

# Variant Curation Interface

## Help Documentation - June 2017

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*Feedback / Comments?*

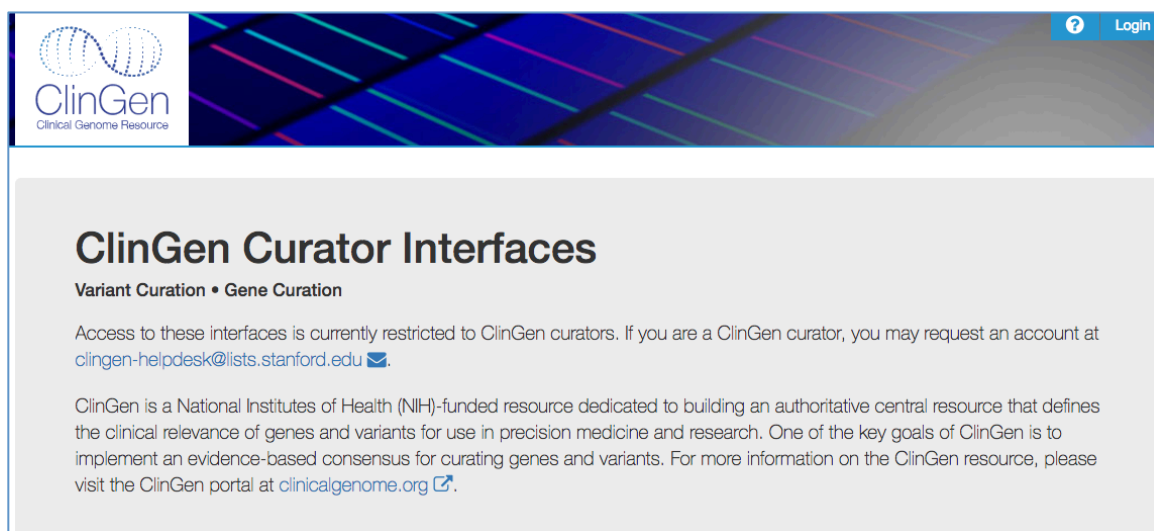
Please email us at: [clingen-helpdesk@lists.stanford.edu](mailto:clingen-helpdesk@lists.stanford.edu)

## GENERAL NAVIGATION

### 1. Logging in to the interfaces

To register for a ClinGen curator account you will need to send an email to [clingen-helpdesk@lists.stanford.edu](mailto:clingen-helpdesk@lists.stanford.edu). When you write to us please let us know your preferred email address (which you will use to log in to the interfaces), your preferred display name, and the ClinGen CDWG(s) with which you are affiliated. If your email is associated with a Google account, you can log in using Google.

We will write back to you to confirm that your email address has been registered and can now be used for logging in to the interfaces. You can then login to the interfaces via Google or the Auth0 authentication system; both options will appear when you click on the 'Login' button in the header.



You can also explore the ClinGen test/demo curation interfaces (<https://curation-test.clinicalgenome.org/>) without registering as a ClinGen curator (using the 'Demo Login' button in the header).



## 2. Dashboard view

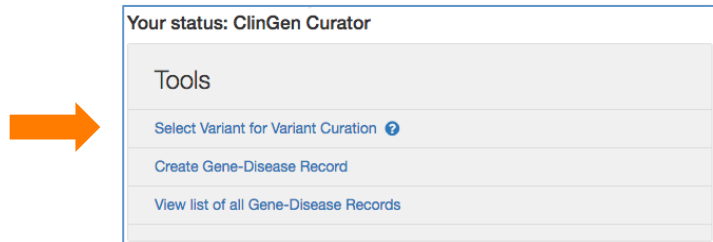
- a. Dashboard home – available from all pages
- b. Navigating to “Select Variant for Variant Curation” – available from all pages
- c. Navigating to “Create Gene-Disease Record” – available from all pages
- d. Navigating to this Help documentation online – available from all pages
- e. Tools – useful 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

The screenshot shows the ClinGen Test Curator dashboard. At the top, there is a navigation bar with the ClinGen logo, a help icon, and links for 'New Variant Curation', 'New Gene Curation', and 'Logout ClinGen Test Curator'. Below the navigation bar is a red banner with a note: 'Note: This is a demo version of the site. Any data you enter will not be permanently saved.' The main content area is titled 'Welcome, ClinGen Test Curator!' and shows the user's status as 'ClinGen Curator'. The dashboard is divided into four main sections: 'Tools' (with links for 'Select Variant for Variant Curation', 'Create Gene-Disease Record', and 'View list of all Gene-Disease Records'), 'Your Variant Interpretations' (showing a record for 'NM\_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)' with status 'Provisional' and creation date '2016 Sep 30, 1:35 pm'), 'Your Recent History' (showing a record for 'Mode of inheritance X-linked recessive inheritance (HP:0001419) associated with Variant NM\_020061.5(OPN1LW):c.607T>C (p.Cys203Arg) interpretation; 2016 Sep 30, 1:38 pm'), and 'Your Gene-Disease Records' (showing a message: 'You have not created any Gene-Disease-Mode of Inheritance entries.'). Red letters a-i are placed over the dashboard to indicate the location of various features: 'a' is over the 'Logout ClinGen Test Curator' link, 'b' is over the 'Select Variant for Variant Curation' link, 'c' is over the 'Create Gene-Disease Record' link, 'd' is over the help icon, 'e' is over the 'Tools' section header, 'f' is over the 'Your Recent History' section header, 'g' is over the 'Your Variant Interpretations' section header, 'h' is over the 'Your Gene-Disease Records' section header, and 'i' is over the 'Logout ClinGen Test Curator' link.

## SELECTING A VARIANT FOR VARIANT CURATION

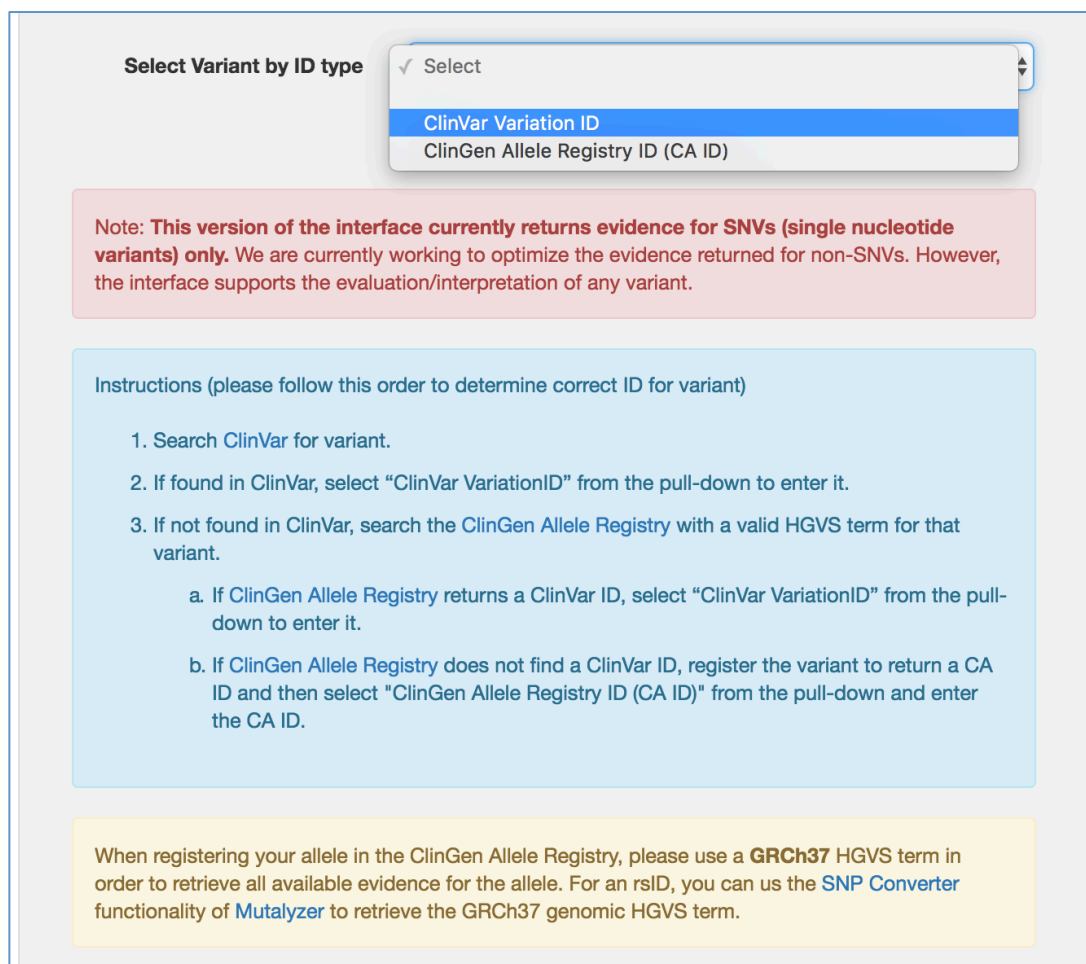
### 1. Begin variant curation

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 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 this is a light 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)**

<b>ClinVar Variant ID</b>	<b>10505</b>
<b>HGVS terms</b>	<a href="#">NC_000023.11:g.154154602T&gt;C (GRCh38)</a> <a href="#">NC_000023.10:g.153420077T&gt;C (GRCh37)</a> <a href="#">NG_009105.2:g.15352T&gt;C</a> <a href="#">NM_020061.5:c.607T&gt;C</a> <a href="#">NP_064445.2:p.Cys203Arg</a> <a href="#">NG_009105.1:g.15353T&gt;C</a> <a href="#">NM_020061.4:c.607T&gt;C</a> <a href="#">NP_064445.1:p.Cys203Arg</a>

Cancel Save and View Evidence

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

## GENERAL ORGANIZATION OF EVIDENCE (EVIDENCE VIEW PAGE)

### 1. Evidence View: Overall tab organization

*Note: The Evidence View is viewable by any logged in curator and includes both aggregated external evidence and evidence curated manually by individual curators (see “Overall Workflow” section for more details).*

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. Evidence View 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

Missense **Loss of Function** Silent & Intron In-frame Indel

**Functional, Conservation, and Splicing Predictors**

**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 (see previous section)
2. Interpretation
3. Interpretation with Disease Association

### 1. Evidence View (see previous section for tab organization)

*Note: The Evidence View is viewable by any logged in curator and includes both aggregated external evidence and evidence curated manually by individual curators.*

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

The Evidence View mode displays the following types of evidence:

#### External evidence

The curation interface aggregates evidence from external resources such as ExAC, 1000 Genomes, ESP, ClinVar, dbNSFP, etc. Each curator logged in to the interface can view this evidence when on the Evidence View pages.

#### Manually curated evidence

Any evidence a curator enters for a PubMed ID (PMID) when in Interpretation mode (see next section) will be viewable by all curators in the Evidence View. Note: Evaluations (i.e. PS4 “Met”) and Interpretations are specific to the curator who makes them and are not currently viewable by anyone other than the curator who made them. See below for more information regarding workflow.


### 2. Interpretation

*Note: An Interpretation is specific to the curator who creates it and can only be viewed or edited by that curator. This means that evaluations of the various criteria codes and the value of the interpretation (e.g. pathogenic) are specific to the curator who makes them and cannot be viewed by other curators.*

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

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

**Evidence View**


Basic Information	Population	Predictors	Experimental	Segregation/Case	Gene-centric
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**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

<b>Variant ID Sources</b> ClinVar VariationID: 10505 dbSNP ID: rs121434621	<b>Variant Genomic Context</b> UCSC [GRCh38/hg38   GRCh37/hg19] Variation Viewer [GRCh38   GRCh37] Ensembl Browser [GRCh38   GRCh37]	<b>All Existing Interpretations</b> Blue cone monochromatism-X-linked recessive inheritance, ClinGen Test Curator , <i>In progress</i> , last edited: 2016 Sep 30, 2:01 pm 
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**Interpretation** 

**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)



Once you click on "Interpretation +" or the pencil icon if you have previously begun an Interpretation, you will be in Interpretation mode (see next page).

Note: If another curator(s) has started/completed an Interpretation for the same variant, you will be able to see their name and the status of their Interpretation (*In progress*, *Provisional Classification*), but will not be able to view their Interpretation.



- Criteria bar – scroll over individual criteria codes to see a description for each criteria
- Interpretation Progress bar that indicates the strength of criteria met and the calculated pathogenicity
- The ACMG criteria evaluations where you can indicate whether an individual criterion is “Met” (*see next section, “Evaluating Criteria”*)
- “Disease +” and “Inheritance +” buttons for associating a Disease and Mode of Inheritance with the variant
- “View Summary” button to view a Summary of all the evaluations

**3. Evaluation Summary/Provisional Interpretation** (Please see Evaluation Summary/Provisional Interpretation Section, p. 16)

## EVALUATING CRITERIA

### 1. Criteria placement & organization

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

**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:** Not Evaluated

**PM2:** Not Evaluated

**BS1:** Not Evaluated

**MAF cutoff:** 5 %

**Explanation:**

**Save**

### 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:

**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

**PM2:** Not Evaluated

**BS1:** Not Evaluated

**MAF cutoff:** 5 %

**Explanation:**

**Save**

### 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

## 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).

The screenshot displays the 'Variant Interpretation Record' for the variant **NM\_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)**. The interface is divided into three main sections: 'Variant ID Sources', 'Variant Genomic Context', and 'My Interpretation'. Below these is a 'Criteria Bar' containing various criteria codes. A tooltip points to the 'BS2' criterion, stating 'Missense in gene where primarily truncating cause disease'. The 'Criteria Bar' shows the following status for each criterion: BA1 (not met), BS1 (not met), BS2 (not met), BS3 (not met), BS4 (not met), BP1 (not met), BP2 (not met), BP3 (not met), BP4 (not met), BP5 (not met), BP6 (not met), BP7 (not met), PP1 (not met), PP2 (not met), PP3 (not met), PP4 (not met), PP5 (not met), PM1 (met), PM2 (not met), PM3 (not met), PM4 (not met), PM5 (not met), PM6 (not met), PS1 (not met), PS2 (not met), PS3 (not met), PS4 (not met), and PVS1 (not met). The 'My Interpretation' section indicates: Disease: Not associated, Calculated Pathogenicity: Likely pathogenic, Modified Pathogenicity: None, Status: In Progress, and Last Edited: 2016 Sep 30, 3:28 pm.

## 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 were all met, the Progress bar would appear as follows immediately upon saving the last evaluation:

The screenshot displays the 'Variant Interpretation Record' for the variant **NM\_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)**. The interface shows the 'Calculated Pathogenicity' bar, which indicates the following status: Benign (No criteria met), Pathogenic (Very strong: 1, Moderate: 2), and 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
<b>Hotspot or functional domain</b> ^					
<p>PM1: Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of enzyme) without benign variation</p> <p><b>Disease-specific</b></p>		PM1: <input type="text" value="Met"/>	Explanation: <input type="text"/>	<input type="button" value="Update"/>	
<b>Experimental Studies</b> ^					
<p>BS3: Well established <i>in vitro</i> or <i>in vivo</i> functional studies show no damaging effect on protein function or splicing</p> <p><b>Disease-specific</b></p>		BS3: <input type="text" value="Not Evaluated"/>	Explanation: <input type="text"/>	<input type="button" value="Save"/>	
<p>PS3: Well established <i>in vitro</i> or <i>in vivo</i> functional studies supportive of a damaging effect on the gene or gene product</p> <p><b>Disease-specific</b></p>		PS3: <input type="text" value="Not Evaluated"/>			
<b>Curated Literature Evidence (Experimental Studies)</b>					
<input type="button" value="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) <input checked="" type="checkbox"/>					

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

## 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

View Summary

<b>Variant ID Sources</b> ClinVar VariationID: 10505 dbSNP ID: rs121434621	<b>Variant Genomic Context</b> UCSC [GRCh38/hg38   GRCh37/hg19] Variation Viewer [GRCh38   GRCh37] Ensembl Browser [GRCh38   GRCh37]	<b>My Interpretation</b> Disease: Not associated Calculated Pathogenicity: Uncertain significance - insufficient evidence Modified Pathogenicity: None Status: <i>In Progress</i> Last Edited: 2016 Sep 30, 5:44 pm
--	---	--

BA1BS1BS2BS3BS4BP1BP2BP3BP4BP5BP6BP7PP1PP2PP3PP4PP5PM1PM2PM3PM4PM5PM6PS1PS2PS3PS4PVS1

Variant Interpretation Record

Disease +Inheritance +

Benign  
No criteria met

Pathogenic  
Moderate: 1 Supporting: 2

Calculated Pathogenicity  
Uncertain significance - insufficient evidence

Basic InformationPopulationPredictorsExperimentalSegregation/CaseGene-centric

After clicking the “Associate with Disease” button, you will see an Add Disease box pop up for entering a disease. Enter the desired ID or, if you are unable to find an appropriate term, free text and click “Save” (note: use of an ontology term is highly recommended). You can find further help on searching MonDO using the MonDO Search Help link in the pop-up that appears -see arrow):

Add Disease

Search MonDO using the OLS (Ontology Lookup Service).  
[MonDO Search Help](#)  
Enter a MonDO term "id" from MonDO OLS search (Orphanet, DOID, OMIM and NCIt id's allowed). The term "id" can be found in the "Term info" box displayed on the right hand side of the OLS term page (e.g. [Orphanet:93545](#)): \*  
  
  

Note: We strongly encourage use of an allowed MonDO ontology term and therefore specific database identifier for a disease. If you have searched and there is no appropriate database identifier you may contact us at [clingen-helpdesk@lists.stanford.edu](mailto:clingen-helpdesk@lists.stanford.edu) and/or create a term using free text.

Check this box *only* if you were unable to find a suitable ontology term and need to enter a free text term: ☐

After entering an ID and selecting “Retrieve from OLS,” the term name and definition (if one exists) will be returned. Select “Save” if this is the desired term.

**Add Disease**

Search [MonDO](#) using the OLS (Ontology Lookup Service).

[MonDO Search Help](#)

**Enter a MonDO term "id" from MonDO OLS search (Orphanet, DOID, OMIM and NCIt id's allowed).** The term "id" can be found in the "Term info" box displayed on the right hand side of the OLS term page (e.g. [Orphanet:93545](#)): \*

OMIM:615273

[Retrieve from OLS](#)

Below are the data from OLS for the ID you submitted. Select "Save" below if it is the correct disease, otherwise revise your search above:

**[NGLY1-deficiency](#)**

A carbohydrate metabolic disorder that has\_material\_basis\_in homozygous or compound heterozygous mutation in the NGLY1 gene on chromosome 1p24. It is characterized by global developmental delay, hypotonia, abnormal involuntary movements, and alacrima or poor tear production.

[Cancel](#)
[Save](#)

Now you will see the disease term under the variant name in the gray title area and in the green “My Interpretation” section (note: this depicts a different disease than in the example above):

**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: <a href="#">rs121434621</a>	UCSC [ <a href="#">GRCh38/hg38</a>   <a href="#">GRCh37/hg19</a> ] Variation Viewer [ <a href="#">GRCh38</a>   <a href="#">GRCh37</a> ] Ensembl Browser [ <a href="#">GRCh38</a>   <a href="#">GRCh37</a> ]	<b>Disease:</b> Blue cone monochromatism, <a href="#">ORPHA16</a> <b>Calculated Pathogenicity:</b> Uncertain significance - insufficient evidence <b>Modified Pathogenicity:</b> None <b>Status:</b> <i>In Progress</i> <b>Last Edited:</b> 2016 Sep 30, 5:47 pm

## 2. Free text option for disease

If there is no MonDO term, a free text term may be entered for the disease. *Note: using a disease identifier if highly recommended. If you cannot find an appropriate one, please feel free to contact us at [clingen-helpdesk@lists.stanford.edu](mailto:clingen-helpdesk@lists.stanford.edu) and we will be happy to assist.*

To enter a free text term, verify you click on the checkbox (see arrow below)

Add Disease

Search [MonDO](#) using the OLS (Ontology Lookup Service).

[MonDO Search Help](#)

**Enter a MonDO term "id" from MonDO OLS search (Orphanet, DOID, OMIM and NCIt id's allowed).** The term "id" can be found in the "Term info" box displayed on the right hand side of the OLS term page (e.g. [Orphanet:93545](#)): \*

e.g. Orphanet:93545, DOID:0050776, OMIM:100800 OR NCIT:C4089

Retrieve from OLS

Note: We strongly encourage use of an allowed MonDO ontology term and therefore specific database identifier for a disease. If you have searched and there is no appropriate database identifier you may contact us at [clingen-helpdesk@lists.stanford.edu](mailto:clingen-helpdesk@lists.stanford.edu) and/or create a term using free text.

Check this box *only* if you were unable to find a suitable ontology term and need to enter a free text term: ☐

Cancel

Save



This will take you to a page where you can enter a free text term (up to 100 characters in length). You must also provide either a set of HPO terms (preferred) or a Definition for the term you are entering. You may also provide both. *Please remember that if someone else enters a different phrase for the same ID, the interface will not be able to determine they are equivalent.*

Add Disease

Search [MonDO](#) using the OLS (Ontology Lookup Service).

[MonDO Search Help](#)

Use of free text could result in different terms being used for the same disease. Please make certain there is no appropriate ontology term before applying a free text disease name.

**Disease name: \***

Short phrase (max 100 characters)

Either HPO term(s) or a definition is required to describe this disease (both fields may be used).

**Phenotype(s) (HPO ID(s)): \***

e.g. HP:0010704, HP:0030300

**Disease definition: \***

Describe this disease

Cancel

Save



## 2. Interpretation with Mode of Inheritance

You can add the mode of inheritance by clicking the “Inheritance +” button.

**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	Variant Genomic Context	My Interpretation
ClinVar VariationID: 10505 dbSNP ID: rs121434621	UCSC [GRCh38/hg38   GRCh37/hg19] Variation Viewer [GRCh38   GRCh37] Ensembl Browser [GRCh38   GRCh37]	<b>Disease:</b> Not associated <b>Calculated Pathogenicity:</b> Uncertain significance - insufficient evidence <b>Modified Pathogenicity:</b> None <b>Status:</b> <i>In Progress</i> <b>Last Edited:</b> 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** [Disease +](#) [Inheritance +](#)

☒ **Benign**  
No criteria met

☒ **Pathogenic**  
Moderate: 1 Supporting: 2

**Calculated Pathogenicity**  
Uncertain significance - insufficient evidence

[Basic Information](#) [Population](#) [Predictors](#) [Experimental](#) [Segregation/Case](#) [Gene-centric](#)



**Associate this interpretation with a different mode of Inheritance**

**Mode of Inheritance**

**Select an adjective**

Select a Mode of Inheritance:

**Associate this interpretation with a different mode of inheritance**

**Mode of Inheritance**

**Select an adjective**

- ☒ No mode of inheritance
- Autosomal dominant inheritance (HP:0000006)
- Autosomal recessive inheritance (HP:0000007)
- Mitochondrial inheritance (HP:0001427)
- X-linked inheritance (HP:0001417)
- Other
- Unknown

Select an adjective (the list of adjectives displayed will depend on the selected mode of inheritance):

Associate this interpretation with a mode of inheritance

Mode of Inheritance

X-linked inheritance (HP:0001417)

Select an adjective

✓ Select

dominant

recessive

primarily recessive with milder female expression

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 inheritance*

## 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](#)

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

<b>Variant ID Sources</b> ClinVar VariationID: 10505 dbSNP ID: rs121434621	<b>Variant Genomic Context</b> UCSC [GRCh38/hg38   GRCh37/hg19] Variation Viewer [GRCh38   GRCh37] Ensembl Browser [GRCh38   GRCh37]	<b>My Interpretation</b> <b>Disease:</b> Blue cone monochromatism, <a href="#">ORPHA16</a> <b>Calculated Pathogenicity:</b> Uncertain significance - insufficient evidence <b>Modified Pathogenicity:</b> None <b>Status:</b> <i>Provisional</i> <b>Last Edited:</b> 2016 Sep 30, 5:58 pm
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At the bottom of the Summary page, all the ACMG criteria are split into three separate tables according to 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 criterion 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 criterion.

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

The screenshot shows a web form for interpreting a variant. It includes the following elements:

- a** Calculated Pathogenicity: Uncertain significance - insufficient evidence
- b** Modified Pathogenicity: None
- c** Provisional Interpretation Status: In Progress
- d** Disease: Blue cone monochromatism
- e** Mode of Inheritance: X-linked recessive inheritance (HP:0001419)
- f** Modify Pathogenicity: (optional) No Selection (dropdown menu)
- g** Explain reason(s) for change: (required for modified pathogenicity) [Text box with note: "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): ☐ (checkbox)
- i** Save (button)
- 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.

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](mailto:clingen-helpdesk@lists.stanford.edu)