

Variant Curation Interface

Help Documentation - November 2016

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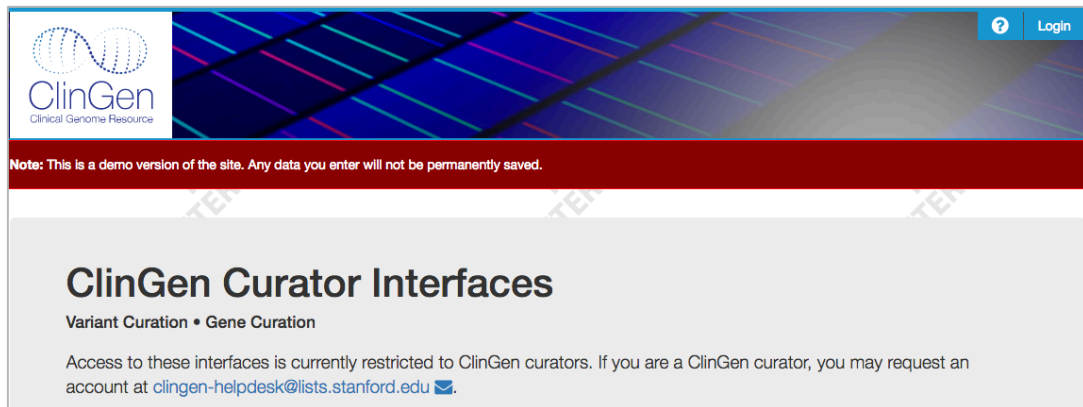
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*Feedback / Comments?*Please email us at: clingen-helpdesk@lists.stanford.edu

GENERAL NAVIGATION

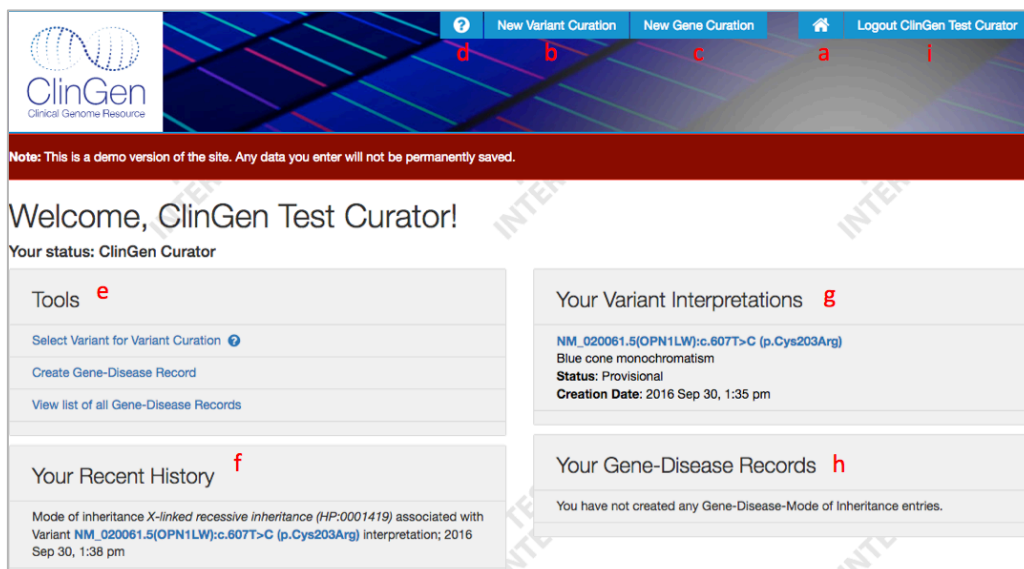
1. Logging in to the interfaces

Go to curation.clinicalgenome.org and click the “Login” button. If you are registered but have not yet created a Persona account, you will be prompted to do so.



2. Dashboard view

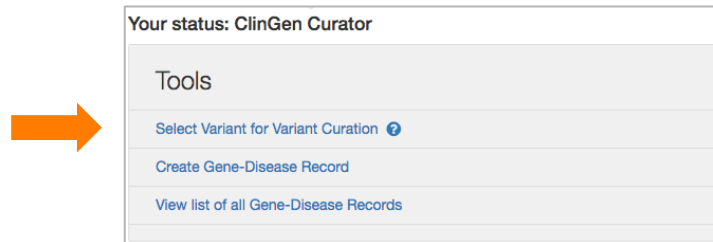
- a. Dashboard home – available from all pages
- b. Navigating to “Select Variant for Variant Curation” – available from all pages
- c. Navigating to “Create Gene-Disease Record” – available from all pages
- d. Navigating to this Help documentation online – available from all pages
- e. Tools – useful links
- f. View of your recent history
- g. View of your current Variant Interpretation curation records
- h. View of your current Gene-Disease curation records
- i. Logout – available from all pages



SELECTING A VARIANT FOR VARIANT CURATION

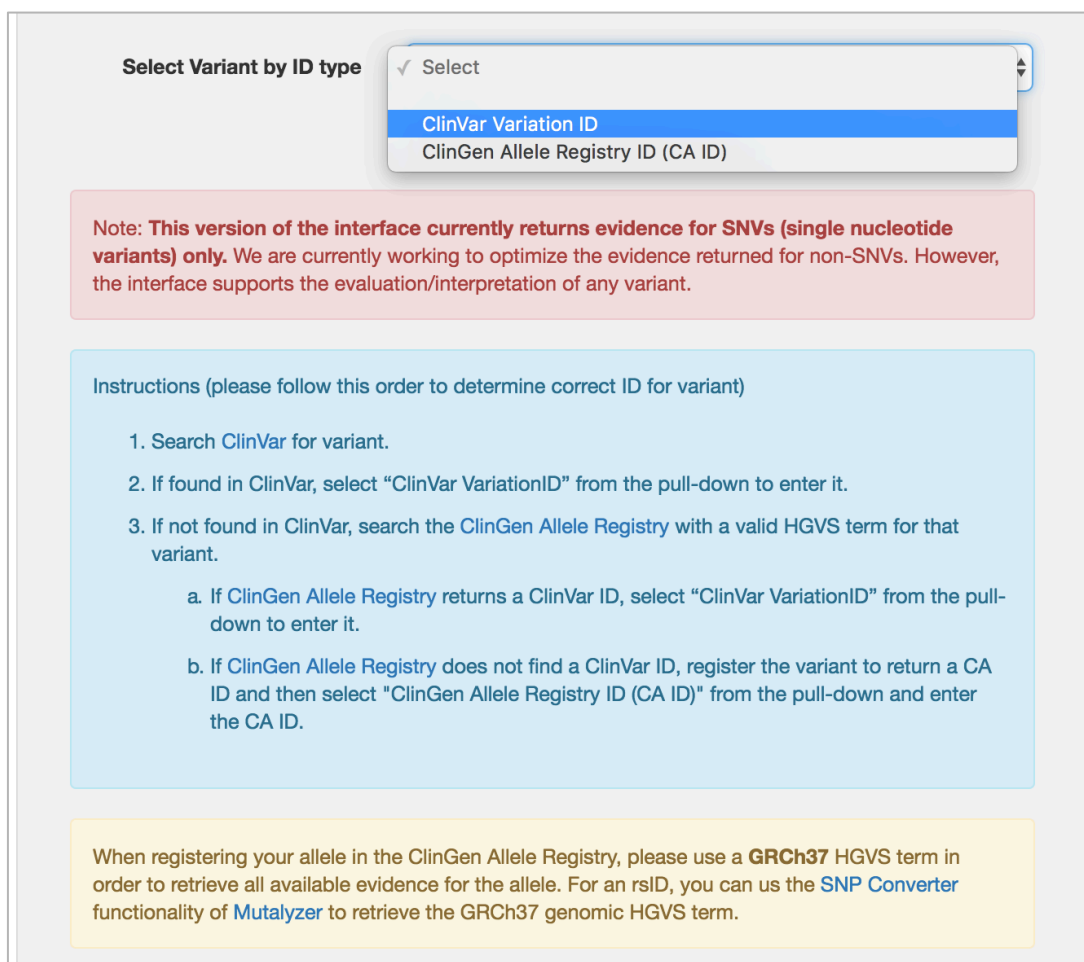
1. Begin variant curation

Select “Select Variant for Variant Curation” under the “Tools” Section



2. Select variant ID

Read instructions carefully on how to select a variant, and then choose whether you want to enter a ClinVar variant using a ClinVar Variation ID or a novel variant that you have registered with Baylor’s [ClinGen Allele Registry](#). Select “Add ClinVar ID.”

A screenshot of a web interface for selecting a variant ID. At the top, there is a section titled "Select Variant by ID type" with a dropdown menu. The dropdown menu is open, showing three options: "Select" (with a checkmark), "ClinVar Variation ID" (highlighted in blue), and "ClinGen Allele Registry ID (CA ID)". An orange arrow points from the right towards the "ClinVar Variation ID" option. Below the dropdown menu is a red box with a note: "Note: This version of the interface currently returns evidence for SNVs (single nucleotide variants) only. We are currently working to optimize the evidence returned for non-SNVs. However, the interface supports the evaluation/interpretation of any variant." Below the note is a blue box with instructions: "Instructions (please follow this order to determine correct ID for variant)" followed by a numbered list: 1. Search ClinVar for variant. 2. If found in ClinVar, select "ClinVar VariationID" from the pull-down to enter it. 3. If not found in ClinVar, search the ClinGen Allele Registry with a valid HGVS term for that variant. a. If ClinGen Allele Registry returns a ClinVar ID, select "ClinVar VariationID" from the pull-down to enter it. b. If ClinGen Allele Registry does not find a ClinVar ID, register the variant to return a CA ID and then select "ClinGen Allele Registry ID (CA ID)" from the pull-down and enter the CA ID. At the bottom is a yellow box with a note: "When registering your allele in the ClinGen Allele Registry, please use a GRCh37 HGVS term in order to retrieve all available evidence for the allele. For an rsID, you can use the SNP Converter functionality of Mutalyzer to retrieve the GRCh37 genomic HGVS term."

Type in the variant ID (ClinVar VariationID or CA ID, depending on selection); click “Retrieve from ClinVar” (or “Retrieve from ClinGen Allele Registry, if you have entered a CA ID). Once you are convinced the ID you have entered represents the correct variant, select “Save and View Evidence.”

ClinVar Variant

Enter ClinVar VariationID *

10505

Retrieve from ClinVar

Below are the data from ClinVar for the VariationID you submitted. Select "Save and View Evidence" below if it is the correct variant, otherwise revise your search above:

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)

ClinVar Variant ID	10505
HGVS terms	NC_000023.11:g.154154602T>C (GRCh38)
	NC_000023.10:g.153420077T>C (GRCh37)
	NG_009105.2:g.15352T>C
	NM_020061.5:c.607T>C
	NP_064445.2:p.Cys203Arg
	NG_009105.1:g.15353T>C
	NM_020061.4:c.607T>C
	NP_064445.1:p.Cys203Arg

Cancel Save and View Evidence

3. You will now be in the “Evidence View” for your selected variant (see next section)

GENERAL ORGANIZATION OF INFORMATION AND EVIDENCE

1. Overall tab organization


Once you are in the “Evidence View,” you will see the information and evidence for the selected variant is organized into various tabs. These include: **Basic Information**, **Population**, **Predictors**, **Experimental**, **Segregation/Case**, and **Gene-centric**. Click between the tabs to view different types of information and evidence.

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
Evidence View

Variant ID Sources	Variant Genomic Context	All Existing Interpretations
ClinVar VariationID: 10505 dbSNP ID: rs121434621	UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37]	Blue cone monochromatism-X-linked recessive inheritance, ClinGen Test Curator , Provisional Interpretation, last edited: 2016 Sep 30, 1:40 pm

Evidence View Interpretation ↕

Basic Information	Population	Predictors	Experimental	Segregation/Case	Gene-centric
Genomic NC_000023.11:g.154154602T>C (GRCh38) NC_000023.10:g.153420077T>C (GRCh37)					



2. Predictors tab: sub-tab organization by variant type


The Predictors tab contains sub-tabs such that you can look at the appropriate evidence and evaluate the appropriate criteria according to the variant type (**Missense**, **Loss of Function**, **Silent & Intron**, and **In-frame indel**).

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
Evidence View

Variant ID Sources	Variant Genomic Context	All Existing Interpretations
ClinVar VariationID: 10505 dbSNP ID: rs121434621	UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37]	Blue cone monochromatism-X-linked recessive inheritance, ClinGen Test Curator , Provisional Interpretation, last edited: 2016 Sep 30, 5:58 pm

Evidence View

Basic Information	Population	Predictors	Experimental	Segregation/Case	Gene-centric																																
<div>Missense Loss of Function Silent & Intron In-frame Indel</div> <div>Functional, Conservation, and Splicing Predictors</div> <table border="1"><thead><tr><th colspan="4">ClinGen Predictors</th></tr><tr><th>Source</th><th>Score Range</th><th>Score</th><th>Prediction</th></tr></thead><tbody><tr><td>REVEL (meta-predictor)</td><td>0 to 1</td><td>0.71</td><td>higher score = higher pathogenicity</td></tr></tbody></table> <table border="1"><thead><tr><th colspan="4">Other Predictors 🟢</th></tr><tr><th>Source</th><th>Score Range</th><th>Score</th><th>Prediction</th></tr></thead><tbody><tr><td>SIFT</td><td>--</td><td>--</td><td>D</td></tr><tr><td>PolyPhen2-HDIV</td><td>--</td><td>1</td><td>D</td></tr><tr><td>PolyPhen2-HVAR</td><td>0 to 1</td><td>0.982</td><td>D</td></tr></tbody></table>						ClinGen Predictors				Source	Score Range	Score	Prediction	REVEL (meta-predictor)	0 to 1	0.71	higher score = higher pathogenicity	Other Predictors 🟢				Source	Score Range	Score	Prediction	SIFT	--	--	D	PolyPhen2-HDIV	--	1	D	PolyPhen2-HVAR	0 to 1	0.982	D
ClinGen Predictors																																					
Source	Score Range	Score	Prediction																																		
REVEL (meta-predictor)	0 to 1	0.71	higher score = higher pathogenicity																																		
Other Predictors 🟢																																					
Source	Score Range	Score	Prediction																																		
SIFT	--	--	D																																		
PolyPhen2-HDIV	--	1	D																																		
PolyPhen2-HVAR	0 to 1	0.982	D																																		



OVERALL WORKFLOW

Once you have selected a variant, there are currently 3 major modes:

1. Evidence View (described above)
2. Interpretation
3. Interpretation with Disease Association

1. Evidence View (see above)

In this mode, you can view all the evidence associated with a variant, clicking between tabs. The ACMG criteria do not appear in this mode.

2. Interpretation Mode

To begin an Interpretation in which you can evaluate the evidence according to the ACMG criteria, select “Interpretation +” (see arrow below).

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
Evidence View

Variant ID Sources
ClinVar VariationID: 10505
dbSNP ID: rs121434621

Variant Genomic Context
UCSC [GRCh38/hg38 | GRCh37/hg19]
Variation Viewer [GRCh38 | GRCh37]
Ensembl Browser [GRCh38 | GRCh37]

All Existing Interpretations
Blue cone monochromatism-X-linked recessive inheritance, ClinGen Test Curator ,
Provisional Interpretation, last edited: 2016 Sep 30, 1:40 pm

Evidence View

Interpretation +

Basic Information

Population

Predictors

Experimental

Segregation/Case

Gene-centric

Genomic

NC_000023.11:g.154154602T>C (GRCh38)
NC_000023.10:g.153420077T>C (GRCh37)

Note: if you had previously begun an Interpretation for the variant, you can continue by selecting the pencil icon (see arrow below) next to your previous Interpretation in the ‘All Existing Interpretations’ table in the header.

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
Evidence View

Variant ID Sources
ClinVar VariationID: 10505
dbSNP ID: rs121434621

Variant Genomic Context
UCSC [GRCh38/hg38 | GRCh37/hg19]
Variation Viewer [GRCh38 | GRCh37]
Ensembl Browser [GRCh38 | GRCh37]

All Existing Interpretations
Blue cone monochromatism-X-linked recessive inheritance,
ClinGen Test Curator , In progress, last edited: 2016 Sep 30, 2:01 pm

Evidence View

Basic Information

Population

Predictors

Experimental

Segregation/Case

Gene-centric

Genomic

NC_000023.11:g.154154602T>C (GRCh38)
NC_000023.10:g.153420077T>C (GRCh37)

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)

This interpretation is not yet associated with a disease or mode of inheritance

e. View Summary

View Summary

Variant ID Sources		Variant Genomic Context		My Interpretation	
ClinVar VariationID: 10505 dbSNP ID: rs121434621	UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37]	Disease: Not associated Calculated Pathogenicity: None Modified Pathogenicity: None Status: In Progress Last Edited: 2016 Sep 30, 4:01 pm			

Misense in gene where primarily truncating cause disease

a. Criteria Bar

b. Progress Bar

c. Add Disease and Add Inheritance

Variant Interpretation Record

Disease + Inheritance +

Benign		Pathogenic		Calculated Pathogenicity	
No criteria met		No criteria met		None	
<input type="checkbox"/>		<input checked="" type="checkbox"/>		<input type="checkbox"/>	

Basic Information	Population	Predictors	Experimental	Segregation/Case	Gene-centric
<h4>Highest Minor Allele Frequency</h4> <p>Population: N/A # Variant Alleles: N/A Total # Alleles Tested: N/A</p> <p>Source: N/A Allele Frequency: 0</p> <p>Desired CI: <input type="text" value="95"/></p> <p>CI - lower: N/A CI - upper: N/A</p>					

Population Criteria Evaluation

c. Criteria Evaluation

BA1: Allele frequency is > 5% in ExAC, 1000 Genomes, or ESP	BA1: <input type="text" value="Not Evaluated"/>	MAF cutoff: <input type="text" value="5"/> %
PM2: Absent from controls (or at extremely low frequency if recessive) in ExAC, 1000 Genomes, or ESP	PM2: <input type="text" value="Not Evaluated"/>	Explanation: <input type="text"/>
BS1: Allele frequency greater than expected due to disorder	BS1: <input type="text" value="Not Evaluated"/>	

Save

EVALUATING CRITERIA

1. Criteria placement & organization

Criteria are grouped according to the evidence required for their evaluation and on the appropriate tab page.

The screenshot shows a web form titled "Population Criteria Evaluation". On the left, there is a light blue box containing three criteria descriptions: BA1 (Allele frequency is > 5% in ExAC, 1000 Genomes, or ESP), PM2 (Absent from controls or at extremely low frequency if recessive in ExAC, 1000 Genomes, or ESP), and BS1 (Allele frequency greater than expected due to disorder). Below these descriptions is a small orange button labeled "Disease-specific". To the right of this box are three dropdown menus for BA1, PM2, and BS1, each currently set to "Not Evaluated". Between these dropdowns are two "- or -" labels. To the right of the dropdowns is a "MAF cutoff:" field set to "5 %" and an "Explanation:" text area. A blue "Save" button is located at the bottom right of the form.

2. Criteria evaluation choices:

The pull-downs allow the following criteria evaluation choices:

- **Not Evaluated:** The default state of an Evaluation is “Not Evaluated”
- **Met:** If the evidence supports a positive evaluation of a criterion at its original strength (e.g. PM2 = moderate strength in the pathogenic range), the curator should select “Met”
- **Not Met:** If the evidence does not support a positive evaluation of the criterion, the curators should select “Not Met.”
- **_Strong, _Moderate, _Supporting, _Very strong, _Stand-alone:** The strength of evaluation for a criterion can be adjusted by selecting one of the above representations of the criterion (e.g. PM2_Supporting would be PM2 evaluated at the “Supporting” level rather than its inherent level, Moderate. *Note: Benign criteria allow _Supporting, _Strong, and _Stand-alone adjustments. Pathogenic criteria allow _Supporting, _Moderate, and _Strong adjustments (except for PS2, which also allows _Very strong).*

Benign pull-down choices – example:

This screenshot shows the same form as before, but with the BA1 dropdown menu open. The menu lists five options: "Not Evaluated" (which is selected with a checkmark), "Met", "Not Met", "BA1_Supporting", and "BA1_Strong". The other parts of the form, including the PM2 and BS1 dropdowns, the MAF cutoff, and the Save button, remain the same.

Pathogenic pull-down choices – example:

BA1: Allele frequency is > 5% in ExAC, 1000 Genomes, or ESP

PM2: Absent from controls (or at extremely low frequency if recessive) in ExAC, 1000 Genomes, or ESP

BS1: Allele frequency greater than expected due to disorder

BA1: Not Evaluated

- or -

PM2: Not Evaluated

- or -

BS1: Not Evaluated

MAF cutoff: 5 %

Explanation:

Save

3. Steps for evaluating a criterion or criteria:

- Examine evidence associated with criteria being evaluated
- Select an evaluation for all criteria related to the evidence from the pull-down
- Select Save
- Note that the button will now change from “Save” to “Update” – if you would like to change an evaluation, change it and be sure to click “Update” after. The update button appears as a visual clue that the criterion/criteria for that section have already been evaluated.

Population Criteria Evaluation

BA1: Allele frequency is > 5% in ExAC, 1000 Genomes, or ESP

PM2: Absent from controls (or at extremely low frequency if recessive) in ExAC, 1000 Genomes, or ESP

BS1: Allele frequency greater than expected due to disorder

BA1: Met

- or -

PM2: Not Evaluated

- or -

BS1: Not Evaluated

MAF cutoff: 5 %

Explanation:

Evaluations for BA1, PM2, BS1 saved successfully!

Update

Note: When 2 (or more) criteria are opposites or cannot otherwise be “Met” at the same time, the interface will not allow “Met” to be selected for more than one of the criteria.

Population Criteria Evaluation

BA1: Allele frequency is > 5% in ExAC, 1000 Genomes, or ESP

PM2: Absent from controls (or at extremely low frequency if recessive) in ExAC, 1000 Genomes, or ESP

BS1: Allele frequency greater than expected due to disorder

BA1: Met

- or -

PM2: Met

- or -

BS1: Not Evaluated

MAF cutoff: 5 %

Explanation:

Only one of the criteria (BA1, PM2, or BS1) can have a value other than "Not Met" or "Not Evaluated"

Save

4. Additional note:

PS4 and PM2 may not both have positive evaluations – for instance, you will see this error if you select “Met” for PS2 (Population tab) and PM4 (Segregation/Case tab)

Case-control

PS4: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls

PS4: Met

Explanation:

PM4 cannot have a value other than "Not Met" or "Not Evaluated" because PM2 has already been evaluated as being Met

Save

CRITERIA BAR

As you Save your evaluations, you will notice that the Criteria bar will indicate which criteria have been “Met” (solid color background with white criteria code), “Not Met” (grey background with colored criteria code), or remain “Not Evaluated” (white background with colored criteria code).

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
This interpretation is not yet associated with a disease or mode of inheritance

View Summary

Variant ID Sources
ClinVar VariationID: 10505
dbSNP ID: rs121434621

Variant Genomic Context
UCSC [GRCh38/hg38 | GRCh37/hg19]
Variation Viewer [GRCh38 | GRCh37]
Ensembl Browser [GRCh38 | GRCh37]

My Interpretation
Disease: Not associated
Calculated Pathogenicity: Likely pathogenic
Modified Pathogenicity: None
Status: In Progress
Last Edited: 2016 Sep 30, 3:28 pm

Missense in gene where primarily truncating cause disease

BA1 BS1 BS2 BS3 BS4 BP1 BP2 BP3 BP4 BP5 BP6 BP7 PP1 PP2 PP3 PP4 PP5 PM1 PM2 PM3 PM4 PM5 PM6 PS1 PS2 PS3 PS4 PVS1

not met met not evaluated

Variant Interpretation Record

Disease Inheritance

CALCULATED PATHOGENICITY

As you Save your evaluation, you will notice the Progress bar will indicate the number of criteria met according to the strength of the evaluation and whether they are Benign or Pathogenic. Additionally, it will automatically calculate the Pathogenicity each time you Save or update an evaluation:

For instance, if PM2, PVS1 and PM1 are all met, the Progress bar would appear as follows immediately upon saving the last evaluation:

Variant Interpretation Record
Disease
Inheritance

Benign
No criteria met
 Pathogenic
Very strong: 1 Moderate: 2
 Calculated Pathogenicity
Pathogenic

The Calculated Pathogenicity outcomes are as follows:

1. Benign
2. Likely benign
3. Pathogenic
4. Likely Pathogenic
5. Uncertain significance – insignificant evidence: there is not enough evidence to meet any of the above (1-4); there can be conflicting evidence
6. Uncertain significance – conflicting evidence: there is enough evidence to meet the above (1-4), but some of it is conflicting

CURATION CHECKBOXES ON TAB PAGES

If you have evaluated all the evidence on a particular tab page to your satisfaction, you can click the checkbox at the bottom of the tab page (for the Predictor tab, this means you have evaluated any relevant sub-tabs to your satisfaction) and a check will appear on the tab for your reference:

Basic Information
Population
Predictors
Experimental
Segregation/Case
Gene-centric

Hotspot or functional domain

PM1: Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of enzyme) without benign variation

Disease-specific

PM1: Met
Explanation:

Update

Experimental Studies

BS3: Well established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing

Disease-specific

PS3: Well established *in vitro* or *in vivo* functional studies supportive of a damaging effect on the gene or gene product

Disease-specific

BS3: Not Evaluated
Explanation:

- or -

PS3: Not Evaluated

Save

Curated Literature Evidence (Experimental Studies)

Add PMID

Select "Add PMID" to curate and save a piece of evidence from a published article.

The evaluations on the Experimental tab have been reviewed to my satisfaction (optional)

This checkbox will remain regardless of which tab you are on in the interface and can be unchecked as well:

Basic Information	Population ✓	Predictors	Experimental ✓	Segregation/Case	Gene-centric
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ADDING DISEASE & MODE OF INHERITANCE

1. Interpretation with Disease Association

When you are ready to evaluate disease-specific criteria for your Interpretation, you can click the “Disease +” button to add the Orphanet ID for the disease. Be sure you’ve saved your evaluations before clicking this button.

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
This interpretation is not yet associated with a disease or mode of inheritance

Variant ID Sources
 ClinVar VariationID: 10505
 dbSNP ID: rs121434621

Variant Genomic Context
 UCSC [GRCh38/hg38 | GRCh37/hg19]
 Variation Viewer [GRCh38 | GRCh37]
 Ensembl Browser [GRCh38 | GRCh37]

My Interpretation
 Disease: Not associated
 Calculated Pathogenicity: Uncertain significance - insufficient evidence
 Modified Pathogenicity: None
 Status: In Progress
 Last Edited: 2016 Sep 30, 5:44 pm

BA1 BS1 BS2 BS3 BS4 BP1 BP2 BP3 BP4 BP5 BP6 BP7 PP1 PP2 PP3 PP4 PP5 PM1 PM2 PM3 PM4 PM5 PM6 PS1 PS2 PS3 PS4 PVS1

Variant Interpretation Record

☒ Benign
No criteria met

☒ Pathogenic
Moderate: 1 Supporting: 2

☐ Calculated Pathogenicity
Uncertain significance - insufficient evidence

Basic Information Population Predictors Experimental Segregation/Case Gene-centric

After clicking the “Associate with Disease” button, you will see an entry box pop up for entering an Orphanet ID. Enter the desired Orphanet ID and click OK.

Associate this interpretation with a different disease

Enter Orphanet ID

Now you will see the disease term under the variant name in the gray title area and in the green “My Interpretation” section:

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
This interpretation is associated with **Blue cone monochromatism**
View Summary

Variant ID Sources	Variant Genomic Context	My Interpretation
ClinVar VariationID: 10505 dbSNP ID: rs121434621	UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37]	Disease: Blue cone monochromatism, ORPHA16 Calculated Pathogenicity: Uncertain significance - insufficient evidence Modified Pathogenicity: None Status: <i>In Progress</i> Last Edited: 2016 Sep 30, 5:47 pm

2. Interpretation with Mode of Inheritance

You can add the mode of inheritance by clicking the “Inheritance +” button and selecting from the pull-down menu:

The screenshot shows a modal dialog titled "Associate this interpretation with a mode of inheritance". Inside the dialog, there is a "Mode of Inheritance" section with a dropdown menu. The dropdown is open, showing a list of inheritance modes. The selected option is "X-linked recessive inheritance (HP:0001419)". Other options include "No mode of inheritance", "Autosomal dominant inheritance (HP:0000006)", "Autosomal dominant inheritance with maternal imprinting (HP:0012275)", "Autosomal dominant inheritance with paternal imprinting (HP:0012274)", "Autosomal recessive inheritance (HP:0000007)", "Autosomal unknown", "Codominant", "Genetic anticipation (HP:0003743)", "Mitochondrial inheritance (HP:0001427)", "Multifactorial inheritance (HP:0001426)", "Sex-limited autosomal dominant (HP:0001470)", "Somatic mutation (HP:0001428)", "X-linked dominant inheritance (HP:0001423)", "X-linked inheritance (HP:0001417)", "Y-linked inheritance (HP:0001450)", and "Other".

Now you will see the mode of inheritance term under the variant name in the gray title area:

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
This interpretation is associated with **Blue cone monochromatism - X-linked recessive inheritance**
View Summary

EVALUATION SUMMARY/PROVISIONAL INTERPRETATION

If you have evaluated all the evidence to your satisfaction, you can click the “View Summary” button in the grey header to view a Summary of all your evaluations:

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
 This interpretation is associated with **Blue cone monochromatism** - *X-linked recessive inheritance*

[View Summary](#)

Variant ID Sources	Variant Genomic Context	My Interpretation
ClinVar VariationID: 10505 dbSNP ID: rs121434621	UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37]	Disease: Blue cone monochromatism, ORPHA16 Calculated Pathogenicity: Uncertain significance - insufficient evidence Modified Pathogenicity: None Status: <i>In Progress</i> Last Edited: 2016 Sep 30, 5:50 pm

Once in the Summary View, the “View Summary” button will change to a “Return to Interpretation” button. This can be used at any time to return to the “Evidence View”.

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
 This interpretation is associated with **Blue cone monochromatism** - *X-linked recessive inheritance*

[Return to Interpretation](#)

Variant ID Sources	Variant Genomic Context	My Interpretation
ClinVar VariationID: 10505 dbSNP ID: rs121434621	UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37]	Disease: Blue cone monochromatism, ORPHA16 Calculated Pathogenicity: Uncertain significance - insufficient evidence Modified Pathogenicity: None Status: <i>Provisional</i> Last Edited: 2016 Sep 30, 5:58 pm

At the bottom of the Summary page, all the ACMG criteria are split into three separate tables according their evaluation status:

1. **Criteria meeting an evaluation strength:** for criteria with evidence that supports a positive evaluation of the criteria

Criteria meeting an evaluation strength					
B/P	Criteria	Criteria Descriptions	Modified	Evaluation Status	Evaluation Explanation
✓	BA1	Allele frequency greater than 5% in a population database	Yes ↓	BA1_strong	
✓	PM1	Mutational hot spot or well-studied functional domain without benign variation	Yes ↑	PM1_strong	
✓	PP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product	No	Supporting	
✓	PP2	Missense in gene with low rate of benign missense variants and path. missenses common	No	Supporting	

2. **Criteria evaluated as “Not met”:** for criteria with evidence that does not support a positive evaluation of the criterion

Criteria evaluated as "Not met"					
B/P	Criteria	Criteria Descriptions	Modified	Evaluation Status	Evaluation Explanation
⊗	BS2	Observation in controls inconsistent with disease penetrance	N/A	Not Met	
⊗	PM5	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before	N/A	Not Met	

3. Criteria "Not yet evaluated": for criteria which have yet to be evaluated

Criteria "Not yet evaluated"					
B/P	Criteria	Criteria Descriptions	Modified	Evaluation Status	Evaluation Explanation
○	PVS1	Predicted null variant in a gene where LOF is a known mechanism of disease	N/A	Not Evaluated	
○	BS1	MAF is too high for disorder	N/A	Not Evaluated	
○	PS1	Same amino acid change as an established pathogenic variant	N/A	Not Evaluated	
○	BS3	Well-established functional studies show no deleterious effect	N/A	Not Evaluated	
○	BS4	Non-segregation with disease	N/A	Not Evaluated	
○	PS2	De novo (paternity and maternity confirmed)	N/A	Not Evaluated	
○	PS3	Well-established functional studies show a deleterious effect	N/A	Not Evaluated	
○	PS4	Prevalence in affecteds statistically increased over controls	N/A	Not Evaluated	

These tables summarize the evaluations made for each criteria into the following fields:

- **B/P:** The color of these icons, red for pathogenic and purple for benign, indicates whether each criteria is pathogenic or benign. "Met" criteria have ticks in a circle, "Not met" have crosses in a circle, and "Not evaluated" criteria have an empty circle.
- **Criteria:** All of the criteria are listed using their ACMG criteria codes, and their color indicates their pathogenicity on a scale from 'purple' benign to 'red' pathogenic.
- **Criteria Descriptions:** Short descriptions to explain the ACMG criteria
- **Modified:** 'yes' or 'no' indicates whether or not a criterion has been modified. If it has, then 'purple down arrows' indicate a benign modification, and 'red up arrows' indicate a pathogenic modification.
- **Evaluation Status:** Criteria are shown as "Met", "Not Met" and "Not evaluated". Additionally, "Met" indicates any modifications: _Strong, _Moderate, _Supporting, _Very strong, _Stand-alone.
- **Evaluation Explanation:** This shows the explanation provided by the curator when evaluating each criteria.

Above these Summary tables is an overview of the interpretation so far, including the pathogenicity calculations:

- a. Calculated Pathogenicity – the pathogenicity calculated based on all the evaluations saved so far
- b. Modified Pathogenicity – the pathogenicity selected by the curator
- c. Provisional Interpretation Status – indicates the current status of the Interpretation
- d. Disease – shows a disease where one has been associated with the variant
- e. Mode of inheritance – shows inheritance type where one has been associated with the variant
- f. Modify Pathogenicity – pull-down which allows curator to select the pathogenicity
- g. Explain reason(s) for change – allows curators to add free text to explain why they have selected an alternative pathogenicity to the one calculated
- h. Change status to “Provisional Interpretation” – this tick box allows curators to change the status of their Interpretation to “Provisional”
- i. Save – must be clicked to save a modification to the pathogenicity and/or a change in the status of the Interpretation

<p>a Calculated Pathogenicity: Uncertain significance - insufficient evidence</p> <p>b Modified Pathogenicity: None</p> <p>c Provisional Interpretation Status: In Progress</p>	<p>d Disease: Blue cone monochromatism</p> <p>e Mode of Inheritance: X-linked recessive inheritance (HP:0001419)</p>
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f Modify Pathogenicity: (optional) No Selection

g Explain reason(s) for change: (required for modified pathogenicity)

Note: If you selected a pathogenicity different from the Calculated Pathogenicity, you must provide a reason for the change here.

h Change status to "Provisional Interpretation" (optional): ☐

Note: If the Calculated Pathogenicity is "Likely Pathogenic" or "Pathogenic," a disease must first be associated with the interpretation before it can be marked as a "Provisional Interpretation". Please select "Return to Interpretation" to add a disease.

i Save

If the curator decides to select an alternative pathogenicity to the one calculated, they can do so by selecting an alternative option from the “Modify Pathogenicity” pull-down (f), however they must provide a reason for the change in the free text box (g) provided. The ‘Modified Pathogenicity’ (b) will only change to the new modified pathogenicity when the Save’ button (i) is clicked. Likewise once a curator feels they have fully evaluated the variant they can select the tick box to change the Interpretation status (c) to “Provisional”, but this will only be saved when the Save’ button (i) is clicked.

Upon saving a modified pathogenicity and/or change in the status of an interpretation the ‘Save’ button will change to an ‘Update’ button and an adjacent “Provisional changes updated successfully!” text will appear.

Calculated Pathogenicity: Uncertain significance - insufficient evidence

Modified Pathogenicity: Likely pathogenic

Provisional Interpretation Status: Provisional

Disease: Blue cone monochromatism

Mode of Inheritance: *X-linked recessive inheritance (HP:0001419)*

Modify Pathogenicity:
(optional)

Likely Pathogenic

Explain reason(s) for change:
(required for modified pathogenicity)

Because because because...

Change status to "Provisional Interpretation" *(optional)*: ☒

Note: If the Calculated Pathogenicity is "Likely Pathogenic" or "Pathogenic," a disease must first be associated with the interpretation before it can be marked as a "Provisional Interpretation". Please select "Return to Interpretation" to add a disease.

Provisional changes updated successfully!

Update



Feedback and Comments?

Please email us at: clingen-helpdesk@lists.stanford.edu