Classification report

variant	chr2-214730440-G-A
class	3
date	2022-07-27
comment	rgadg
rsid	rs3738999

Scores & annotations:

phylop_100way	5.269
cadd_scaled	24.3
revel	0.104
spliceai_details	0.00|0.00|0.00|0.01|46|-25|43|-29
spliceai_max_delta	0.01
gnomad_ac	1114
gnomad_af	0.00732654
gnomad_hom	15
gnomad_het	1084
gnomad_popmax	eas
flossies_num_afr	9
flossies_num_eur	130
hexplorer	-1.71
hexplorer_mut	4.34
hexplorer_wt	6.05
hexplorer_rev	-0.51
hexplorer_rev_mut	7.99
hexplorer_rev_wt	8.51
max_hbond	-4.50
max_hbond_wt	4.50
max_hbond_rev	0.00
max_hbond_rev_mut	10.10
max_hbond_rev_wt	10.10
clinvar_variant_annotation	criteria provided, conflicting interpretations

Variant consequences:

Flags column: first number = is_gencode_basic, second number: is_mane_select, third number: is_mane_plus_clinical, fourth number: is_ensembl_canonical

Transcript Name	HGVSc	HGVSp	Consequence	Impact	Exon Nr.	Intron Nr.	Gene Symbol	Protein Domain	Flags
ENST00000260947	c.1972C>T	p.Arg658Cys	missense variant	moderate	10	None	BARD1	None	1101
ENST00000471590	n.307C>T	None	non coding transcript exon variant	modifier	2	None	BARD1	None	0000

Transcript Name	HGVSc	HGVSp	Consequence	Impact	Exon Nr.	Intron Nr.	Gene Symbol	Protein Domain	Flags
ENST00000432456	c.70C>T	p.Arg24Cys	missense variant	moderate	1	None	BARD1	None	0000
ENST00000619009	c.433C>T	p.Arg145Cys	missense variant	moderate	4	None	BARD1	None	1000
ENST00000617164	c.1915C>T	p.Arg639Cys	missense variant	moderate	9	None	BARD1	None	1000
ENST00000613374	c.562C>T	p.Arg188Cys	missense variant	moderate	5	None	BARD1	None	1000
ENST00000650978	c.*2050C>T	None	3 prime UTR variant & NMD transcript variant	modifier	9	None	BARD1	None	0000
ENST00000613706	c.1564C>T	p.Arg522Cys	missense variant	moderate	10	None	BARD1	None	1000
ENST00000421162	c.619C>T	p.Arg207Cys	missense variant	moderate	6	None	BARD1	None	1000
ENST00000613192	c.*35C>T	None	3 prime UTR variant & NMD transcript variant	modifier	2	None	BARD1	None	0000
ENST00000620057	c.*638C>T	None	3 prime UTR variant	modifier	9	None	BARD1	None	1000
ENST00000455743	c.*1592C>T	None	3 prime UTR variant & NMD transcript variant	modifier	9	None	BARD1	None	0000
NR_104215	n.1880C>T	None	non coding transcript exon variant	modifier	8	None	BARD1	None	0000
NR_104212	n.1937C>T	None	non coding transcript exon variant	modifier	9	None	BARD1	None	0000
NR_104216	n.1136C>T	None	non coding transcript exon variant	modifier	9	None	BARD1	None	0000
NM_001282548	c.562C>T	p.Arg188Cys	missense variant	moderate	5	None	BARD1	None	1000
NM_001282543	c.1915C>T	p.Arg639Cys	missense variant	moderate	9	None	BARD1	None	1000
NM_001282545	c.619C>T	p.Arg207Cys	missense variant	moderate	6	None	BARD1	None	1000
NM_001282549	c.433C>T	p.Arg145Cys	missense variant	moderate	4	None	BARD1	None	1000
NM_000465	c.1972C>T	p.Arg658Cys	missense variant	moderate	10	None	BARD1	None	1101
XM_017004613	c.2071C>T	p.Arg691Cys	missense variant	moderate	11	None	BARD1	None	0000
ENSR00001044281	None	None	regulatory region variant	modifier	None	None	None	None	NoneNoneNoneNone
XR_002959322	n.2162C>T	None	non coding transcript exon variant	modifier	11	None	BARD1	None	NoneNoneNoneNone

PubMed IDs:

32039725, 31258718, 29458332, 25741868, 26315354, 25994375, 26350354, 20077502, 19584272, 19412175, 16741161, 16333312, 16061562, 15342711, 9425226

Classifications:

HerediVar consensus scheme classifications:

Class	Submitter	Affiliation	Date	Scheme	Selected criteria
1	Marvin Döbel	UKT	2022-07-19	acmg_standard	pp1 Strength: strong pathogenic Evidence: this was copied ## ba1 Strength: stand-alone benign Evidence: this is benign
5	Marvin Döbel	UKT	2022-07-19	acmg_standard	ps2 Strength: strong pathogenic Evidence: afdafas ## pp1 Strength: strong pathogenic Evidence: fasdfasfas

Class	Submitter	Affiliation	Date	Scheme	Selected criteria
3	Marvin Döbel	UKT	2022-07-19	acmg_standard	pp1 Strength: moderate pathogenic Evidence: evidence here
5	Marvin Döbel	UKT	2022-07-20	acmg_standard	ps2 Strength: strong pathogenic Evidence: afdafas ## pp1 Strength: strong pathogenic Evidence: fasdfasfas testscht
3	Max Mustermann	testaffiliation	2022-07-22	acmg_standard	pp1 Strength: supporting pathogenic Evidence:
4	Max Mustermann	testaffiliation	2022-07-22	acmg_standard	ps2 Strength: strong pathogenic Evidence: bvd ## pp1 Strength: moderate pathogenic Evidence: fasdfasfas testscht
3	Max Mustermann	testaffiliation	2022-07-27	task-force	5.2 Strength: pathogenic Evidence: yoho test ## 4.4 Strength: likely pathogenic Evidence: dsaaD
3	Max Mustermann	testaffiliation	2022-07-27	acmg_standard	pp1 Strength: strong pathogenic Evidence: fasdfasfas testscht
3	Max Mustermann	testaffiliation	2022-07-27	acmg_standard	pp1 Strength: strong pathogenic Evidence: fasdfasfas testscht
3	Max Mustermann	testaffiliation	2022-07-27	acmg_standard	pp1 Strength: strong pathogenic Evidence: fasdfasfas testscht
3	Max Mustermann	testaffiliation	2022-07-27	acmg_standard	pp1 Strength: strong pathogenic Evidence: fasdfasfas testscht
3	Max Mustermann	testaffiliation	2022-07-27	acmg_standard	pp1 Strength: strong pathogenic Evidence: fasdfasfas testscht

HerediVar user classifications:

Class	Submitter	Affiliation	Date	Comment
5	Max Mustermann	testaffiliation	2022-07-22	This is a test comment which is supposed to be a little bit longer than usual. You can really put any text in here that you like. ANOTHER UPDATE
4	Mirco testtest	sometest	2022-07-19	A comment 4 U UPDATE
5	Marvin Döbel	UKT	2022-06-03	fwaeeaca
4	Maria Müller	UKT	2022-05-31	This is another test

HerediVar user scheme classifications:

Class	Submitter	Affiliation	Date	Scheme	Selected criteria
5	Max Mustermann	testaffiliation	2022-07-27	acmg_standard	ps2 Strength: strong pathogenic Evidence: bvd ## pp1 Strength: strong pathogenic Evidence: fasdfasfas testscht ## bs1 Strength: strong benign Evidence: benign criterium ## pvs1 Strength: very strong pathogenic Evidence: ie belgische Föderalregierung oder föderale Regierung (niederländisch Federale regering, französisch Gouvernement fédéral), manchmal vereinfacht belgische Regierung oder nationale Regierung (veraltet) genannt, ist auf föderaler Ebene das exekutive Verfassungsorgan Belgiens. Die ausführende Gewalt liegt zwar verfassungsrechtlich allein beim König, dieser benötigt jedoch für alle Rechtshandlungen, die er ausführt, die Gegenzeichnung eines Ministers der Regierung. In Wirklichkeit wird die Politik der föderalen Exekutiven im belgischen Staatsgefüge allein durch die Regierung ausgeübt. Die Regierung ist aus einem Premierminister und höchstens vierzehn anderen Ministern, die den Ministerrat bilden, und eventuell aus mehreren Staatssekretären zusammengestellt. Die vornehmlichsten Befugnisse der Regierung sind die Erstellung von Gesetzesentwürfen und die Ausführung von Gesetzen, die im Föderalen Parlament verabschiedet wurden. Zudem führt die Regierung die auswärtigen Beziehungen, organisiert die föderale Verwaltung des Landes und verfügt über die belgischen Streitkräfte. Die Föderalregierung muss sich allein vor der Abgeordnetenk
5	Max Mustermann	testaffiliation	2022-07-19	acmg_TP53	ps1 Strength: strong pathogenic Evidence: abebra ## pp1 Strength: very strong pathogenic Evidence: VERRRYY STRONG! ## bp7 Strength: supporting benign Evidence: fsafbadfasfwababetn sgg f f f
2	Mirco testtest	sometest	2022-07-19	acmg_standard	pp1 Strength: strong pathogenic Evidence: aednr hae hrthztrj zt j ## bp4 Strength: supporting benign Evidence: evonei vbiuebiebgie bie ## bs2 Strength: strong benign Evidence: adbvebrag g g
5	Max Mustermann	testaffiliation	2022-07-21	acmg_CDH1	ps1 Strength: strong pathogenic Evidence: gdsgsgf ## pp1 Strength: moderate pathogenic Evidence: suppporting evidence ## ps2 Strength: strong pathogenic Evidence: ycavsvavasv
3	Max Mustermann	testaffiliation	2022-07-27	task-force	4.4 Strength: likely pathogenic Evidence: dsaaD ## 5.3 Strength: pathogenic Evidence: rhtrh ## 3.2 Strength: uncertain Evidence: asvabaerb a rg af a ## 2.8 Strength: likely benign Evidence: aga raga ## 1.1 Strength: benign Evidence: aarfaeff a

ClinVar submissions:

Interpretation	Last evaluated	Review status	Condition	Submitter	Comment
Likely benign	2021-09-27	no assertion criteria provided	Hereditary cancer-predisposing syndrome	Institute for Biomarker Research, Medical Diagnostic Laboratories, L.L.C.	None
Benign	2021-02-25	criteria provided, single submitter	Familial cancer of breast	ARUP Laboratories, Molecular Genetics and Genomics, ARUP Laboratories	None
Benign	2020-12-04	criteria provided, single submitter	Familial cancer of breast	Invitae	None

Interpretation	Last evaluated	Review status	Condition	Submitter	Comment
Benign	2020-05-27	criteria provided, single submitter	not specified	Genetic Services Laboratory, University of Chicago	None
Uncertain significance	2018-07-02	criteria provided, single submitter	Familial cancer of breast	Mendelics	None
Benign	2017-08-19	criteria provided, single submitter	not provided	Quest Diagnostics Nichols Institute San Juan Capistrano	None
Likely benign	2017-05-01	criteria provided, single submitter	not provided	CeGaT Praxis fuer Humangenetik Tuebingen	None
Likely benign	2017-04-27	criteria provided, single submitter	Familial cancer of breast	Illumina Laboratory Services, Illumina	description: This variant was observed as part of a predisposition screen in an ostensibly healthy population. A literature search was performed for the gene, cDNA change, and amino acid change (where applicable). Publications were found based on this search. The evidence from the literature, in combination with allele frequency data from public databases where available, was sufficient to determine this variant is unlikely to cause disease. Therefore, this variant is classified as likely benign.
Likely benign	2017-02-06	criteria provided, single submitter	not specified	Quest Diagnostics Nichols Institute San Juan Capistrano	None
Benign	2016-11-22	criteria provided, single submitter	not specified	PreventionGenetics, PreventionGenetics	None
Likely benign	2016-06-03	criteria provided, single submitter	Familial cancer of breast	Counsyl	None
Uncertain significance	2015-02-01	no assertion criteria provided	Triple-Negative Breast Cancer Finding	Lab. Molecular Oncology, VUB, Free University of Brussels	None
Benign	2014-11-11	criteria provided, single submitter	Hereditary cancer-predisposing syndrome	Color Health, Inc	None
Benign	2014-06-26	criteria provided, single submitter	Hereditary cancer-predisposing syndrome	Ambry Genetics	description: This alteration is classified as benign based on a combination of the following: population frequency, intact protein function, lack of segregation with disease, co-occurrence, RNA analysis, in silico models, amino acid conservation, lack of disease association in case-control studies, and/or the mechanism of disease or impacted region is inconsistent with a known cause of pathogenicity.

Interpretation	Last evaluated	Review status	Condition	Submitter	Comment
Benign	2013-10-14	criteria provided, single submitter	not specified	GeneDx	description: This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.
Likely benign	None	no assertion criteria provided	Malignant tumor of breast	Department of Pathology and Laboratory Medicine, Sinai Health System	description: The BARD1 p.Arg658Cys variant was identified in 9 of 2368 proband chromosomes (frequency: 0.004) from individuals or families with breast and/or ovarian cancer (Karppinen 2004, Klonowska 2015, Vahteristo 2006). The variant was also identified in the following databases: dbSNP (ID: rs3738888) as â€šÃ„ÃºWith other alleleâ€šÃ„Ã¹, ClinVar (6x, as benign by GeneDx, Ambry Genetics, Invitae, Color Genomics.Inc, and as likely benign by Illumina Clinical Services, Counsyl), Clinvitae (4x, as benign and likely benign), and Zhejiang Colon Cancer Database (6x, as probably pathogenic). The variant was not identified in Cosmic nor MutDB databases. The variant was identified in control databases in 2270 (11 homozygous) of 277098 chromosomes at a frequency of 0.008 in the following populations: Finnish in 336 of 25784 chromosomes (freq. 0.013), Latino in 425 of 34414 chromosomes (freq. 0.012), East Asian in 206 of 18868 chromosomes (freq. 0.01), European in 1067 of 126610 chromosomes (freq. 0.0084), other in 53 of 6462 chromosomes (freq. 0.008), South Asian in 125 of 30782 chromosomes (freq. 0.004), and African in 58 of 2403 chromosomes (freq. 0.0024), increasing the likelihood this could be a low frequency benign variant (Genome Aggregation Consortium Feb 27, 2017). Although the p.Arg658Cys residue is not conserved in mammals and other organisms, computational analyses (PolyPhen-2, SIFT, AlignGVGD, BLOSUM, MutationTaster) suggest that the variant may impact the protein. The variant occurs outside of the splicing consensus sequence and in silico or computational prediction software programs (SpliceSiteFinder, MaxEntScan, NNSPLICE, GeneSplicer, HumanSpliceFinder) do not predict a difference in splicing. There are conflicting predictions in the literature regarding the clinical significance of the p.Arg658Cys variant. Some studies refer to this variant as potentially pathological (Klonowska 2015), but functional studies do not predict clinical significance for this variant although it is in a functional domain (Lee 2015). In another study this variant has been utilized as putative benign polymorphism in multiple functional assays (Sauer 2005). A co-occurring pathogenic BRCA1 variant (c.709G>T, p.Glu237X) was identified in 1 individual with breast cancer by our laboratory, increasing the likelihood that p.Arg658Cys variant does not have clinical significance. In summary, based on the above information the clinical significance of this variant cannot be determined with certainty at this time although we would lean towards a more benign role for this variant. This variant is classified as likely benign.