



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: **SpliceAI** **Lookup**

ACMG Improvements

Occurrence Management Update

Small improvements



**New database:
MITOMAP for
mitochondrial variants**

New Database: MITOMAP for mitochondrial variants

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

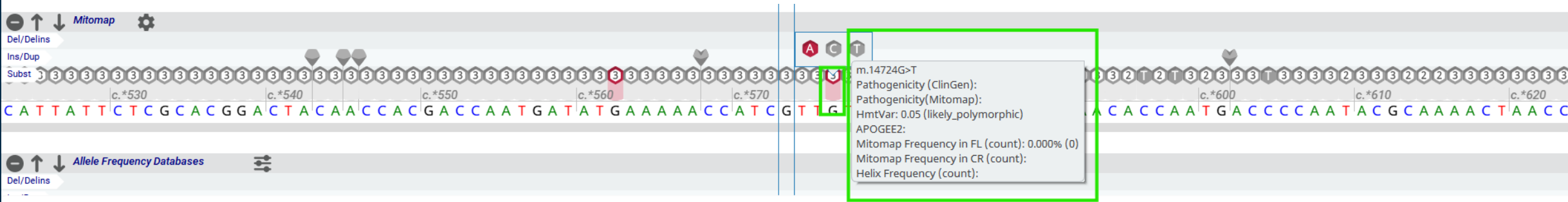
The screenshot displays the MITOMAP variant report for the variant **NC_012920.1(MT-CO3):c.*408A>G**. The interface includes a navigation bar with tabs for Splicing, Occurrences, Variant History, and Report. The variant overview section provides details on the substitution's location, HGVS nomenclature, and phyloP score. The external databases section lists ClinVar, dbSNP, and MITOMAP annotations. The gene features table provides a comprehensive overview of the gene's characteristics, including disease names, pathogenicity, haplogroup, and various frequencies.

Gene Features			
MITOMAP (v2024-09-11)	Disease name(s): PD protective factor, longevity, altered cell pH, metabolic syndrome, breast cancer risk, Leigh Syndrome risk, ADHD, cognitive decline, SCA2 age of onset, Fuchs endothelial corneal dystrophy	Pathogenicity (ClinGen): Benign	Haplogroup: L (L0, L1, L2, L3, L4, L5, L6) / M (C, 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)
Gene type: protein coding	Pathogenicity (Mitomap): Reported	Mitomap Frequency in FL (count): 42.376% (25902)	Mitomap Frequency in CR (count): 0.000% (0)
Description: Cytochrome c oxidase subunit III	Cell or Tissue type: various tumors	HmtVar:	Helix Frequency (count): 25.166% (49322)
Strand: heavy	MitoTIP:	APOGEE2: 0.04 (B)	GnomAD Frequency (count/total): 41.848% (23506/56170)
Pathogenicity Classification		Homoplasmy/Heteroplasmy: +/-	

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)

The screenshot displays the MITOMAP web interface for a mitochondrial variant. At the top, the 'Mitochondrial Genome' is shown with various genes like TF, RNR1, TV, RNR2, TL1, ND1, TM, ND2, TY, CO1, TD, CO2, ATP8, ATP6, CO3, ND3, ND4L, ND4, TL2, ND5, ND6, TE, CYB, and TP. A red box highlights the ATP6 gene. Below the genome map, the DNA sequence for MT-ATP6 is shown with positions from 125 to 151. A variant is highlighted at position 146. A 'Mitomap' filter dialog box is open, showing the following settings:

- Filter:
 - HmtVar
 - APOGEE2
- Show:
 - Unclassified
 - Benign
 - Likely Benign
 - Uncertain Significance
 - Likely pathogenic
 - Pathogenic

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

Annotation tab: Variant Features

Variant Features

Genomic Level
 Assembly: GRCh37
 Chromosome: ChrMT
 gDNA: m.10437G>A
 Type: Substitution

Protein Level
 Coding Effect:
 pNomen:
 Compare AA:

Transcript Level
 cDNA: NC_012920.1(MT-TR):n.33G>A
 Location: Exon 1 of 1
 Exon naming: Systematic numbering (1..n)

External Tools
[SpliceAI Lookup](#)
[VariantValidator](#) [Mutalyzer](#)

Pathogenicity class
 ACMG standards and guidelines
 PM2_Moderate
 Suggested classification: Uncertain Significance (score: 2)
[Show Details](#)

User defined pathogenicity class
 Classification: 0-Unclassified
 Pathogenicity class is NOT automatically suggested

Missense Predictions

Notes

External databases

dbSNP (v156)	Mitomap (v2024-09-11)	Pathogenicity (ClinGen):	Haplogroup:	Mitomap Frequency in FL (count): 0.000% (0)
rsId: rs2124596177	Disease name(s): Mitochondrial myopathy	Pathogenicity (Mitomap): Reported		Mitomap Frequency in CR (count): 0.000% (0)
Minor Allele:	Cell or Tissue type:	HmtVar: 0.8 (pathogenic)		Helix Frequency (count): 0.000% (0)
Clinical signif.: Uncertain significance	MitoTIP: 12.8155 (possibly pathogenic)	APOGEE2:	Homoplasmy/Heteroplasmy: -/+	GnomAD Frequency (count/total): 0.000% (0/56431)

As a Tool Tip in MitoMap Track

Del/Delins
 Ins/Dup
 Subst

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)



New Splicing Predictor: SpliceAI 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.

The screenshot shows the SpliceAI Lookup tool interface. On the left, the variant details for NM_004119.3 (FLT3):c.1310-3T>C are displayed. The 'SpliceAI Lookup' button is highlighted with a green box. On the right, the 'Alamut Visual Plus Browser' pop-up window is shown, containing the variant ID and a 'Submit' button, both highlighted with green boxes. Below the 'Submit' button is a table of SpliceAI scores for the variant NM_007249.5(KLF12):c.670+15759_670+15763del.

Variant	Gene	Δ type	Δ score	position
NM_007249.5(KLF12):c.670+15759_670+15763del =>13:73830063 GTGCTT>G intron variant UCSC, gnomAD	KLF12 (ENSG00000118922.19 / ENST00000703967.1 / NM_001400136.1) protein coding MANE Select transcript (minus strand) OMIM, GTEx, gnomAD, ClinGen, Ensembl, Decipher, GeneCards	Acceptor Loss	0.00	
		Donor Loss	0.00	
		Acceptor Gain	0.00	
		Donor Gain	0.00	
NM_007249.5(KLF12):c.670+15759_670+15763del =>13:73830063 GTGCTT>G intron variant UCSC, gnomAD	KLF12 (ENSG00000118922.19 / ENST00000377669.7 / NM_001400146.1) protein coding (minus strand) OMIM, GTEx, gnomAD, ClinGen, Ensembl, Decipher, GeneCards	Acceptor Loss	0.00	
		Donor Loss	0.00	
		Acceptor Gain	0.00	
		Donor Gain	0.00	
NM_007249.5(KLF12):c.670+15759_670+15763del	KLF12 (ENSG00000118922.19 / ENST00000703967.1 / NM_001400136.1)	Splice Loss	0.05	2 bp



ACMG improvements

Variant Report Updates

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
<input type="checkbox"/>		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
<input type="checkbox"/>		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 class
 ACMG standards and guidelines

- PS2_Very_Strong
- PM2_Moderate
- BP4_Supporting

User defined classification: Likely Pathogenic (score: 9)

Show Details

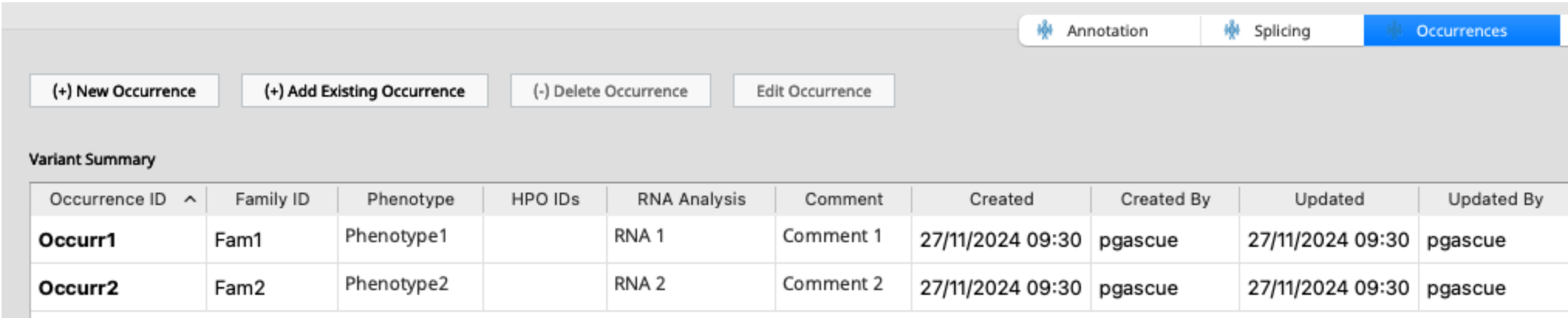


Occurrence

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.



The screenshot shows a software interface for managing occurrences. At the top, there are three tabs: 'Annotation', 'Splicing', and 'Occurrences' (which is selected and highlighted in blue). Below the tabs, there are four buttons: '(+) New Occurrence', '(+) Add Existing Occurrence', '(-) Delete Occurrence', and 'Edit Occurrence'. Underneath these buttons is a section titled 'Variant Summary' containing a table with the following data:

Occurrence ID ^	Family ID	Phenotype	HPO IDs	RNA Analysis	Comment	Created	Created By	Updated	Updated By
Occurr1	Fam1	Phenotype1		RNA 1	Comment 1	27/11/2024 09:30	pgascue	27/11/2024 09:30	pgascue
Occurr2	Fam2	Phenotype2		RNA 2	Comment 2	27/11/2024 09:30	pgascue	27/11/2024 09:30	pgascue



Database version updates

External Annotation Updates

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.

The screenshot displays the SOPHiA GENETICS variant analysis interface. At the top, there are navigation tabs for 'Home', 'BRCA1:n.4400_4401ins582', and a search bar containing a long string of 'G's. Below this, the main interface is split into several panels:

- Annotation Panel (Left):** Shows variant features at genomic and transcript levels. Genomic level includes assembly (GRCh38), chromosome (Chr17), gDNA, and type (Insertion). Transcript level shows the cDNA sequence for NR_027676.1, which is wrapped in a box.
- Protein Level (Middle-Left):** Shows coding effect, pNomen (PM2_Moderate), and a suggested classification of 'Uncertain Significance (score: 2)'. A message states 'Pathogenicity class is NOT automatically suggested'.
- Variant Overview Panel (Right):** Features a warning about data generated by Alamut, user information (User: scretu, Date: 10/17/2024), and a section titled 'BRCA1 (BRCA1 DNA repair associated) Variation'. It displays the variant in HGVS nomenclature and provides a long, wrapped cDNA string.
- External Databases (Bottom):** Includes links to dbSNP, 1000 Genomes, HGVD, and Danis2k.

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](#)