

Unified Variant Interpretation Platform

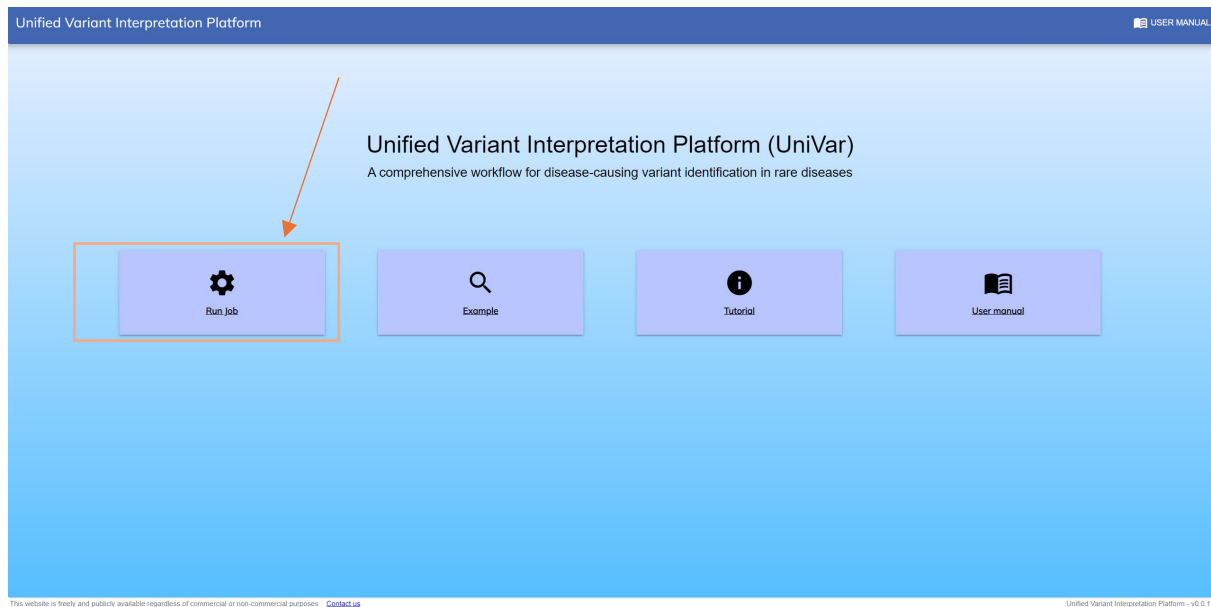
Tutorial

Version: 1.0

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How to submit sample data?



1. On the Landing Page, click the “Run Job” button

2. On the Sample Upload Page, user is required to upload one PED file, one HPO file and at least one VCF file of small variants or structural variants. Example file of each type can be downloaded through the hyperlink next to each file selection box. VCF files need to follow the predefined filename format as stated below the file selection box.

[↑ 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

3. After uploading sample data, user can view the job status on the job status dashboard. User is required to bookmark or save the provided URL to retrieve the job status later. If the job is finished, user can click the sample name to enter the variants table page to browser the annotated results.

How to interpret the annotated results?

Unified Variant Interpretation Platform

USER MANUAL

Select Samples
NA12878_info_1702547898135-08a2c544aa49

Total 3 Not affected 2 Affected 1

Filtering chr1:11000-118043 or OR4F5,OR4F29

Gene Panel Scenario Frequency Quality Impact Pathogenicity Prioritization Others

Read Un-read Export

Note	Chr	Start	End	Ref	Alt	Samples genotypes	Gene	HGVSc	HGVSp	Existing variation	MANE select	CGD Age-group	CGD Inheritance	CGD Manifestationcategory	ExomAD SComb	ExomAR SComb
	chr1	70,728	70,728	C	T		OR4F5	c.*720C>T		rs1259734071	NM_001005484.2				3.1 10 ⁻⁴	3.1 10 ⁻⁴
	chr1	70,761	70,761	T	C		OR4F5	c.*753T>C		rs1179234811	NM_001005484.2				3.1 10 ⁻⁴	3.1 10 ⁻⁴
	chr1	836,442	839,499	C												
	chr1	924,024	924,024	C	G		SAMD11	c.*408C>G		rs17509444	NM_001385641.1				0	0
	chr1	924,310	924,310	C	G		SAMD11	c.*122C>G		rs17509445	NM_001385641.1				0	0
	chr1	924,321	924,321	C	G		SAMD11	c.*111C>G		rs17509448	NM_001385641.1				0	0
	chr1	924,533	924,533	A	G		SAMD11	c.*102A>G	p.Pro34=	rs112703963	NM_001385641.1				0	0
	chr1	925,036	925,036	G	A		SAMD11	c.*517+88G>A		rs6146428	NM_001385641.1				0	0
	chr1	930,939	930,939	G	A		SAMD11	c.*752-100G>A		rs9688021	NM_001385641.1				0	0
	chr1	934,064	934,904	A			SAMD11									
	chr1	935,954	935,954	G	T		SAMD11	c.*967+58G>T		rs4072383&COSV59704945	NM_001385641.1				0	0

Showing 300 / 168486 (Total : 168486)

In the variants table page, variants are displayed as tabular form. Each row represents one variant, and each column represents different variant annotations. User can make use of the filtering options provided in the filtering panel to narrow down the scope of study. Some filtering presets are provided for filtering likely pathogenic variants. For example, the “HKGI_BASIC_FILTER” filters variants based on allele frequencies, mode of inheritance and Clingen haploinsufficiency scores.

chr1:11000-118043

Basic (SNP)

Haploinsufficiency (SNP)

LoF + 5UTR (SNP)

LoF (SNP)

HKGI_FILTER

HKGI_SV_FILTER

HKGI_SNP_FILTER

HKGI_BASIC_FILTER

highest af : ≤ 0.005

scenario : any scenario

clingen hi : sufficient

Unified Variant Interpretation Platform

USER MANUAL

Select Samples
NA12878_info_1702547898135-08a2c544aa49

Total 1 Not affected 2 Affected 1

Filtering

chr1:11000-118043 or OR4F5,OR4F29

Gene Panel Scenario Frequency Quality Import Pathogenicity Prioritization Others

Read Un-read Export

Note	Chr	Start	End	Ref	Alt	Samples genotypes	Gene	HGVSc	HGVSp	Existing variation	MANE select	CGD Agegroup	CGD Inheritance	CGD Manifestationcategory	ExomAD SC
							Total: 2 PKD1 TSC2	c.12765C>T	p.Pro425S	rs6203811	NM_001009944.3	Pediatric	AD	Cardiovascular&Gastrointestin...	3.4 10 ⁻⁴
	chr6	2,088,874	2,088,874	G	A										
	chr6	79,003,673	79,003,673	C	A		PHIP	c.1653+57G>T		rs72902893	NM_017934.7	N/A	AD	Craniofacial&Musculoskeletal&...	7.3 10 ⁻⁴
	chr21	37,519,746	37,519,746	T	TG		DYRK1A	c.*7215_*7216insG		rs1569413785	NM_001347721.2	N/A	AD	Craniofacial&Neurologic	0.00106
							Total: 2 ZBTB32 KMT2B	c.1092G>A	p.Pro364S	rs2234374	NM_014383.3				3.2 10 ⁻⁴
	chr11	44,264,808	44,264,808	C	T		ALX4	c.*46G>A		rs72605941&COSV100240916	NM_021926.4	N/A	AD/AR	Craniofacial&Dermatologic&...	0.0021
	chr12	13,753,999	13,753,999	C	G		GRIN2B	c.412-84G>C		rs3026184	NM_000834.5	N/A	AD	Neurologic	4.5 10 ⁻⁴
	chr9	95,409,941	95,409,942	GA	G		PTCH1	c.1729-11del		rs77900277&COSV59495096	NM_000264.5	Pediatric	AD	Craniofacial&Dermatologic&E...	0.00256
	chr20	32,431,557	32,431,558	AT	A		ASXL1	c.883-19del		rs57957589	NM_015338.6	N/A	AD	Craniofacial&Dermatologic&...	4.2 10 ⁻⁴
	chrX	29,802,906	29,802,906	T	TATATAT...		IL1RAPL1								

Showing 39 / 39 (Total : 168486)

In the example dataset, after applying the “HKGI_BASIC_FILTER” preset, the total number of variants drops down to 39 from 168486. User can still adjust the applied filtering options after applying the preset.

Unified Variant Interpretation Platform

USER MANUAL

Select Samples
NA12878_info_1702547898135-08a2c544aa49

Total 3 Not affected 2 Affected 1

Filtering chr1:11000-118043 or OR4F5,OR4F29

Gene Panel Scenario Frequency Quality Impact Pathogenicity Prioritization Others

Read Un-read Export

Note	Chr	Start	End		HGVSc	HGVSp	MANE select	ExomAD Scombi	ExomAR Scombi	gnomAD AF v.2	gnomAD AF (EAS) v.2	gnomAD AF (AFR) v.2	gnomAD AF (AMR) v.2	gnomAD AF
	chr9	95,469,941	95,469,942		c.1729-11del		NM_000264.5	0.00256	0.00256	0.00113	1.2·10 ⁻⁴	6.7·10 ⁻⁴		0.002
	chr11	44,264,808	44,264,808		c.*46G>A		NM_021926.4	0.0021	0.0021	0.00162	1.7·10 ⁻⁴	9.4·10 ⁻⁴	7.4·10 ⁻⁴	0.002
	chr21	40,055,840	40,055,840		c.4920T>C	p.Ser1640=	NM_001389.5	0.00118	0.00118	7.2·10 ⁻⁴	6.6·10 ⁻⁴			1.6·10 ⁻⁴
	chr21	37,518,533	37,518,533		c.*6002G>A		NM_001347721.2	0.00109	0.00109					
	chr21	37,519,746	37,519,746		c.*7215_*7216insG		NM_001347721.2	0.00109	0.00109					
	chr6	1,610,393	1,610,393		c.-53C>T		NM_001453.3	9.9·10 ⁻⁴	9.9·10 ⁻⁴					
	chr6	79,003,673	79,003,673		c.1653+57G>T		NM_017934.7	7.3·10 ⁻⁴	7.3·10 ⁻⁴					
	chr4	113,381,391	113,381,391		c.11860-66T>C		NM_001148.6	3.4·10 ⁻⁴	3.4·10 ⁻⁴					
	chr16	2,089,874	2,089,874		c.12765C>T	p.Pro425=	NM_001009944.3	3.4·10 ⁻⁴	3.4·10 ⁻⁴	0.00379		0.00117	0.00133	0.007
	chr9	134,812,759	134,812,759		c.3852+52_3852+61dup		NM_000093.5	3.4·10 ⁻⁴	3.4·10 ⁻⁴					

Showing 39 / 39 (Total : 168486)

Besides, user can click the column header to sort the variants list. 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. So in the above example, variants are sorted by Exomiser combined AD scores in descending order and then sorted by gnomAD v.2 AF in ascending order. To cancel column sorting, click the digit of the column header.

Gene	HGVSc
PTCH1	c.1729-11del
Details chr9:95469941 GA → G Symbol: PTCH1 Ensembl: ENSG00000185920 Entrez: 5727 OMIM: Search... ClinGen: Search... GeneReview: Search... UK PanelApp: Search... AU PanelApp: Search... ClinVar: Search... MASTERMIND: Search by gene...	

Upon identifying the interesting variants, user can click the hyperlinks (in blue colour) like gene symbol, chromosome, HGVSc or HGVSp on each row to navigate to external databases for cross-checking.

To validate the variants visually, 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.

Unified Variant Interpretation Platform USER MANUAL

Select Samples: NA12878_tfo_1702547898135-08a2c544aa49 Total: 3 Not affected: 2 Affected: 1

Filtering: chr1:11000-118043 or OR4F5,OR4F29 Gene Panel Scenario Frequency Quality Impact Pathogenicity Prioritization Others

Read Un-read Export Load Cram

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	C	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	839,442	839,499	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		rs61464428	NM_001385641.1			0	0	
<input type="checkbox"/>	chr1	930,939	930,939	G	A		SAMD11	c.*782>100G>A		rs9988021	NM_001385641.1			0	0	
<input type="checkbox"/>	chr1	934,064	934,064	A			SAMD11									
<input type="checkbox"/>	chr1	935,954	935,954	G	T		SAMD11	c.*967>58G>T		rs4072383&CCSV59704945	NM_001385641.1			0	0	

Showing: 300 / 168486 (Total: 168486)

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

Samples selection: Total: 3 Not Affected: 2 Affected: 1 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	Cram file <input type="text"/>	Cram index file <input type="text"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/> NA12878_NA12891_NA12892	<input checked="" type="checkbox"/> NA12892	<input type="radio"/> No <input type="radio"/> Yes	♀		Cram file <input type="text"/>	Cram index file <input type="text"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/> NA12878_NA12891_NA12892	<input checked="" type="checkbox"/> NA12891	<input type="radio"/> No <input type="radio"/> Yes	♂		Cram file <input type="text"/>	Cram index file <input type="text"/>

CLOSE

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.

