala)

FUNCTIONAL/SPLICING ANALYSIS

BOUWMAN ET AL. , 2020

PROBABILITY DELETERIOUS (CISPLATIN)	0.789017624
PREDICTION (CISPLATIN)	Not clear
PROBABILITY DELETERIOUS (OLAPARIB)	0.999999999999998
PREDICTION (OLAPARIB)	Deleterious
PROBABILITY DELETERIOUS (DR-GFP)	1
PREDICTION (DR-GFP)	Deleterious

FERNANDES ET AL. , 2019

FUNCTIONAL CLASS (FCLASS)	5
FUNCTIONAL CLASS (FCLASS) CATEGORY	Pathogenic

FINDLAY ET AL. , 2018

FUNCTION SCORE	-1.6030925993
FUNCTION PROBABILITY	0.9999167107
FUNCTIONAL CLASSIFICATION	LOF
MEAN RNA SCORE	-0.1588668542

BOUWMAN ET AL. , 2013

MUTATION TYPE	VUS
ALIGNGVGD	C65
PREDICTED SPLICE EFFECT	No
LITERATURE PREDICTIONS	No consensus
GROWTH	+/-
IC50	-0.42 to 0.25
CLASSIFICATION	Not clear

WAI ET AL. , 2020

VARIANT POSITION	A+14
SPLICING RESULTS	Normal
RNA-SEQ RESULT	None
SITE OF SPLICE ABERRATION	None

WESSEX CLINICAL GENETICS SERVICE

SPECIMEN	W1214516
SPLICE ABNORMALITY	None
SAMPLE TYPE	PAXGene

CanVar-UK is a repository of data annotations for variants in cancer predisposition genes. Classifications and notes are as provided by members of CanVIG-UK, a national group of UK clinical scientist and genomic clinicians.

Assuming prior probability of a variant being pathogenic is 10%:
Pathogenic (P): >=10 evidence points, >99% posterior probability of being pathogenic
Likely pathogenic (LP): 6-9 points, 90-99% posterior probability of being pathogenic
Variant of uncertain significance (VUS): 0-5 points, 10-90% posterior probability of being pathogenic
Likely benign (LB): (-1) to (-5) points, <10% posterior probability of being pathogenic
Benign (B): <=(-6) points, <0.1% posterior probability of being pathogenic

Points towards pathogenicity
Supporting: LR = 2.1, evidence points (ACMG LLR) = 1
Moderate LR = 4.3, evidence points (ACMG LLR) = 2
Strong: LR = 18.7, evidence points (ACMG LLR) = 4
Very strong: LR = 350.4, evidence points (ACMG LLR) = 8

Points towards benignity
Supporting: LR = 0.48, evidence points (ACMG LLR) = -1
Strong: LR = 0.05, evidence points (ACMG LLR) = -4

Pan-gene resources
PHE data (retrieved from the National Disease Registration Service, July 2023), gnomAD (https://gnomad.broadinstitute.org/), SIFT, MAPP, AlignGVGD, SpliceSiteFinder, MaxEntScan, NNSplice (ANNOVAR, dbnsfp35c database), MutationTaster (http://www.mutationtaster.org/), SuSPect (http://www.sbg.bio.ic.ac.uk/suspect/about.html), CADD (http://cadd.gs.washington.edu/), REVEL (https://sites.google.com/site/revelgenomics/), SpliceAI (https://spliceailookup.broadinstitute.org/), HGMD (Human Gene Mutation Database http://www.biobase-international.com/product/hgmd), DMuDB (http://www.ngrl.org.uk/Manchester/projects/dmudb)

Gene-specific resources
LOVDs (Leiden Open Variation Database; http://chromium.liacs.nl/), BIC (Breast Cancer Information Core; http://research.nhgri.nih.gov/bic/), published literature as per citations. For additional details of thresholds to be applied for *in silico* tools and other resources, see https://www.canvaruk.org/

Functional datasets collated for *BRCA1* variants
CanVar-UK currently houses functional and splicing data from the following datasets for variants in *BRCA1*:

- Bouwman et al. (2020, PMID: 32546644)
- Fernandes et al. (2019, PMID: 30765603)
- Petitalot et al. (2019, PMID: 30257991)
- Findlay et al. (2018, PMID: 30209399)
- Starita et al. (2018, PMID: 30219179)
- Bouwman et al. (2013, PMID: 23867111)
- Walker et al. (2013, PMID: 23893897)
- Houdayer et al. (2012, PMID: 22505045)
- Wai et al. (2020, PMID: 32123317)
- Wessex Clinical Genetics Service

To request the addition of a new functional dataset to CanVar-UK, please email us at CanVIG@icr.ac.uk.