GENE*ie* Report: NM_000487.6:c.465+1G>A

This report was produced for **Demo Admin** of **Demo Account** on Tuesday, 24 September 2024

This report is for research use only. It is not intended for diagnostic or clinical purposes.

Splice-Altering

99.9% PROBABILITY

- Annotated donor splice-site variant.
- Three lines of concordant evidence.
- Risk of cryptic mis-splicing. Competitive cryptic splice-site within 250 nt or in SpliceVault Top4.
- Variants with similar NIF impact at this splice-site are known to be pathogenic.

NIF	Similar Impact	Same Sequence	SpliceVault Top4	Cryptic Risk
★★★	★☆☆	★★★	Mixed Frames	Yes

Variant	NM_000487.6:c.465+1G>A		
Gene	*ARSA*	**Coordinates (GRCh38)**	22:50627165 C>T
Location	(NM_000487.6) Intron 2 donor / Distance from donor: +1		
Variant Databases	VCV000003051 (ClinVar) - Pathogenic CS910416 (HGMD) - DM ARSA_000002 (LOVD) - pathogenic, pathogenic (recessive)		

Native Intron Frequency (NIF)

Relative frequency of a given splice-site sequence among all human splice-site sequences

Zone	Window	Reference (REF)	Variant (VAR)	Frequency		% Scale		NIF Impact VAR/REF
				REF	VAR	REF	VAR	
U5	E4 - D5	CCAG**gt**aggaac	CCAG**a**taggaac	1100	0	0.83	0	-100%
U1	E3 - D6	CCAG**gt**aggaac	CCAG**a**taggaac	1050	0	0.73	0	-100%
	E2 - D7	CCAG**gt**aggaac	CCAG**a**taggaac	767	0			
U6	E1 - D8	CCAG**gt**aggaac	CCAG**a**taggaac	181	0	0.42	0	-100%

NIF-ML Power (Machine Learning)	
ML Score	1.00
Pathogenic	100%
Benign	0%
n	445

Cryptic Splice-site Modification

Cryptic splice-site overlapping the annotated splice-site that is modified by this variant

Splice-site Position	Reference (REF)	Variant (VAR)	REF			VAR			SpliceVault Top-10	In Frame
			U5	U1	U6	U5	U1	U6		
Annotated	CCAG**gt**aggaac	CCAG**a**taggaac	0.83	0.73	0.42	0.00	0.00	0.00	N/A	N/A

Same Splice-site Variants

Variants affecting the same splice-site as the test variant

Test Variant	Distance from Donor	NIF Impact			Classification	Variant ID
		U5	U1	U6		
NM_000487.6:c.465+1G>A	+1	-100%	-100%	-100%	P; P; P	VCV000003051; CS910416; ARSA_000002

Similar Impact Variants	Distance from Donor	NIF Impact			Classification	Variant ID
		U5	U1	U6		
NM_000487.6(ARSA):c.465+2T>A	+2	-100%	-100%	-100%	LP	VCV000553578

Different Impact Variants	Distance from Donor	NIF Impact			Classification	Variant ID
		U5	U1	U6		
NM_000487.6(ARSA):c.465+8C>T	+8	0%	0%	-2%	LB	VCV001608658
NM_000487.6(ARSA):c.465+8C>A	+8	0%	0%	+33%	LB	VCV001626718

Same Sequence Variants

Variants making the same sequence change at a different splice-site

Zone	Window	Reference (REF)	Variant (VAR)	NIF Impact	Pathogenic		Benign	
				VAR/REF	introns	*n*	introns	*n*
U5	E4 - D5	CCAG**gt**aggaac	CCAG**a**taggaac	-100%	23	88	0	0
U1	E3 - D6	CCAG**gt**aggaac	CCAG**a**taggaac	-100%	35	151	0	0
	E2 - D7	CCAG**gt**aggaac	CCAG**a**taggaac		25	73	0	0
U6	E1 - D8	CCAG**gt**aggaac	CCAG**a**taggaac	-100%	8	28	0	0

E4 - D5	NIF Impact			Classification	Variant ID
	U5	U1	U6		
NM_003384.3(VRK1):c.889+1G>A	-100%	-100%	-100%	LP	VCV000941929
NM_013275.5(ANKRD11):c.7713+1G>A	-100%	-100%	-100%	LP	ANKRD11_000173
NM_001042432.2(CLN3):c.790+1G>A	-100%	-100%	-100%	LP	VCV002131001

E4 - D5	NIF Impact	Classification	Variant ID
	U5 | U1 | U6		
NM_006982.3(ALX1):c.531+1G>A	-100% | -100% | -100%	P	ALX1_000002; CS102965; VCV000008111
NM_003060.4(SLC22A5):c.1267+1G>A	-100% | -100% | -100%	LP	VCV000550338
NM_001083961.2(WDR62):c.332+1G>A	-100% | -100% | -100%	P	VCV000160282
NM_007289.4(MME):c.1094+1G>A	-100% | -100% | -100%	LP	VCV001930569
NM_000212.3(ITGB3):c.361+1G>A	-100% | -100% | -100%	P	VCV001330340
NM_145343.2(APOL1):c.235+1G>A	-100% | -100% | -100%	LP	APOL1_000001
NM_000085.5(CLCNKB):c.968+1G>A	-100% | -100% | -100%	LP; P	CLCNKB_000033; CS1211892; VCV001285112
NM_000211.4(ITGB2):c.328+1G>A	-100% | -100% | -100%	P	CS078443; ITGB2_000209
NM_001320.7(CSNK2B):c.557+1G>A	-100% | -100% | -100%	LP; P	CSNK2B_000014; VCV001329627
NM_052874.5(STX1B):c.354+1G>A	-100% | -100% | -98%	LP	VCV000646551
NM_000642.3(AGL):c.3362+1G>A	-100% | -100% | -100%	LP	VCV000556821
NM_015335.5(MED13L):c.1280+1G>A	-100% | -100% | -100%	P	VCV001706430
NM_001243279.3(ACSF3):c.1613+1G>A	-100% | -100% | -100%	P	VCV001404244
NM_001478.5(B4GALNT1):c.490+1G>A	-100% | -100% | -100%	LP	VCV000426168
NM_001206927.2(DNAH8):c.9194+1G>A	-100% | -100% | -100%	LP	VCV000238657
NM_000235.4(LIPA):c.894+1G>A	-100% | -100% | -100%	P	CS963024; VCV000000081
NM_004247.3(EFTUD2):c.619+1G>A	-100% | -100% | -100%	LP; P	CS1211272; EFTUD2_000016
NM_020919.3(ALS2):c.1737+1G>A	-100% | -100% | -98%	P	ALS2_000052
NM_018972.4(GDAP1):c.694+1G>A	-100% | -100% | -100%	LP; P	GDAP1_000093; VCV000574458
NM_000523.4(HOXD13):c.781+1G>A	-100% | -100% | -100%	P	CS1310806; VCV000225653

E3 - D6	NIF Impact	Classification	Variant ID
	U5 | U1 | U6		
NM_003384.3(VRK1):c.889+1G>A	-100% | -100% | -100%	LP	VCV000941929
NM_001171.6(ABCC6):c.3506+1G>A	-100% | -100% | -100%	P	VCV002434772
NM_003073.5(SMARCB1):c.986+1G>A	-100% | -100% | -100%	LP; P	CS000900; SMARCB1_000025; VCV000008025
NM_007208.3(MRPL3):c.92+1G>A	-100% | -100% | -100%	LP	MRPL3_000011
NM_001042432.2(CLN3):c.790+1G>A	-100% | -100% | -100%	LP	VCV002131001

E3 - D6	NIF Impact U5 | U1 | U6	Classification	Variant ID
NM_006982.3(ALX1):c.531+1G>A	-100% | -100% | -100%	P	ALX1_000002; CS102965; VCV000008111
NM_001848.3(COL6A1):c.227+1G>A	-100% | -100% | -98%	LP	VCV001324134
NM_002585.4(PBX1):c.265+1G>A	-100% | -100% | -100%	LP	VCV001179136
NM_052874.5(STX1B):c.354+1G>A	-100% | -100% | -98%	LP	VCV000646551
NM_000642.3(AGL):c.3362+1G>A	-100% | -100% | -100%	LP	VCV000556821
NM_021005.4(NR2F2):c.970+1G>A	-100% | -100% | -100%	P	CS143725; VCV000128235
NM_007186.6(CEP250):c.1209+1G>A	-100% | -100% | -100%	LP	VCV002110425
NM_000287.4(PEX6):c.882+1G>A	-100% | -100% | -100%	P	CS045217; PEX6_000056; VCV000973865
NM_016169.4(SUFU):c.454+1G>A	-100% | -100% | -98%	P	VCV000571265
NM_147127.5(EVC2):c.2706+1G>A	-100% | -100% | -100%	LP	VCV001066264
NM_001206927.2(DNAH8):c.9194+1G>A	-100% | -100% | -100%	LP	VCV000238657
NM_000548.5(TSC2):c.2355+1G>A	-100% | -100% | -98%	P	CS078611; TSC2_000673; VCV000049711
NM_001130987.2(DYSF):c.5457+1G>A	-100% | -100% | -100%	LP	VCV000556639
NM_000504.3(F10):c.502+1G>A	-100% | -100% | -98%	P	CS1211664
NM_152722.5(HEPACAM):c.85+1G>A	-100% | -100% | -98%	LP	VCV000444277
NM_000090.4(COL3A1):c.4011+1G>A	-100% | -100% | -100%	P	COL3A1_000350; CS1512370; VCV002203233
NM_005183.2(CACNA1F):c.2118+1G>A	-100% | -100% | -100%	P	CACNA1F_000285
NM_022787.4(NMNAT1):c.115+1G>A	-100% | -100% | -100%	LP	VCV001486767
NM_004247.3(EFTUD2):c.619+1G>A	-100% | -100% | -100%	LP; P	CS1211272; EFTUD2_000016
NM_001875.5(CPS1):c.2895+1G>A	-100% | -100% | -100%	LP; P	CPS1_000233; CS114443; VCV002203250
NM_001032221.6(STXBP1):c.1110+1G>A	-100% | -100% | -100%	LP; P	CS162490; VCV002136814
NM_020919.3(ALS2):c.1737+1G>A	-100% | -100% | -98%	P	ALS2_000052
NM_001243279.3(ACSF3):c.1366+1G>A	-100% | -100% | -100%	LP	VCV002110345
NM_024426.5(WT1):c.887+1G>A	-100% | -100% | -100%	P	CS156573
NM_000451.3(SHOX):c.486+1G>A	-100% | -100% | -100%	P	CS075226; SHOX_000097
NM_001002295.2(GATA3):c.778+1G>A	-100% | -100% | -100%	P	VCV001174524
NM_001378183.1(PIEZO2):c.1378+1G>A	-100% | -100% | -100%	LP	VCV001910452
NM_000153.4(GALC):c.328+1G>A	-100% | -100% | -100%	P	VCV001498237
NM_000441.2(SLC26A4):c.1263+1G>A	-100% | -100% | -100%	LP; P	CS137115; SLC26A4_000021;

E3 - D6	NIF Impact	Classification	Variant ID
	U5 | U1 | U6		
			VCV000371209
NM_000135.4(FANCA):c.792+1G>A	-100% | -100% | -98%	P	CS1721712; VCV001074963

E2 - D7	NIF Impact	Classification	Variant ID
	U5 | U1 | U6		
NM_003384.3(VRK1):c.889+1G>A	-100% | -100% | -100%	LP	VCV000941929
NM_001171.6(ABCC6):c.3506+1G>A	-100% | -100% | -100%	P	VCV002434772
NM_000094.4(COL7A1):c.7521+1G>A	-100% | -100% | -100%	LP	VCV001525394
NM_005559.4(LAMA1):c.7452+1G>A	-100% | -100% | -100%	LP	VCV001804140
NM_007208.3(MRPL3):c.92+1G>A	-100% | -100% | -100%	LP	MRPL3_000011
NM_000081.3(LYST):c.4862+1G>A	-100% | -100% | -100%	P	CS184540; LYST_000228
NM_001267550.2(TTN):c.55269+1G>A	-100% | -100% | -100%	LP	VCV001796273
NM_002734.5(PRKAR1A):c.440+1G>A	-100% | -100% | -100%	P	CS108944; VCV001421058
NM_000138.5(FBN1):c.6037+1G>A	-100% | -100% | -100%	LP	VCV000423795
NM_052844.4(DYNC2I2):c.1372+1G>A	-98% | -100% | -100%	P	CS1311127; VCV002196170
NM_002585.4(PBX1):c.265+1G>A	-100% | -100% | -100%	LP	VCV001179136
NM_001349338.3(FOXP1):c.869+1G>A	-98% | -100% | -100%	P	VCV000433178
NM_025114.3(CEP290):c.6818+1G>A	-100% | -100% | -100%	LP	CEP290_000415
NM_021005.4(NR2F2):c.970+1G>A	-100% | -100% | -100%	P	CS143725; VCV000128235
NM_007186.6(CEP250):c.1209+1G>A	-100% | -100% | -100%	LP	VCV002110425
NM_015559.3(SETBP1):c.486+1G>A	-100% | -100% | -100%	LP	VCV002000191
NM_000090.4(COL3A1):c.4011+1G>A	-100% | -100% | -100%	P	COL3A1_000350; CS1512370; VCV002203233
NM_001353921.2(ARHGEF9):c.945+1G>A	-100% | -100% | -100%	LP	VCV001700064
NM_014425.5(INVS):c.2786+1G>A	-100% | -100% | -100%	LP	VCV001067538
NM_001875.5(CPS1):c.2895+1G>A	-100% | -100% | -100%	LP; P	CPS1_000233; CS114443; VCV002203250
NM_181486.4(TBX5):c.755+1G>A	-98% | -100% | -100%	P	VCV002050129
NM_024426.5(WT1):c.887+1G>A	-100% | -100% | -100%	P	CS156573
NM_000451.3(SHOX):c.486+1G>A	-100% | -100% | -100%	P	CS075226; SHOX_000097
NM_006031.6(PCNT):c.9393+1G>A	-100% | -100% | -100%	LP	VCV001806717
NM_000441.2(SLC26A4):c.1263+1G>A	-100% | -100% | -100%	LP; P	CS137115; SLC26A4_000021; VCV000371209

E1 - D8	NIF Impact	Classification	Variant ID
	U5 | U1 | U6		
NM_000094.4(COL7A1):c.7521+1G>A	-100% | -100% | -100%	LP	VCV001525394
NM_002734.5(PRKAR1A):c.440+1G>A	-100% | -100% | -100%	P	CS108944; VCV001421058
NM_001349338.3(FOXP1):c.869+1G>A	-98% | -100% | -100%	P	VCV000433178
NM_025114.3(CEP290):c.6818+1G>A	-100% | -100% | -100%	LP	CEP290_000415
NM_007186.6(CEP250):c.1209+1G>A	-100% | -100% | -100%	LP	VCV002110425
NM_000451.3(SHOX):c.486+1G>A	-100% | -100% | -100%	P	CS075226; SHOX_000097
NM_006031.6(PCNT):c.9393+1G>A	-100% | -100% | -100%	LP	VCV001806717
NM_000441.2(SLC26A4):c.1263+1G>A	-100% | -100% | -100%	LP; P	CS137115; SLC26A4_000021; VCV000371209

SpliceVault Top-10

Natural splicing mistakes around this splice-site that may be enhanced by this variant

Event	Same Frame	Skipped Exons	Cryptic Position	Cryptic mean NIF	Samples (GTEx)	Samples (SRA)	Max Reads (GTEx)	Total Samples	Splice Junction
Annotated Splicing	✓				19,030	159,696	639	178,726	chr22:50627053-50627165
Exon Skipping		2			38	232	2	270	chr22:50627053-50627555
Cryptic donor [4]			-95	0.14	3	187	2	190	chr22:50627053-50627260
Exon Skipping		2-3			27	71	2	98	chr22:50626761-50627555
Cryptic donor [4]	✓		-147	0.13	4	12	2	16	chr22:50627053-50627312
Cryptic donor			-199	0.01	0	2	0	2	chr22:50627053-50627364
Cryptic donor	✓		-213	0.02	1	1	1	2	chr22:50627053-50627378
Cryptic donor			-16	0.00	1	0	1	1	chr22:50627053-50627181
Cryptic donor			+44	0.00	0	1	0	1	chr22:50627053-50627122

[4] Cryptic is >= 50% strength of annotated splice-site

Understanding your report

Assertion and Probability

Splice - Altering

Clinical and genetic evidence indicate this variant has a given probability of altering pre-mRNA splicing for this gene.

Splice-Neutral

Clinical and genetic evidence indicate this variant has a given probability of maintaining the existing pattern of pre-mRNA splicing for this gene

Uncertain

Clinical and genetic evidence for pre-mRNA splicing disruption by this variant is weak and/or conflicting; and cannot be assigned a probability.

Flags

Summary

Native Intron Frequency (NIF)

NIF-ML Power (Machine Learning)

Cryptic Splice-site Modification

Same Splice-site Variants

Same Sequence Variants

SpliceVault Top-10

Report MetaData

REPORT DATE	GENEIE VERSION	API VERSION
24-Sept-2024	0.0.229.0	0.0.50
ML DONOR VERSION	**ML ACCEPTOR VERSION**	**CLINVAR RELEASE**
v1.0.6	v1.0.5	2023-07
HGMD RELEASE		
2019.1		