GENE*ie* Report: NM_058175.3:c.1817-3C>G

This report was produced for **Demo Admin** of **Demo Account** on Monday, 2 September 2024

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

Splice-Altering

99.9% PROBABILITY

- Annotated acceptor 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_058175.3:c.1817-3C>G		
Gene	*COL6A2*	**Coordinates (GRCh38)**	21:46125462 C>G
Location	(NM_058175.3) Intron 24 acceptor / Distance from acceptor: -3		
Variant Databases	VCV000974882 (ClinVar) - Uncertain significance CS050381 (HGMD) - DM COL6A2_000014 (LOVD) - likely pathogenic, pathogenic		

Native Intron Frequency (NIF)

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

Window	Reference (REF)	Variant (VAR)	Frequency		% Scale		NIF Impact VAR/REF
			REF	VAR	REF	VAR	
A9 - A1	ccccccc**ag**AC	ccccccg**ag**AC	125	1	0.48	0.01	-97%
A8 - E1	cccccc**ag**AC	cccccg**ag**AC	142	2	0.53	0.02	-96%
A7 - E2	cccccc**ag**AC	cccccg**ag**AC	138	4	0.57	0.05	-92%

NIF-ML Power (Machine Learning)	
ML Score	0.99
Pathogenic	98%
Benign	2%
n	424

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
			A9 - A1 | A8 - E1 | A7 - E2	A9 - A1 | A8 - E1 | A7 - E2		
Annotated	ccccccc**ag**AC	ccccccg**ag**AC	0.48 | 0.53 | 0.57	0.01 | 0.02 | 0.05	N/A	N/A

Same Splice-site Variants

Variants affecting the same splice-site as the test variant

Test Variant	Distance from Acceptor	NIF Impact	Classification	Variant ID
		A9 - A1 | A8 - E1 | A7 - E2		
NM_058175.3:c.1817-3C>G	-3	-97% | -96% | -92%	VUS; P; LP	VCV000974882; CS050381; COL6A2_000014

Similar Impact Variants	Distance from Acceptor	NIF Impact	Classification	Variant ID
		A9 - A1 | A8 - E1 | A7 - E2		
NM_001849.4(COL6A2):c.1817-2A>C	-2	-100% | -100% | -100%	P	VCV002444282
NM_001849.4(COL6A2):c.1817-2A>G	-2	-100% | -100% | -100%	LP	VCV001068195

Different Impact Variants	Distance from Acceptor	NIF Impact	Classification	Variant ID
		A9 - A1 | A8 - E1 | A7 - E2		
NM_001849.4(COL6A2):c.1817-4C>T	-4	+17% | +6% | -12%	LB	VCV001103311

Same Sequence Variants

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

Window	Reference (REF)	Variant (VAR)	NIF Impact	Pathogenic		Benign	
			VAR/REF	introns	*n*	introns	*n*
A9 - A1	ccccccc**ag**AC	ccccccg**ag**AC	-97%	0	0	0	0
A8 - E1	cccccc**ag**AC	cccccg**ag**AC	-96%	0	0	0	0
A7 - E2	ccccccc**ag**AC	ccccccg**ag**AC	-92%	1	6	0	0

A9 - A1	NIF Impact	Classification	Variant ID
	A9 - A1 | A8 - E1 | A7 - E2		
No same sequence variants for this window			

A8 - E1	NIF Impact	Classification	Variant ID
	A9 - A1 | A8 - E1 | A7 - E2		
No same sequence variants for this window			

A7 - E2	NIF Impact	Classification	Variant ID
	A9 - A1 | A8 - E1 | A7 - E2		
NM_000062.2(SERPING1):c.686-3C>G	-97% | -97% | -92%	P	CS053491; SERPING1_000694

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	✓				19,161	139,433	15,650	158,594	46125312-46125464
Cryptic acceptor [4]			+49	0.05	13,447	24,306	1,114	37,753	46125312-46125513
Cryptic acceptor [4]	✓		-49	0.16	9,628	22,952	38	32,580	46125312-46125416
Cryptic acceptor [4]			+11	0.02	79	62	2	141	46125312-46125475
Cryptic acceptor			+8	0.00	9	47	2	56	46125312-46125472
Cryptic acceptor	✓		-91	0.10	18	23	3	41	46125312-46125374
Cryptic acceptor			-41	0.02	15	6	3	21	46125312-46125424
Exon Skipping	✓	25-26			2	6	1	8	46125312-46126502
Cryptic acceptor			+115	0.24	4	2	1	6	46125312-46125579
Cryptic acceptor			+58	0.00	2	3	1	5	46125312-46125522

[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
02-Sept-2024	0.0.223.0	0.0.50

ML DONOR VERSION	ML ACCEPTOR VERSION	CLINVAR RELEASE
v1.0.6	v1.0.5	2023-07

HGMD RELEASE
2019.1