

Unified Variant Interpretation Platform

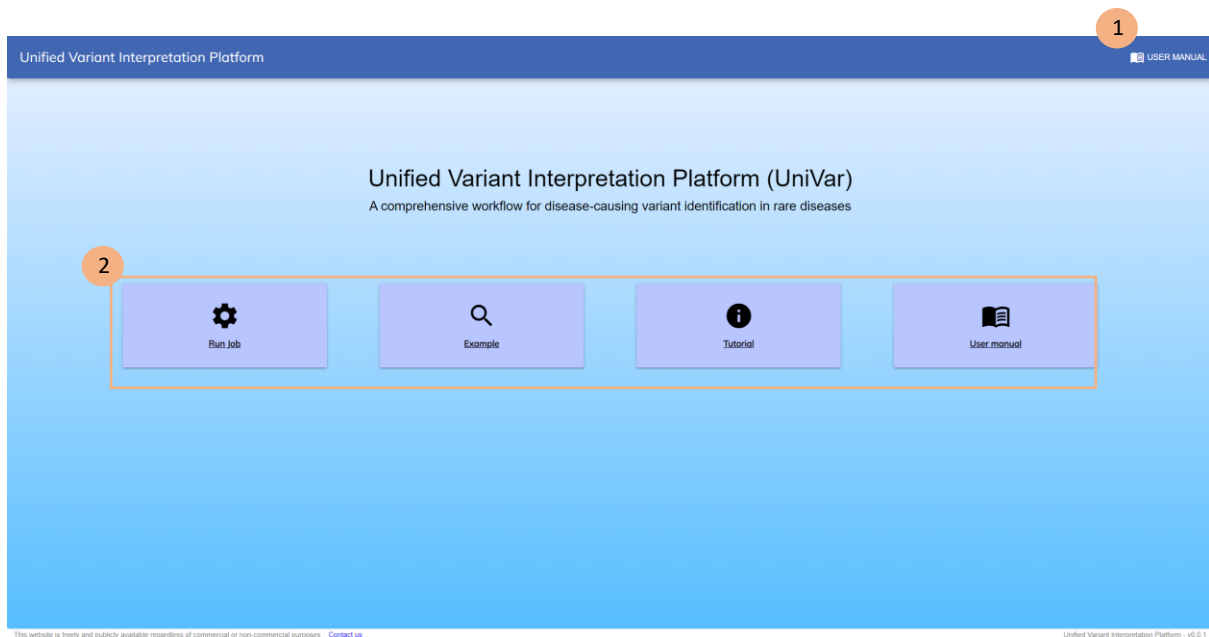
User Manual

Version: 1.1

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Landing Page



The landing page serves as the entry point for users and provides access to various pages and guides within the application.

1. Link to download user manual in PDF format (this document)
2. Menu buttons: Provide buttons for the following options: "Run Job," "Example Data," "Tutorial," and "User Manual"
 - "Run Job": Allows users to upload their own samples with ped, HPO terms, SNP VCF file, and SV VCF files. Refer to the [Sample Upload Page](#) section for more details
 - "Example": Case study demonstration to let first-time users explore the functionality of UniVar.
 - "Tutorial": Offers a downloadable PDF file with step-by-step instructions on how to use the application
 - "User Manual": Provides a download link to this document in PDF format, which helps users understand each page of the application

Sample Upload Page

***Required :**

"Proband ID

Upload File	Add sample
PED file <small>* Only accept .ped format</small>	X 0 (0.0B)

Upload at least one of them :

SNP file <small>Only accept: .vcf.gz format</small>	X 0 (0.0B)
SV files <small>[Multiple files] Only accept .vcf.gz format</small>	X 0 (0.0B)

Optional: Choose a way to input HPO Terms for Exomiser (Version: 2023-09-01)

Upload File	Select HPO terms	Input HPO terms	Select Gene Panels
HPO file <small># Please notice that the Exomiser result is based on the original ped file uploaded with the above HPO terms. * Each Exomiser run take about 10 mins to process</small>			

The interface includes several numbered callouts:
1: Points to the "Example File" link next to the PED upload field.
2: Points to the database icon in the bottom left navigation bar.
3: Points to the "UPLOAD" button in the bottom center.

The Sample Upload Page allows users to provide their own files for executing the UniVar's annotation pipeline and viewing the results in the [Variant Tables Page](#).

Users are required to provide the following items:

- Familial relationships among the samples (users can upload a PED file or input the details in the “Add sample” section)
 - At least one VCF file in vcf.gz format:
 - Small variants file
 - Structural variants file (multiple files with different callers are accepted)
 - HPO terms for prioritization (optional)
 - Users can upload an .hpo file
 - Select HPO terms in a drop-down list
 - Input HPO terms in string format, separated by commas, tabs or spaces
 - Select gene panel(s)
1. Example files of each type can be downloaded through the hyperlink provided next to each file selection box. These examples can help users understand the required file formats and serve as a source of example data in the [Variant Tables Page](#).

2. Annotation pipeline information button: allows users to check the current details and version of the annotation database.
3. Upload button: Clicking this button initiates the file upload process, enabling users to submit their files for annotation.

Job Status Page

Unified Variant Interpretation Platform

USER MANUAL

UPLOAD NEW SAMPLE

Samples Name	Upload Datetime	Finish Datetime	Status	Delete
demo1_trio_1702867897105-36afa537c144	12/18/2023, 10:51:38 AM		Processing....	

Records per page: 10 1-1 of 1

* Please bookmark or save this URL to retrieve the job status later

★

Bookmark

Copy URL

* Your uploaded files will be ready within a day, the Job ID: 1702867897105-36afa537c144

The Job Status Page allows users to view the status of the files they have uploaded. Each time a user uploads files, a unique and private URL is generated. Users can save this URL to view the upload result later.

1. If the job is finished, users can click on the sample name to enter the [Variant Table Page](#) and browse the annotated results.
2. It is important for users to bookmark or save the provided URL. This allows them to retrieve the job status and access the results later.

Variant Tables Page

The screenshot displays the Unified Variant Interpretation Platform interface. The top navigation bar includes a 'USER MANUAL' link. Below the navigation bar, there are several panels and a main table:

- 1. Sample Panel:** Shows 'Select Samples' with 'simulated_case_study_patho_comHel_ATM' and a 'Total' count of 3 (Not affected: 2, Affected: 1). A 'SHORT TUTORIAL FOR CASE STUDY' button is also present.
- 3. Filtering Panel:** Includes a search bar with 'chr1:11000-118043 or OR4F5,OR4F29' and various filter dropdowns like 'Gene Panel', 'Scenario', 'Frequency', 'Quality', 'Impact', 'Pathogenicity', 'Prioritization', and 'Others'.
- 4. Control Panel:** Contains buttons for 'Read', 'Un-read', 'Export', and 'Run Exomiser'.
- 5. Exomiser Panel:** Includes a 'SELECT EXOMISER' dropdown and a 'Run Exomiser' button.
- 6. Variants Panel:** A table displaying variant information. The table has columns: Note, Chr, Start, End, Ref, Alt, Samples genotypes, Gene, HGVSc, HGVSp, Existing variation, MANE select, Exomiser Gene Symbol, Exomiser MOI, Exomiser REMM Score, and E. The table lists several variants, including CDK11A, CCDC27, SMIM1, VAMP3, CAMTA1, RNF19B, ZNF328, METTL25B, ISG20L2, and OR6P1.

At the bottom of the interface, it shows 'Showing: 300 / 118018 (Total: 118018)'.

The Variant Tables Page provides detailed information about the annotated variants for further analysis and exploration.

1. [Sample Panel](#): Sample selection, sample status and annotation pipeline information
2. Short tutorial for case study: the steps to identify the disease-causing variants in this case study presented in the paper
3. [Filters Panel](#): Settings for filtering and prioritization
4. [Control Panel](#): Miscellaneous settings for UI layout, data export and bookmarks
5. [Exomiser Panel](#): Manage and submit Exomiser jobs for prioritization
6. [Variants Panel](#): Display variants based on the selected filtering and prioritization options

Sample Panel

Select Samples
family_trio_20230927-y3rtcOi

Total: 3 Not affected: 2 Affected: 1

1 2 3

1. Dropdown box for family selection
2. Sample status: View samples' family relationship, phenotype and gender

Samples selection: Total: 3 Not Affected: 2 Affected: 1 Search

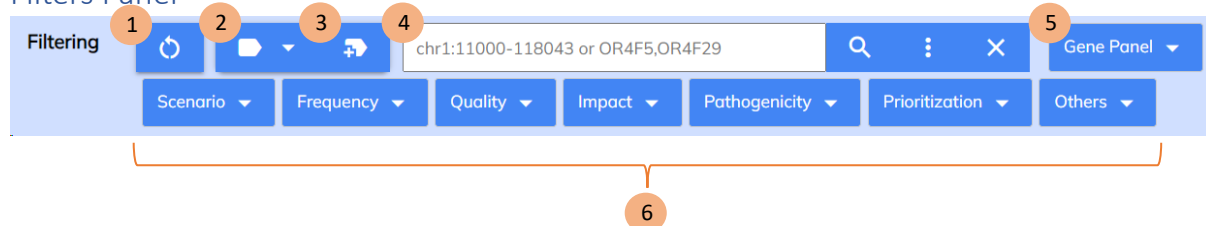
Restore

	Family	Sample	Affected	Sex	Mother	Father	Cram File	Cram Index
<input type="checkbox"/>	<input checked="" type="checkbox"/> NA12878_NA12891_NA12892	<input checked="" type="checkbox"/> NA12878	<input type="radio"/> No <input checked="" type="radio"/> Yes	♀	NA12892	NA12891	<input type="text"/> Cram file	<input type="text"/> Cram index file
<input type="checkbox"/>	<input checked="" type="checkbox"/> NA12878_NA12891_NA12892	<input checked="" type="checkbox"/> NA12892	<input checked="" type="radio"/> No <input type="radio"/> Yes	♀			<input type="text"/> Cram file	<input type="text"/> Cram index file
<input type="checkbox"/>	<input checked="" type="checkbox"/> NA12878_NA12891_NA12892	<input checked="" type="checkbox"/> NA12891	<input checked="" type="radio"/> No <input type="radio"/> Yes	♂			<input type="text"/> Cram file	<input type="text"/> Cram index file

CLOSE

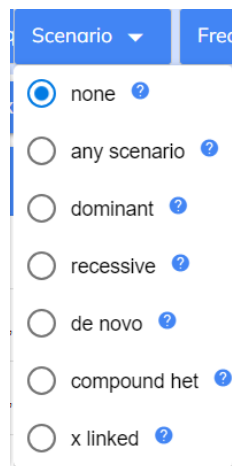
- Select all samples, only non-affected, or affected. User can use the search bar on the right to search samples based on sample name.
 - Select/deselect family
 - Select/deselect sample
 - Sample phenotype based on the input pedigree file. User can modify the affected/unaffected status shown in the variant panel when necessary
 - Restore the sample selection and the sample phenotype
 - For the [IGV feature](#)
3. Annotation pipeline version details of the selected family in the dropdown box

Filters Panel



1. Reset filters button
2. Preset filters, including default presets provided by UniVar and presets saved by user. One of our preset is 'High risk (SNV/INDEL + SV)' filter, the parameter consists of (1) any scenarios that correspond to the mode of inheritance (MOI) in Mendelian disease (dominant, recessive, de novo, compound heterozygous and X-linked), (2) AF is 0.005 or less in any of the global population frequency database: gnomAD v2, gnomAD v3, 1KGP and inhouse, (3) genes that have a ClinGen HI score of 3 (sufficient evidence for HI) or 30 (gene associated with AR phenotype), (4) SV that are pLoF or SNV/INDEL that satisfy one of the following conditions: (4.1) high impact in the protein, predicted to cause protein truncation, loss of function or triggering nonsense mediated decay, (4.2) Polyphen score higher than 0.85, or SIFT score lower than 0.05, or CADD higher than 20, or REVEL higher than 0.5, and (4.3) reported as pathogenic or likely pathogenic in ClinVar
3. Save preset button. Save current applied filters as a preset.
4. Genomic location filter. Filter variants by chromosome coordinates or gene symbols. For filtering by gene symbols, multiple values (separated by commas) are supported.
5. Gene panel filters. Filter variants by gene panels from PanelApp UK, PanelApp AU and ClinGen Gene Curation Expert Panels. User can enter keywords to search gene panels. Multi-panel selection is supported.
6. Group of filters. Click to unfold.

Genomic Scenario Filters

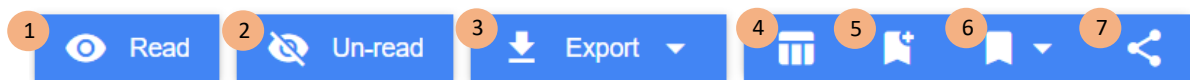


Scenario ▼ Freq

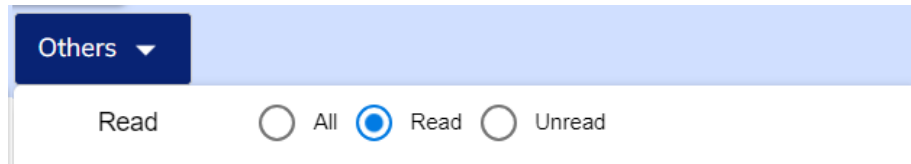
- ☒ none ?
- ☐ any scenario ?
- ☐ dominant ?
- ☐ recessive ?
- ☐ de novo ?
- ☐ compound het ?
- ☐ x linked ?

- None: Variants that are present in at least one selected sample
- Any scenario: Variants that match any scenario below (dominant/recessive/de novo/compound het/x linked)
- Dominant: Variants that are present in all affected individuals, and absent in the unaffected individuals
- Recessive: Variants that are homozygous in affected individuals, carried by the parents and not homozygous in unaffected individuals
- De novo: Variants that are present in all affected individuals, and not carried by the parents
- Compound het: pairs of variants affecting the same gene, one being carried by one parent, the second by the other parent, and both present in affected individuals.
- X linked: chromosome X recessive variants, carried by either affected sons and their mother, or by affected daughters (homozygous) and both their parents (and the father is affected). For dominant X-linked variants, use the “dominant” scenario while filtering on “chrX” in the Genomic location search box.

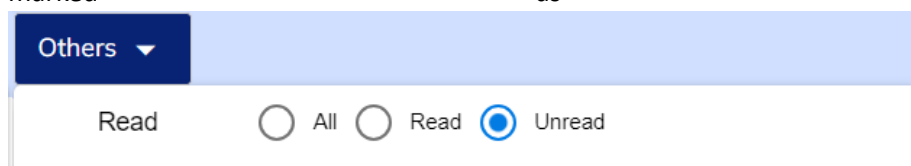
Control Panel



1. Mark selected variants as **Read**, which will showed with different background colour in the variants panel. In Filters Panel >> Others, there is a filtering option for selecting all variants marked as "Read".



2. Mark selected variants as **Unread**, which will showed with default background colour in the variants panel. In Filters Panel >> Others, there is a filtering option for selecting all variants marked as "Unread".



3. Export variants filtering results based on current applied filters as TSV or VCF
4. Column selection panel:

Column Selection

The Column Selection panel is divided into three main sections: **All Variant** (a), **Small Variant** (b), and **Structural Variant** (c). A refresh button (h) is located at the top right.

The panel contains three columns of column lists:

- Frozen Display Columns (Max:5)** (d): A list of columns that are frozen in the display.
- Display Columns (36)** (e): A list of columns that can be displayed. It includes a search bar and a list of columns such as Chr, Ref, Alt, Samples genotypes, Gene, HGVS, etc.
- Hidden Columns (89)** (f): A list of columns that are hidden. It includes a search bar and a list of columns such as Location, Variant type, Allelic depths, Genotype quality, Caller, SV Length, etc.

Each column in the Display and Hidden sections has a category tag (g) on the right, such as 'basic', 'genomic', or 'prioritization'. A 'Select a category' dropdown (g) is located at the top right of the Hidden Columns section.

At the bottom left, there is a note: "Swipe to change order". At the bottom right, there is a 'CLOSE' button (i).

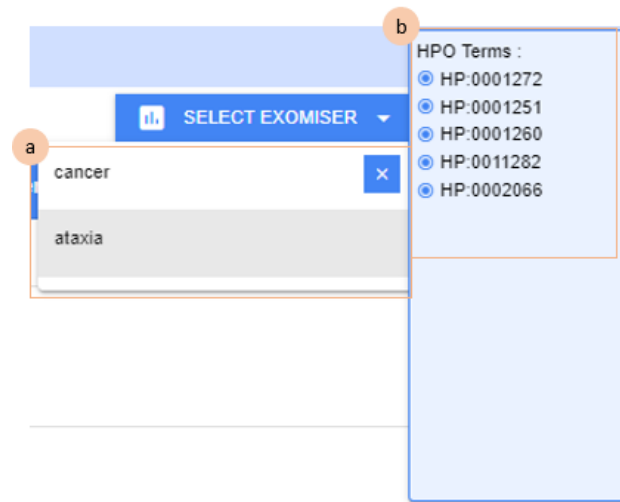
- a. Columns for display in the combined view of both small variants and structural variants
- b. Columns for display when viewing only small variants
- c. Columns for display when viewing only structural variants
- d. Freeze columns in the variants panel. Support maximum 5 frozen columns.

- e. Current selected columns for display. To add a column, drag a column from the “Hidden Columns” panel and then drop in the “Display Columns”, and vice versa. Columns can be reordered using drag-and-drop.
 - f. Columns that are currently hidden
 - g. Dropdown list for filtering the hidden columns by category
 - h. Restore button. Reset the column selection settings to default.
 - i. Close button. Close the column selection panel
- 5. Save bookmark button. For saving the current analysis settings, like filtering, sorting, and column selection options.
 - 6. Bookmark list button. For retrieving the saved analysis settings.
 - 7. Sharing button. Copy a URL to clipboard for sharing the current analysis state with others who have same access to the selected family. Another user who opens this URL can see the same filtering and prioritization results in the variants panel.

Exomiser Panel



1. Manage Exomiser jobs



- Select a job from the drop-down list of Exomiser jobs to display the corresponding Exomiser results in the [Variant Tables Page](#).
- The selected HPO terms for each of the Exomiser jobs

2. Submit Exomiser jobs

The image shows the 'Submit Exomiser jobs' form. It includes a 'Display Name *' field (labeled 'a'). Below it is a section titled '* Choose a way to input HPO Terms for Exomiser (Version: 2023-09-01)' (labeled 'b'). This section has four tabs: 'Upload File', 'Select HPO terms', 'Input HPO terms', and 'Select Gene Panels'. The 'Upload File' tab is active, showing an 'HPO file' input field with a file icon and a close button. A file size indicator shows '0 (0.0B)'. There is a link for 'Example File'. Below the tabs, there are two lines of text: '# Please notice that the Exomiser result is based on the original ped file uploaded with the above HPO terms.' and '* Each Exomiser run take about 10 mins to process'. At the bottom right, there are two buttons: 'RUN EXOMISER' (labeled 'c') and 'CLOSE'.

- Enter a name to define this Exomiser job.
- There are four ways to input HPO terms
 - Upload an HPO file
 - Select HPO terms from a drop-down list
 - Input HPO terms in string format, separated by commas, tabs or spaces.
 - Select gene panel(s)
- Execute the current Exomiser job

Variant Panel

1

Note	Chr	Start	End	Alt	Samples genotypes	Gene	HGVSc	MANE select	ExomAD SCombi	ExomAR SCombi	Highest AF	Z-score mis
4	chr6	1,610,393	1,610,393	T	5	FOXC1	c.-53C>T	NM_001453.3	9.9 10 ⁻⁴	9.9 10 ⁻⁴	6.8 10 ⁻⁶	
	chr1	193,203,898	193,203,898	G	6	CDC73	c.1030+46A>G	NM_024529.5	3.2 10 ⁻⁴	3.2 10 ⁻⁴	2.4 10 ⁻⁵	3.7315
	chr21	40,055,840	40,055,840	G		DSCAM	c.4920T>C	NM_001389.5	0.00118	0.00118	9.2 10 ⁻⁵	3.2228
	chr21	37,518,533	37,518,533	A		DYRK1A	c.*6002G>A	NM_001347721.2	0.00109	0.00109	1.9 10 ⁻⁴	
	chr9	134,812,759	134,812,759	TGTGTGT...		COL5A1	c.3852+52_3852+61dup	NM_000093.5	3.4 10 ⁻⁴	3.4 10 ⁻⁴	2.1 10 ⁻⁴	2.0682
	chr2	178,675,596	178,675,596	G		TTN	c.34637+75A>C	NM_001267550.2	1.7 10 ⁻⁴	1.7 10 ⁻⁴	6.9 10 ⁻⁴	-1.1021
	chr20	32,431,557	32,431,558	A		ASXL1	c.883-19del	NM_015338.6	4.2 10 ⁻⁵	4.2 10 ⁻⁵	0.00109	0.63581
	chr9	95,469,941	95,469,942	G		PTCH1	c.1728-11del	NM_000284.5	0.00256	0.00256	0.00113	1.6774
	chr12	13,753,999	13,753,999	G		GRIN2B	c.412-84G>C	NM_000834.5	4.5 10 ⁻⁵	4.5 10 ⁻⁵	0.00145	5.4168
	chr11	44,264,808	44,264,808	T		ALX4	c.*46G>A	NM_021926.4	0.0021	0.0021	0.00179	
Total: 2												
Showing: 14 / 14 (Total: 182618)												

789

1. Select variants to mark as "Read"/"Unread"
2. Click column names to sort by values. The arrow next to the column name indicates the sorting direction, which can be changed by clicking. Multi-column sorting is supported. The rightmost digit in the column header represents the sorting priority. To cancel column sorting, click the digit of the column header.
3. Detail information of the variant.
 - Small Variant: Show annotated transcripts information. Non-MANE transcripts are hidden by default. Click the "Show more transcripts" to view all transcripts.

Detail Information :

Position: chr9:95469941-95469942

Type: snp

Gene: PTCH1

Search Gene Table

Gene	Gene Ensembl	Gene Entrez	Transcript Ensembl	HGVSc	HGVSp	PolyPhen pred	PolyPhen score	SIFT pred
PTCH1	ENSG00000185920	5727	ENST00000331920	c.1729-11del				
PTCH1	ENSG00000185920	5727	ENST00000437951	c.1726-11del				

Records per page: 100 1-2 of 2

+ SHOW MORE TRANSCRIPTS

- Structural Variant: Show annotated gene, related variants (overlapped external database records like Decipher), external sources, exon overlap, clinical interpretation, AF and Exomiser results.

Detail Information:

Position: chr1:108190703-108194629
Type: DEL
Ref: T

[Close](#)

[blast search](#)

Gene: SLC25A24

Search Gene Table

Gene	Gene Ensembl	Gene Entrez	Transcript Ensembl	Strand	Clingen HI	Clingen TS	pHaplo	pTripto	gnomAD pLI	gnomAD LOEUF	Annotation Overlap	Reciprocal Overlap	Is MANE Plus Clinical
SLC25A24	ENSG00000285491	29957	ENST00000265488				0.3182	0.21449	3.3527e-12	1.126	0.05921	0.05921	false

Records per page: 100 1-1 of 1

[+ SHOW MORE TRANSCRIPTS](#)

External Sources:

Source	Start	Source End	Length	Annotation Overlap	Reciprocal Overlap
DECIPHER	108190733	108194783	4051	0.962	0.962

Records per page: All 1-1 of 1

Exon Overlap:

Allele Frequency:



Source	Start	Source End	Length	Type	AF	Sample Count	Annotation Overlap	Reciprocal Overlap
1KGP - East Asian	108190704	108194829	3926	DEL	0.497	504	1	1
1KGP - Global	108190704	108194829	3926	DEL	0.317	2500	1	1
1KGP - Survtiper - East Asian	108190704	108194829	3910	DEL	0.495	504	1	1
1KGP - Survtiper - Global	108190704	108194829	3910	DEL	0.312	2500	1	1
DGV Gold (inner)	108190666	108194837	3972	Loss	0.236		0.988	0.988

- Note button. Click to save a note for a variant. In Filters Panel >> Others, there is a filtering option for selecting all variants with notes.

Note ☐ All ☒ Yes ☐ No

- Genotypes. Each column represents one sample, and each square represents an allele. A square is filled if the allele is present. Affected sample is showed in colour red, and unaffected sample is showed in colour blue. User can click the value to view the details, like sample name and family relationship.

Details chr1:948519
T → G
NOC2L

Name	Genotype	Parents
♀ sample1		♀ sample3 ♂ sample2
♀ sample3		Mother

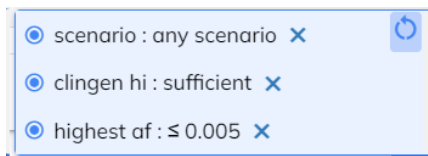
- Annotated gene. Click the gene symbol can open a pop-up window for linking to external databases like Clingen, OMIM, GeneReview etc.

Details chr1:965337
CTTAT → C

Symbol:	KLHL17
Ensembl:	ENSG00000187961
Entrez:	339451
OMIM:	Search...
ClinGen:	Search...
GeneReview:	Search...
UK PanelApp:	Search...
AU PanelApp:	Search...
ClinVar:	Search...
MASTERMIND:	Search by gene...

- Expand button: load more variants into the variant list for scrolling.
- Full screen button: show the variants panel in full screen mode.

- Filter summary button: show all the applied filters. User can click the delete button to remove filter or the reset button to clear all filters when necessary.



Reads alignment: Integrative Genomics Viewer (IGV)

If the local path of cram files is provided, user can view reads alignment of variants through Integrative Genomics Viewer (IGV). To use this feature, user first needs to click the “Load Cram” button on the top right corner of the variants table.

Note	Chr	Start	End	Ref	Alt	Samples genotypes	Gene	HGVSc	HGVSp	Existing variation	MANE select	CGD Agegroup	CGD Inheritance	CGD Manifestationcategory	ExomAD SComb	ExomAR SComb
<input type="checkbox"/>	chr1	70,728	70,728	G	T		OR4F5	c.720C>T		rs1259734071	NM_001005484.2				3.1 10 ⁻⁴	3.1 10 ⁻⁴
<input type="checkbox"/>	chr1	70,761	70,761	T	C		OR4F5	c.753T>C		rs1179234811	NM_001005484.2				3.1 10 ⁻⁴	3.1 10 ⁻⁴
<input type="checkbox"/>	chr1	939,442	939,499	C												
<input type="checkbox"/>	chr1	924,024	924,024	C	G		SAMD11	c.408C>G		rs71509444	NM_001385641.1			0	0	
<input type="checkbox"/>	chr1	924,310	924,310	C	G		SAMD11	c.122C>G		rs71509445	NM_001385641.1			0	0	
<input type="checkbox"/>	chr1	924,321	924,321	C	G		SAMD11	c.111C>G		rs71509446	NM_001385641.1			0	0	
<input type="checkbox"/>	chr1	924,533	924,533	A	G		SAMD11	c.102A>G	p.Pro34=	rs112703963	NM_001385641.1			0	0	
<input type="checkbox"/>	chr1	925,036	925,036	G	A		SAMD11	c.517+88G>A		rs61454428	NM_001385641.1			0	0	
<input type="checkbox"/>	chr1	930,939	930,939	G	A		SAMD11	c.792-100G>A		rs9988021	NM_001385641.1			0	0	
<input type="checkbox"/>	chr1	934,964	934,964	A			SAMD11									
<input type="checkbox"/>	chr1	935,954	935,954	G	T		SAMD11	c.967+58G>T		rs40723838/CCSV9704945	NM_001385641.1			0	0	

Then user can specify the local storage location of the cram files and the cram index files in the pop-up panel.

Family	Sample	Affected	Sex	Mother	Father	Cram File	Cram Index
<input checked="" type="checkbox"/> NA12878_NA12891_NA12892	<input checked="" type="checkbox"/> NA12878	<input type="radio"/> No <input checked="" type="radio"/> Yes	♀	NA12892	NA12891	<input type="text" value="Cram file"/> X	<input type="text" value="Cram index file"/> X
<input checked="" type="checkbox"/> NA12878_NA12891_NA12892	<input checked="" type="checkbox"/> NA12892	<input checked="" type="radio"/> No <input type="radio"/> Yes	♀			<input type="text" value="Cram file"/> X	<input type="text" value="Cram index file"/> X
<input checked="" type="checkbox"/> NA12878_NA12891_NA12892	<input checked="" type="checkbox"/> NA12891	<input checked="" type="radio"/> No <input type="radio"/> Yes	♂			<input type="text" value="Cram file"/> X	<input type="text" value="Cram index file"/> X

After that, user can view reads alignment of a variant by double clicking a row in the variants panel. An IGV will be opened with one track per sample, centred at the selected variant's position.

