

Alamut[™] Visual Plus v1.12

Extended Release Notes

16 December 2024



Additional Details on New Features & Improvements



New mitochondrial annotations from MitoMap db including MitoTip Scores

New Splicing Predictor: SpliceAl Lookup

ACMG Improvements

Occurrence Management Update

Small improvements

New database: MITOMAP for mitochondrial variants

SOPHIA GENETICS SOPHIA GENETICS

Summary

• MITOMAP, a human mitochondrial genome database uses the mtDNA sequence as the unifying element for bringing together information on mitochondrial genome structure and function, pathogenic mutations and their clinical characteristics, population associated variation, and gene-gene interactions.

Where can you see MITOMAP annotations?

• In the Variant Panel annotations and the Report section

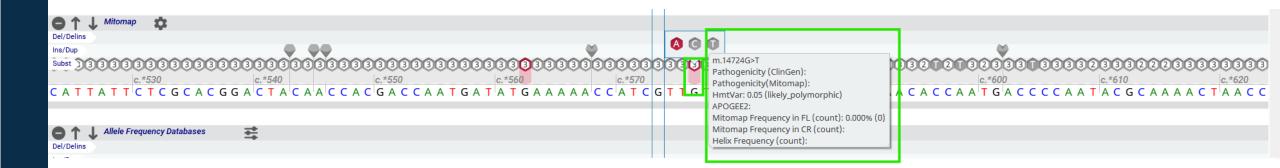
·x· IV	11-CO3.C.*406A2G 🙆											
IT-CO3	I) MT-CO3 V Local Variant Database: alamut	✓ ♦ Report					Mitomap (v2024-09-11)					
	- vananchistory	* Report										
			NC_012920.1(MT-CO3):c.*408A>	G			Gene type:	protein coding				
	Variant Overview						-		1 1. ***			
	The substitution is located in 'MT-CO3' downstream.						Description:	Cytochrome c oxidase	è subunit III			
	HGVS Nomenclature: cDNA Level: NC_012920.1(MT-CO3):c.*408A>G gDNA Level: ChrMT(GRCh37):m.10398A>G Protein Level: p.(=)						Strand:	heavy				
	The variation shows a not conserved nucleotide (phyloP: -0.12	[-19.0, 10.9]).										
	External Databases											
	This variant is known to:											
	ClinVar (2024-07-08): 9713 (Benign* - Leigh syndrome Parkinso	on disease resistance to).										
	dbSNP (156): rs2853826 (No Minor Allele - Clinical significance:	e: Benign, Likely benign, Protective)										
	MITOMAP (v2024-09-11) tamors, Pathogenicity (Clingen): Benign, Pathogenicity (Mitoma Homoplasmy/heteroplasmy: +/-, Mitomap Frequency in FL (cou	ap): Reported, HmtVar: , APO	GEE2: 0.04 (B), Haplogroup: L (L0, L1, L2, L3, L4, L5, L6) / M (C, I	D, E, G, M, Q, Z) / N (A, B, F, H, HV, I, J,	K, N, P, R, S, T, U, V, W, X, Y),	Conservations: 51.11%,						
	Gene Features	Mitomap (v2024-09-	<u>11)</u>									
	MITOMAP (v2024-09-11) Gene type: protein coding Description: Cytochrome c oxidase subunit III	Disease name(s):	PD protective factor, longevity, altered cell pH, metabolic syndrome, breast cancer risk, Leigh	Pathogenicity (ClinGen):	Benign	Haplogroup:	L (L0, L1, L2, L3, L4, L5, L6) M (C, D, E, G, M, Q, Z) N (I, J, K, Y)	Mitomap Frequency in FL (count):	42.376% (25902)			
	Strand: heavy		Syndrome risk, ADHD, cognitive	Pathogenicity (Mitomap):	Reported			Mitomap Frequency in CR (count):	0.000% (0)			
	Pathogenicity Classification		decline, SCA2 age of onset, Fuchs endothelial corneal dystrophy					,				
	Save report as PDF Save report as HTML Use short fra											
		Cell or Tissue type:	various tumors	HmtVar:				Helix Frequency (count):	25.166% (49322)			
		MitoTIP:		APOGEE2:	0.04 (B)	Homoplasmy/Heteroplasmy:	+/-	GnomAD Frequency (count/total):	41.848% (23506/56170)			

MITOMAP for mitochondrial variants



Where can you see MITOMAP Data for mitochondrial variants?

• From the mitochondrial genome track, you can see an overview of variant statistics by hovering over a variant on the 'MitoMap' track



MITOMAP for mitochondrial variants

How can you filter for mitochondrial variants based on pathogenicity?

- It is possible to filter based on pathogenicity as derived from HmtVar and Apogee2:
 - **VUS** (Apogee2: VUS+, VUS, VUS-; HmtVar: VUS, likely polymorphic, and polymorphic)
 - Benign (Apogee2: B)
 - Likely Benign (Apogee2: LB)
 - **Pathogenic** (Apogee2: P; HmtVar: pathogenic)
 - **Likely Pathogenic** (Apogee2: LP; HmtVar: likely_pathogenic)

✿ Home	CO1 (GRCh38 chrMT) 🛛										
View configuration Default	Transcript MT-CO1	Exon naming System	atic numbering (1n)			TRANSCRIPT VIEW	REGION VIEW				
Mitochondrial Genome											
TF RNR1 TV RNR2	TL1 ND1 TM		CO1 TTD CO2	ATP8 ATP6 CO3	TND	ND4	ND6 TE	CYB			
MT-ATP6 MT-ATP6: Mitochondrially encoded ATP synthase me	mbrane subunit 6										
c.370 c.380	c.390	c.400		c.420	c.430	C.440	CTACTCATTCA	c.460			
K N A L A H 125	F L P Q 130	G T P	T P L I 135	P M L 140		E T I S 145	L L I Q 150	P M A 155			
●↑↓ alamut 로 Del/Delins											
Ins/Dup Subst											
A A A A A T G C C C T A G C C C A C 1	C.*1470	AGGCACACCT	A C A C C C C T T A T C	C C C A T A C T A	GTTAT ^{C.*1510}	G A A A C C A T C A G C	C T A C T C A T T C A	A C C A A T A G C			
Del/Delins Ins/Dup Subst Phriter:	APOGEE2										
c.*145) Show:		c.*1480	c.*1490	c.*1500	c.*1510	c.*1520	c.*1530	c.*1540			
A A A A A T G C C 🛃 Unclassified	Uncertain Significance	A G G C A C A C C T	A C A C C C C T T A T C	C C C A T A C T A	GTTATTATC	G A A A C C A T C A G C	C T A C T C A T T C A	A C C A A T A G C			
🕑 Benign	Likely pathogenic										
O↑↓ Allele Fre que. Ukely Benign	Pathogenic										
Ins/Dup T G A 2 0 Subst 3 T 3 A T T G A A C C *1450 C *1460 C *1460 A A A T G C <th>c.*1470</th> <th>c.*1480</th> <th>GTGTTTTZCGCT c.*1490 A C A C C C C T T A T C</th> <th>c.*1500</th> <th>ACCGCC 20 c.*1510 G T T A T C C</th> <th>c.*1520</th> <th>c.*1530</th> <th>GGCG2 c.*1540 A C C A A T A G C</th>	c.*1470	c.*1480	GTGTTTTZCGCT c.*1490 A C A C C C C T T A T C	c.*1500	ACCGCC 20 c.*1510 G T T A T C C	c.*1520	c.*1530	GGCG2 c.*1540 A C C A A T A G C			
						«	< > » «	2 Q A- A+			



MitoTIP database

- MitoTIP data are available in the variant annotation panel and as a tooltip when hovering over the MITOMAP track.
- The following fields are displayed in annotation panel:
 - Score
 - MitoTIP prediction

Variant Features		Pathogenicity class		
Genomic Level	Protein Level	ACMG standards and guidelines	Missense Predictions	
Assembly: GRCh37	Coding Effect:	PM2_Moderate		
Chromosome: ChrMT	pNomen:	Suggested classification: Uncertain Significance (score: 2)		
gDNA: m.10437G>A	Compare AA:	Show Details		
Type: Substitution	SpliceAI Lookup	User defined pathogenicity class	Notes	
Transcript Level	External Tools	Classification: 0-Unclassified		
cDNA: NC_012920.1(MT-TR):n.33G>A	VariantValidator Mutalyzer	Pathogenicity class is NOT automatically suggested		
Location: Exon 1 of 1				
Exon naming: Systematic numbering (1n)				
External databases				
dbSNP (v156)	Mitomap (v2024-09-11)			
rsId: rs2124596177	Disease name(s): Mitochondrial myopathy	Pathogenicity (ClinGen):	Haplogroup:	Mitomap Frequency in FL (count): 0.000% (0)
Minor Allelle:		Pathogenicity (Mitomap): Reported		Mitomap Frequency in CR (count): 0.000% (0)
Clinical signif.: Uncertain significance	Cell or Tissue type:	HmtVar: 0.8 (pathogenic)		Helix Frequency (count): 0.000% (0)
	MitoTIP: <u>12.8155 (possibly pathogenic</u>	APOGEE2:	Homoplasmy/Heteroplasmy: -/+	GnomAD Frequency (count/total): 0.000% (0/56431)

As a Tool Tip in MitoMap Track

• ↑ ↓ Mitomap • ↓ • ↓ Mitomap • ↓ • ↓ • ↓	
ins/Dup Subsi 2 6 0 6 2 2 2 8 6 6 2 8 2 6 6 2 9 6 2 6 6 6 6 6 6 6 6 6 6 6 6 6	n.50 n.60 n.66 n.70 n.80
Subri 2 6 0 60228 6622 62 60 60 0 0 0 0 0 0 0 0 0 0 0 0 0	n.50 n.60 n.66 n.70 n.80
in.10 in.1 in.10 in.20 in.30 in.40	n.50 n.60 n.66 n.70 n.80
	G A'T A A T C A T A T T'T A C C A A'A T G C'C C C T C A T T A'C A T
m.10437G>A	
Pathogenicity (ClinGen):	
Pathogenicity (Mitomap): Reported	
HmtVar: 0.8 (pathogenic)	
APOGEE2:	
Mitomap Frequency in FL (count): 0.000% (0)	
Mitomap Frequency in CR (count): 0.000% (0)	
Helix Frequency (count): 0.000% (0)	
MitoTIP: 12.8155 (possibly pathogenic)	« < > » Q ⊕ д- д+

Annotation tab: Variant Features

New Splicing Predictor: SpliceAl Lookup

New Splicing Predictor: SpliceAI Lookup

Summary

The **SpliceAI Lookup** tool developed by Broad Institute is now accessible from the Annotations tab, where clicking on the button opens a pop-up window with pre-filled entries - pressing "submit" enables you to view the SpliceAI scores.

A Open gene GRCh37 G	RCh38 Mitochondrial view			🕴 Alamut Visual Plus Browser					
Home Image: FLT3:c.1310-3T>C Image: FLT3:c.1310-3T>C ranscript: (FLT3) NM_004119.3 Image: Local Value	ariant Database: alamut 🗸			NM_007249.5(KLF12):c.670+15759_670+15763del		- fixed SpliceAl vis predicted splicing	ualizations to clarif changes. See issue		
Annotation 🚸 Splicing 🚸 Occurrence	s 🚸 Variant History 🚸 Report		5	Genome version: O hg19 hg38 Gencode:	[show older updates]				
Variant Features Genomic Level Assembly: GRCh38 Chromosome: Chr13 (q12.2) gDNA: g.28036046A>G Type: Substitution	Pathogenicity class ACMG standards and guidelines BA1_Very_Strong BP6_Supporting Suggested classification: Benign (score: -9) Show Details		Max distance: 500 ⑦ masked scores ⑦	Related web tools: Iifftover: for variants/positions/intervals (hg19 <=> hg38 <>> TGG Viewer: igvjs-based web viewer for public reference tracks and private data in Google Storage buckets. Has custom track types for RNA-seq splice junctions and gCI variants.					
Transcript Level	SpliceAI Lookup External Tools	Classification: 0-Unclassif		SpliceAl scores: ③ Variant	Gene = MANE Select transcript = non-coding transcript	∆ type	∆ score ⑦	position ⑦	
NA: NM_004119.3(FLT3):c.1310-3T>C VariantValidator Mutalyzer Pathogenicity on naming: Systematic numbering (1n)		Pathogenicity class is NC	OT automatically sug	NM_007249.5(KLF12):c.670+15759_670+15763del KLF12 (ENSG00000118922.19/ENST00000703967.1/NM_001400136.1) = 13:73830063 GTGCTT>G protein coding MANE Select transcript (minus strand)			0.00		
ternal databases bSNP (v156)	1000 Genomes (2020-06-30)	HGVD (v2.30 - Aug. 2017)		intron variant UCSC, gnomAD	OMIM, GTEx, gnomAD, ClinGen, Ensembl, Decipher, GeneCards	Acceptor Gain Donor Gain	0.00		
sId: rs2491231	All: 56.3299% EAS: 73.51%	Filter: MAF:	PASS 0	NM_007249.5(KLF12):c.670+15759_670+15763del	KLF12 (ENSG00000118922.19/ENST00000377669.7/NM_001400146.1)	Acceptor Loss	0.00		
finor Allelle: A	EUR: 77.24% AFR: 19.44%	Ref/Ref: Ref/Alt:	145 551	⇒ 13:73830063 GTGCTT>G	protein coding (minus strand) OMIM, GTEx, gnomAD, ClinGen, Ensembl, Decipher, GeneCards	Donor Loss Acceptor Gain	0.00		
Clinical signif.: Benign	AMR: 71.61% SAS: 56.13%	Alt/Alt:	509	UCSC, gnomAD		Donor Gain	0.00		
Genome Exome Genome+Exome			ESP (v0.0.30) GoNL Filter:	MANE Select Transcript or All Transcripts					
Filters: PASS (Genome) and PASS (Exome)	Number of Allele Frequency FAF 95	_ FAF 99	Alt allele count:	Pangolin scores: ⑦					
Display in Genomic View				Variant NM_007249.5(KLF12):c.670+15759_670+15763del	Gene KLF12 (ENSG00000118922.19/ENST00000703967.1/NM_001400136.1)	∆ type Splice Loss	∆ score ⑦	position ③	

ACMG improvements

Variant Report Updates

SOPHIA GENETICS[™]

Summary

- The ACMG criteria strength suffix has been added in the ACMG dialog suggested/selected labels
- The ACMG rule strength used by each user is now saved in the local variant database (LVD)
- All categories of user-defined rule strengths are now displayed in the variant classification

Selected	Suggested	Evidence symbol	Strength	Category
		PVS1	Very strong (8pt)	Null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease. Caveats: - Beware of genes where LOF is not a known disease mechanism (e.g., GFAP, MYH7) - Use caution interpreting LOF variants at the extreme 3' end of a gene - Use caution with splice variants that are predicted to lead to exon skipping but leave the remainder of the protein - Use caution in the presence of multiple transcripts See reference article for updated rule specific ACMG guidelines
		PS1	Strong (4pt)	Same amino acid change as a previously established pathogenic variant regardless of nucleotide change. Example: Val->Leu caused by either G>C or G>T in the same codon Caveat: Beware of changes that impact splicing rather than at the amino acid/protein level

2 suggested: PM2_Moderate, BP4_Supporting

3 selected: PS2_Very_Strong, PM2_Moderate, BP4_Supporting

Score: 9

Pathogenicity class	Rules for combining criteria to classify sequence variants
Pathogenic	Score >= 10
Likely Pathogenic	Score between [6, 9]
Uncertain Significance	Score between [0, 5]
Likely Benign	Score between [-6, -1]
Benign	Score <= -7

Please note that these criteria for classifying variants Richards et al., 2015. Genet Med are available to help you to determine the pathogenicity class.

This is the publication describing point based Scoring framework for Pathogenicity - Fitting a naturally scaled point system to the ACMG

Pathogenicity cla ACMG standard	ls and guidelines
PS2_Very_Strop	-
PM2_Moderat	2
BP4_Supporti	
User defined cla	assification: Likely Pathogenic (score: 9)

© SOPHiA GENETICS 2024 | Confidential - For research use only - Not for use in diagnostic procedures

Occurrence Management Update

Occurrence Management Update

• There is a **new column** in the Occurrence tab: "Created By"

• New Occurrence Management system, whereby the unique identifiers for a variant are the occurrence ID + Family ID. Other columns (Phenotype, HPO IDs, RNA Analysis, Comment, Created/Created By and Updated/Updated By) are independent of the variant occurrence and any changes in those fields will not impact other variants linked to the same occurrence.

			· · · · · · · · · · · · · · · · · · ·	nnotation	👾 Splicing	Occurrences						
(+) New Occurrence (-) Delete Occurrence Edit Occurrence												
Variant Summary	/ariant Summary											
Occurrence ID A	Family ID	Phenotype	HPO IDs	RNA Analysis	Comment	Created	Created By	Updated	Updated B	y		
Occurr1	Fam1	Phenotype1		RNA 1	Comment 1	27/11/2024 09:3) pgascue	27/11/2024 0	9:30 pgascue			
Occurr2	Fam2	Phenotype2		RNA 2	Comment 2	27/11/2024 09:3) pgascue	27/11/2024 0	9:30 pgascue			

Database version updates

External Annotation Updates

SOPHIA GENETICS

The following external annotations were updated:

- ClinVar updated to 2024-10-02
- Mastermind updated to 2024-10-02
- HGNC updated to November 2024
- RefSeq transcripts updated to November 2024

Small improvements

Small Improvements

• The Variant Panel layout has been improved for large insertion variants, by wrapping the long string of nucleotides in one box. In addition, long cDNA strings are now displayed on multiple lines in the Report tab, rather than being cropped.

SOPHIA GENETICS[™]

Open gene GRCh37 GRCh38 Mitochondrial view	N			666666666666666666666666666666666666666					
				-					
BRCA1:n.									
4400_4401insAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA			ITTTTTTTGGGGGGGGG	66666666666666666666666666666666666666					
🚸 Annotation 🚸 Splicing 🚸 Occurrences 🚸 Variant History	🔅 Report								
Variant Features	Protein Level	Pathogenicity class	Missense Predictions						
Genomic Level Assembly: GRCh38		ACMG standards and guidelines							
Chromosome: Chr17 (g21.31)	Coding Effect:								
qDNA: q.43082497_43082498ins582	pNomen:	PM2_Moderate	Notes						
Type: Insertion	Compare AA:								
Alternatively: g.43082496_43082497ins582									
(Not HGVS compliant, see User Manual)	Check predictions in the Splicing Tab								
Transcript Level	External Tools	Suggested classification: Uncertain Significance (score: 2)							
cDNA: NR_027676.1(BRCA1):n.4400_4401insAAAAAAAAAAAAAAAAAAAAAAAAAAAA									
		Show Details	🕈 Home 🗵 🔺 BF	CA1:n.4400_4401insAAAAAAAAAAAAAAAAAAAAAAA	VAAA 🗵				
		User defined pathogenicity class	Transcript: (BRCA1	Transcript: (BRCA1) NR.027676.1 V Local Variant Database: alamut					
TTTTTTTTTTTTTTTTTTTTTTTTTGGGGGGGGG		User defined padlogenicity class		* Annotation * Splicing * Occurrences * Variant History * Report					
GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG									
TTTTTTTTTTTTTGGGGGGGGGGGGGGGGGGGGGGGGGG	VariantValidator Mutalyzer	Classification: 0-Unclassified		arning: SOPHIA CUSTOMER ACKNOWLEDGES THAT DATA (TERPRETATION BASED ON DATA GENERATED BY ALAMUT		EVENT CONSTITUTE A CLINICAL INTERPRETATION. ACCORDINGLY S	SOPHIA CUSTOMER ACCEPTS SOLE AND EXCLUSIVE RESPONSIBILITY FO	OR ANY RESULTS	
GCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC			Variant		5577777812				
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA				er: scretu			•• .	SOPHIA	
		Pathogenicity class is NOT automatically suggested		te: 10/17/2024				SOPHiA GENETICS [™]	
			Codifect					OLIVETICS	
Location: Exon 12 of 23			8		DDCA1 /D				
Exon naming: Systematic numbering (1n)					BRCAT (B	RCA1 DNA repair associated) Va	riation		
External databases			Amino Acid	B 027676 1/BBCA1) n 4400 4401 insA					
dbSNP (v156) 1000 Genomes (2020-06-30)	HGVD (v2.30 - Aug. 2	017) Danish2k (2013)					TTTTTTTTGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG		
rsId: Not referenced All:	Filter:	MAF:	External				Geeeeeeeeeeeeeeeeeeeeeeeeeeeeeeeeeeeeee		
FAS:				CCCCCCCCCCCCCCAAACCCGGTTTA	AACCCGGTTTAAAAAAAAAAAA	адааааааааааааааааааааааааааааааааа	ААААААААААССССССССССССССССССССССССССССС	200000000000000000000000000000000000000	
Display in Genomic View			■■■	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC		CCCCCCTTTTTTTGGGGGGGGGGGGGGGGGGGGGGGGGG	GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	GGG	
			Gene	ariant Overview					
			FAITIFAS						
			TH 5	e insertion is located in 'NR_027676.1' exon 12 of 23.					
				IVS Nomenclature:		AAAAAAAAAAACCCCCCCCCCCCCCCCCCCCCCCCCCCC			
				TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	GGGGGGGGGGGGGGGGGGGGGGAAAAAAAAAAAAAAAAA	AAAAATTTTTTTTTTTTTTTTTTTTTGGGGGGGGGGGGG	Geeeeeccccccccccccccccccccccccccccccccc	
			G	CCCCCCCCCCCCCCCCCCCCAAACCCGGTTTAACCCGG GGGGGGGGGG		AAAAAAAAAAAAAAAAAAAAAAAAAACCCCCCCCCCCCC		CCCCCCCCCTTTTTTTGGG	
			Clas tion	NA Level: Chr17(GRCh38):g.43082497_43082498ins582					
			Th	is variant is in protein domain:				v	
			Sa	ve report as PDF Save report as HTML	Use short frameshift descriptio	ns(e.g p.Arg123fs)			
			Dicplay in Conon	ic View			Save	Cancol Delete	
			Display in Genom	ic view			Save Export	Cancel Delete	

Small improvements

- Changes to splicing prediction options and flanking region size are now saved when the flanking region size is modified at the bottom of the "Splicing Prediction Options" dialog and the "Apply" button is clicked when generating the splicing report (accessed via the "Report" button in the splicing view).
- You can now view the total number of intron or exon in the Variant Panel when applicable.
- We have now fixed the AVP searches on some selective rs-numbers that did not return gene annotation properly.
- The Variant nomenclature algorithm version has been updated for variants within the -8 or +8 regions of the codon, which are now assigned "p.?", while other intronic variants remain assigned "p.(=)".
- When closing Alamut[™] Visual Plus, if any Variant Panels are open with unsaved changes, a warning will be displayed. If several Variant Panel tabs are open, the warning will be displayed only once.
- You can now close all tabs at once by right clicking on any tab.
- The automatic pop-up indicating the successful opening of a BAM file has now been removed.
- The GeneSplicer value has been added to the splicing variant Report as a percentage, similar to MaxEntScan, SSF, and NN splice.

Useful Links



Download v1.12

v1.12 Release Note

v1.12 User Manual