SOPHiA GENETICS™

Alamut™ Visual Plus v1.12

Extended Release Notes

16 December 2024

Additional Details on New Features & Improvements

alamut™ VISUAL PLUS

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

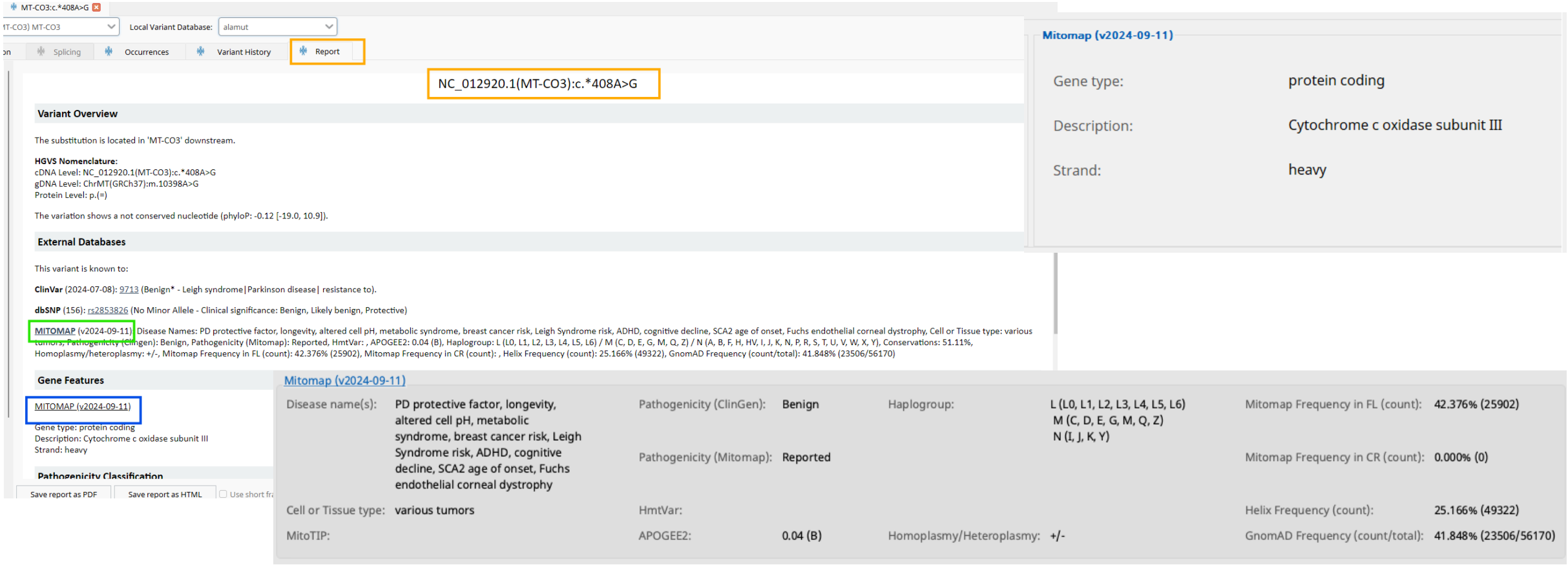
New Database: MITOMAP for mitochondrial variants

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?

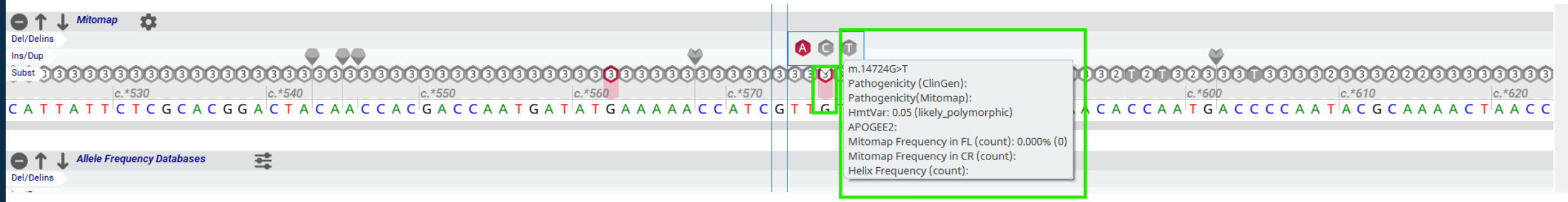
- In the Variant Panel annotations and the Report section



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

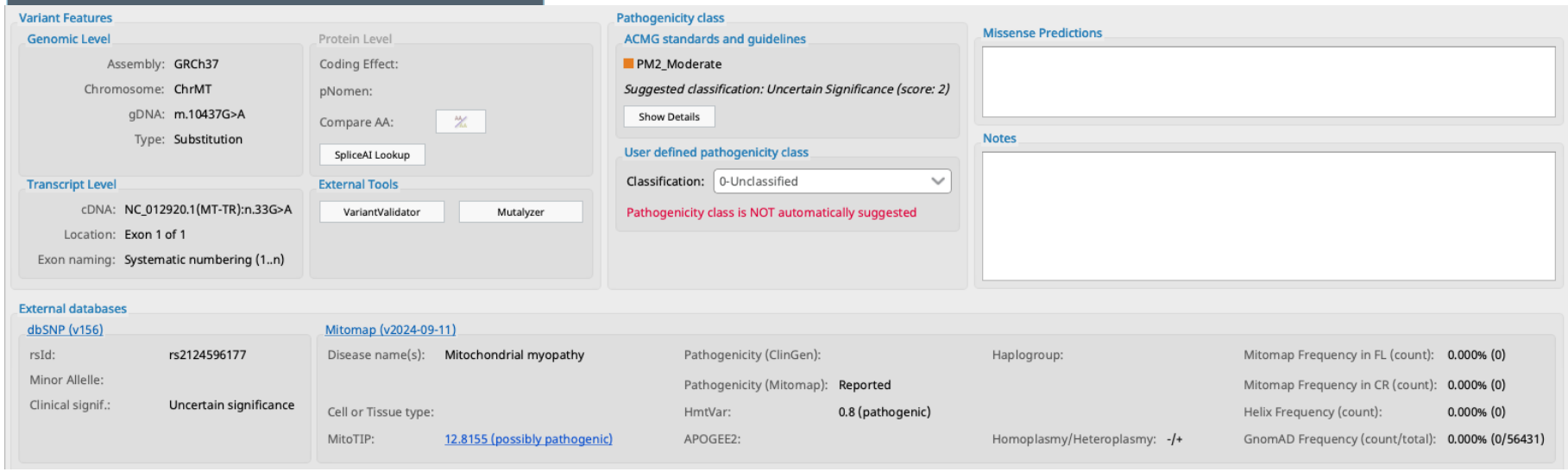
How can you filter for mitochondrial variants based on pathogenicity?

- 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)

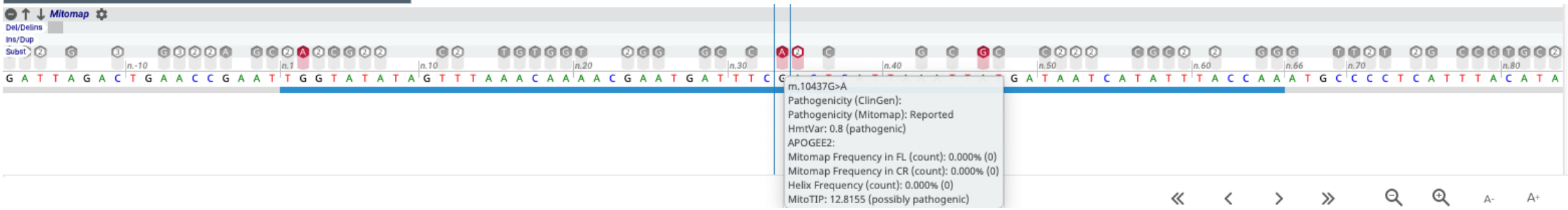
MitoTIP database

- 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



As a Tool Tip in MitoMap Track

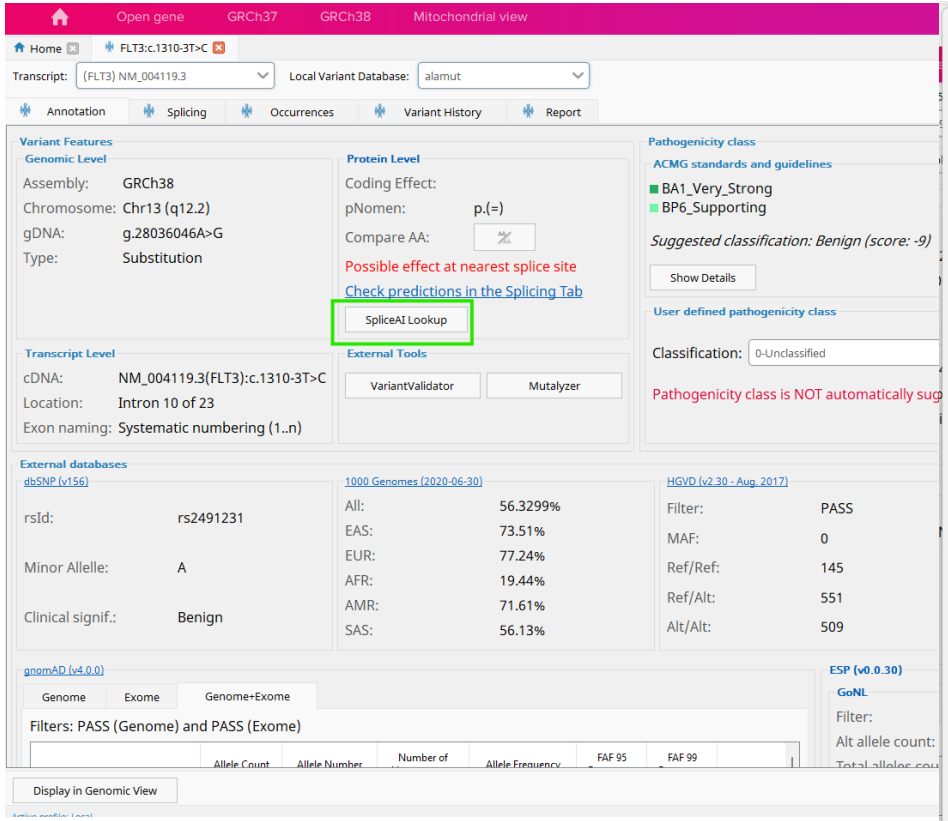


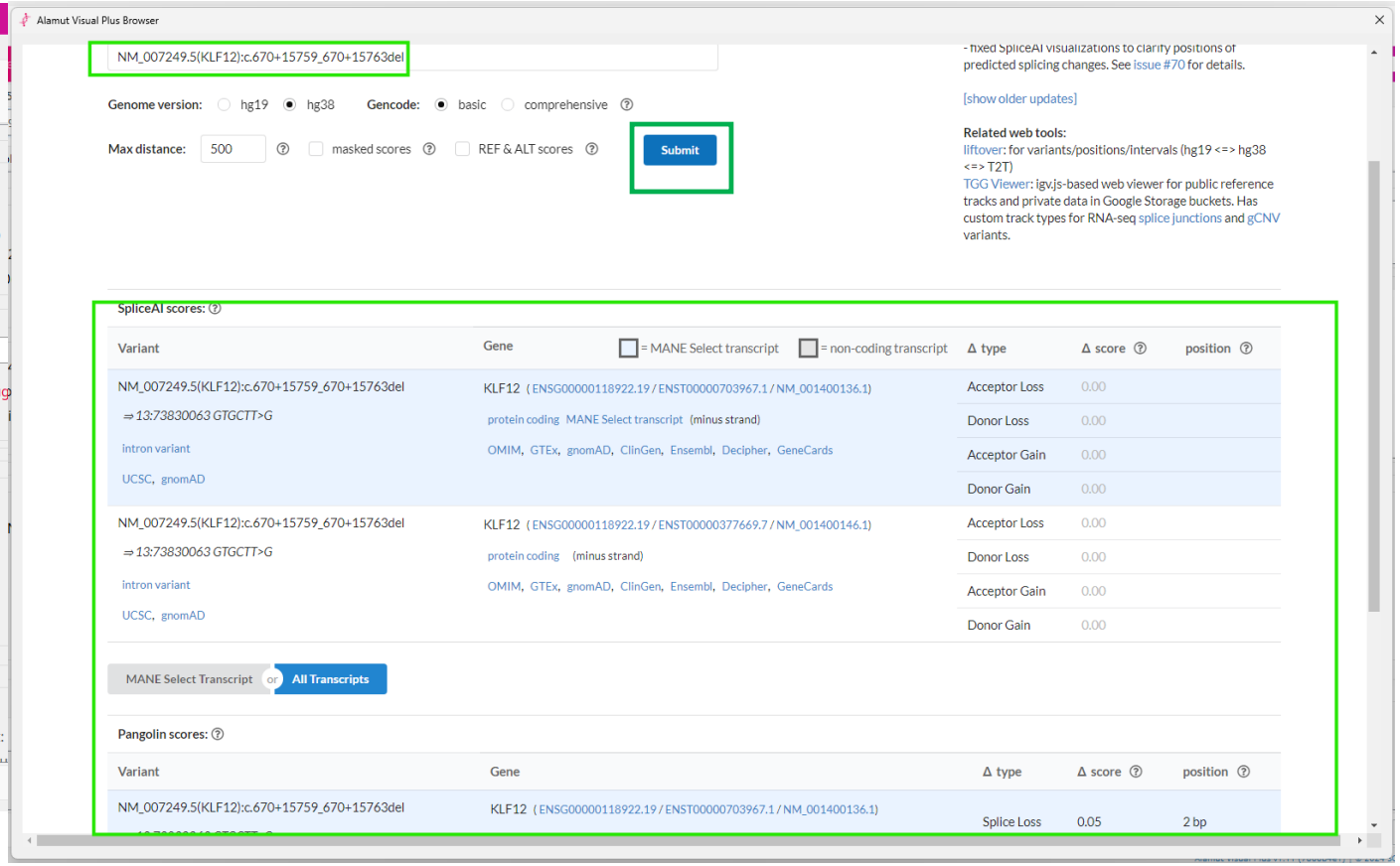
New Splicing Predictor:
SpliceAI Lookup

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.





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
☐		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

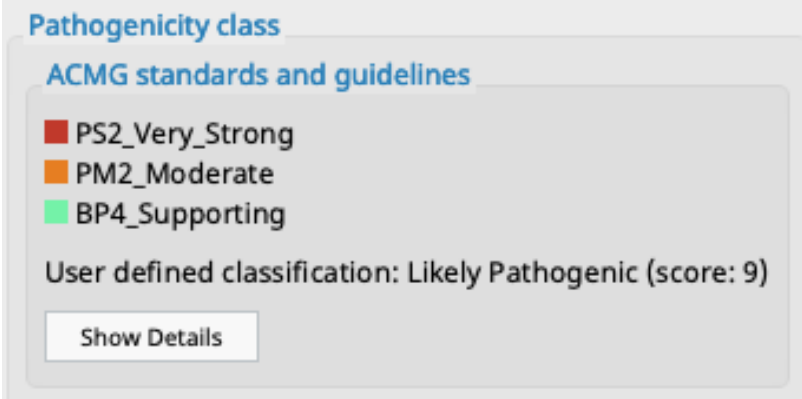
3 selected: PS2_Very_Strong, PM2_Moderate, BP4_Supporting

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.

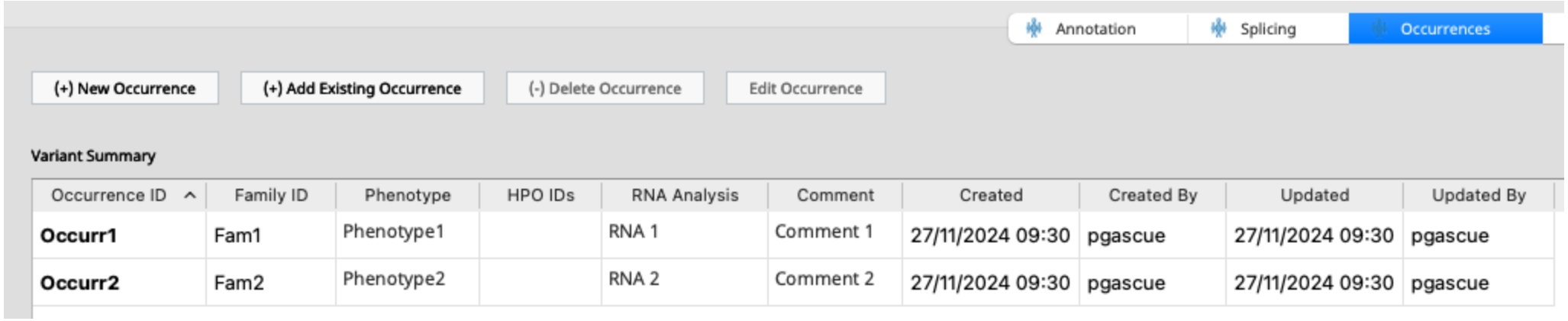
This is the publication describing point based Scoring framework for Pathogenicity - Fitting a naturally scaled point system to the ACMG



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.



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

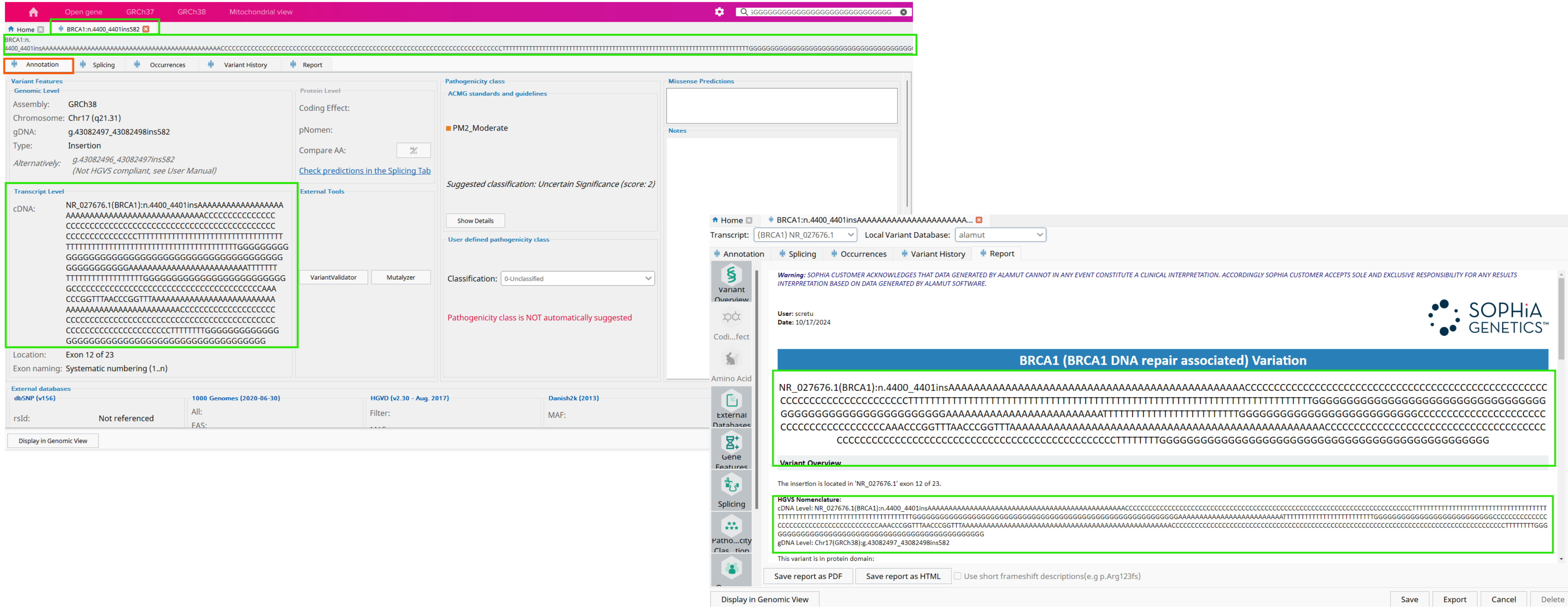
The following external annotations were updated:

- 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.



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.

alamut™ VISUAL PLUS

Useful Links

Download v1.12

v1.12 Release Note

v1.12 User Manual