Variant Curation Interface

Help Documentation - January 2017

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Feedback / Comments?

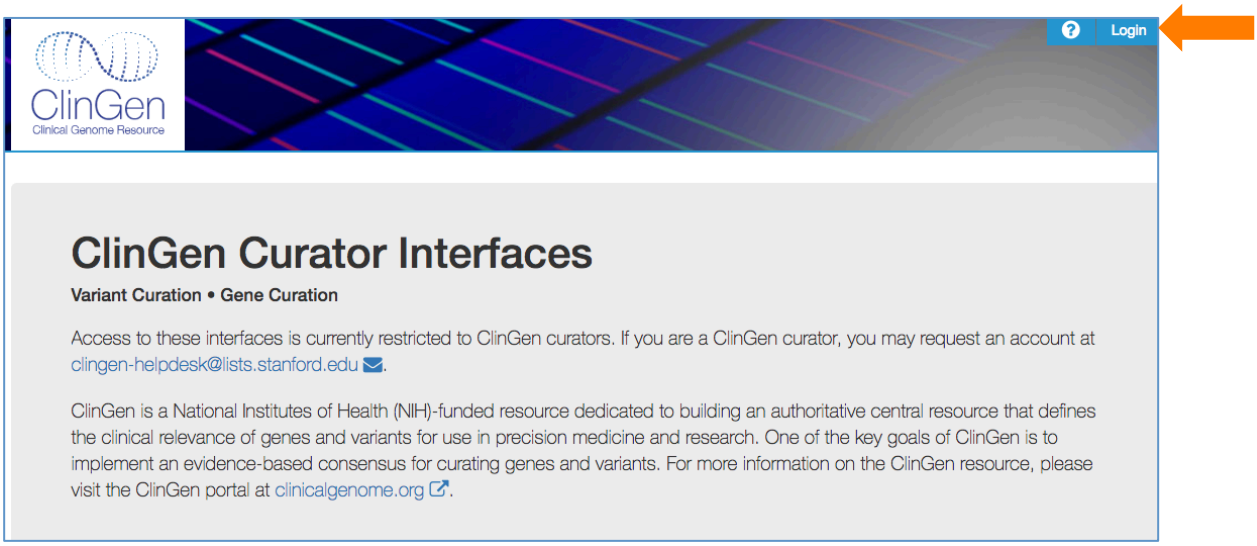
Please email us at: clingen-helpdesk@lists.stanford.edu

GENERAL NAVIGATION

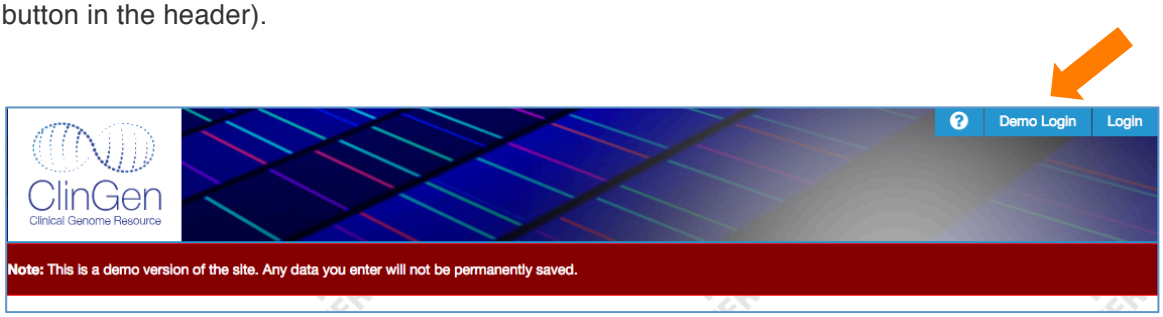
1. Logging in to the interfaces

To register for a ClinGen curator account you will need to send an email to clingen-helpdesk@lists.stanford.edu. 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.

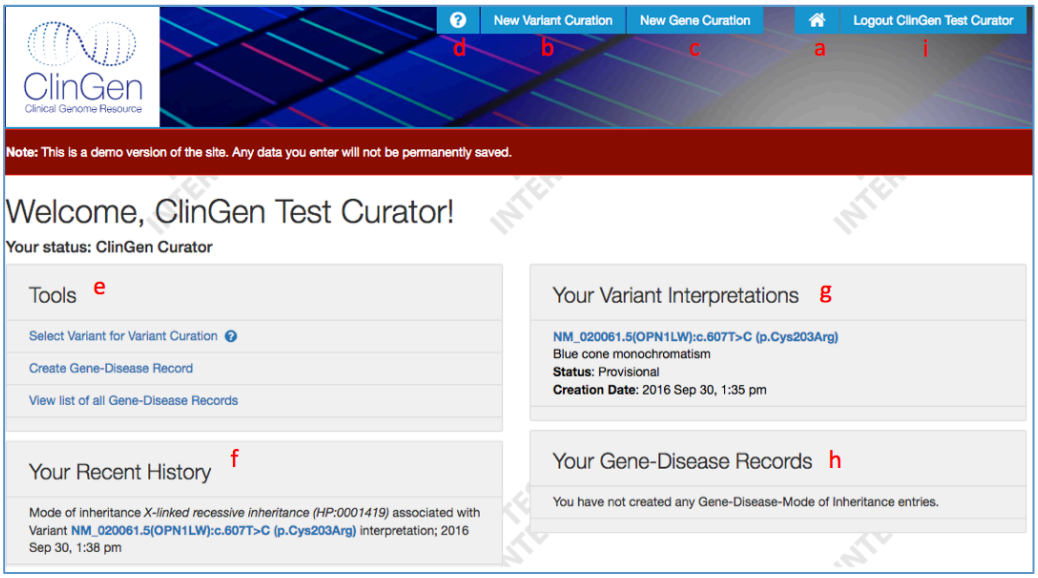


You can also explore the ClinGen test/demo curation interfaces (https://curation-test.clinicalgenome.org/) without registering as a ClinGen curator (using the 'Demo Login' button in the header).



2. Dashboard view

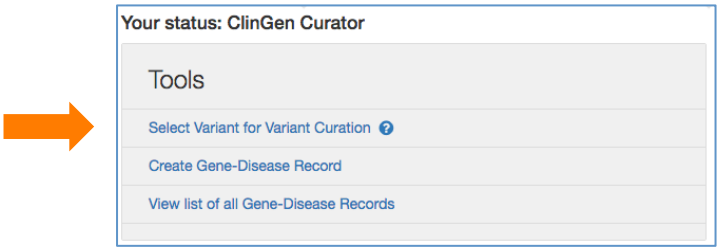
a. Dashboard home – available from all pages
b. Navigating to “Select Variant for Variant Curation” – available from all pages
c. Navigating to “Create Gene-Disease Record” – available from all pages
d. Navigating to this Help documentation online – available from all pages
e. Tools – useful links
f.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



SELECTING A VARIANT FOR VARIANT CURATION

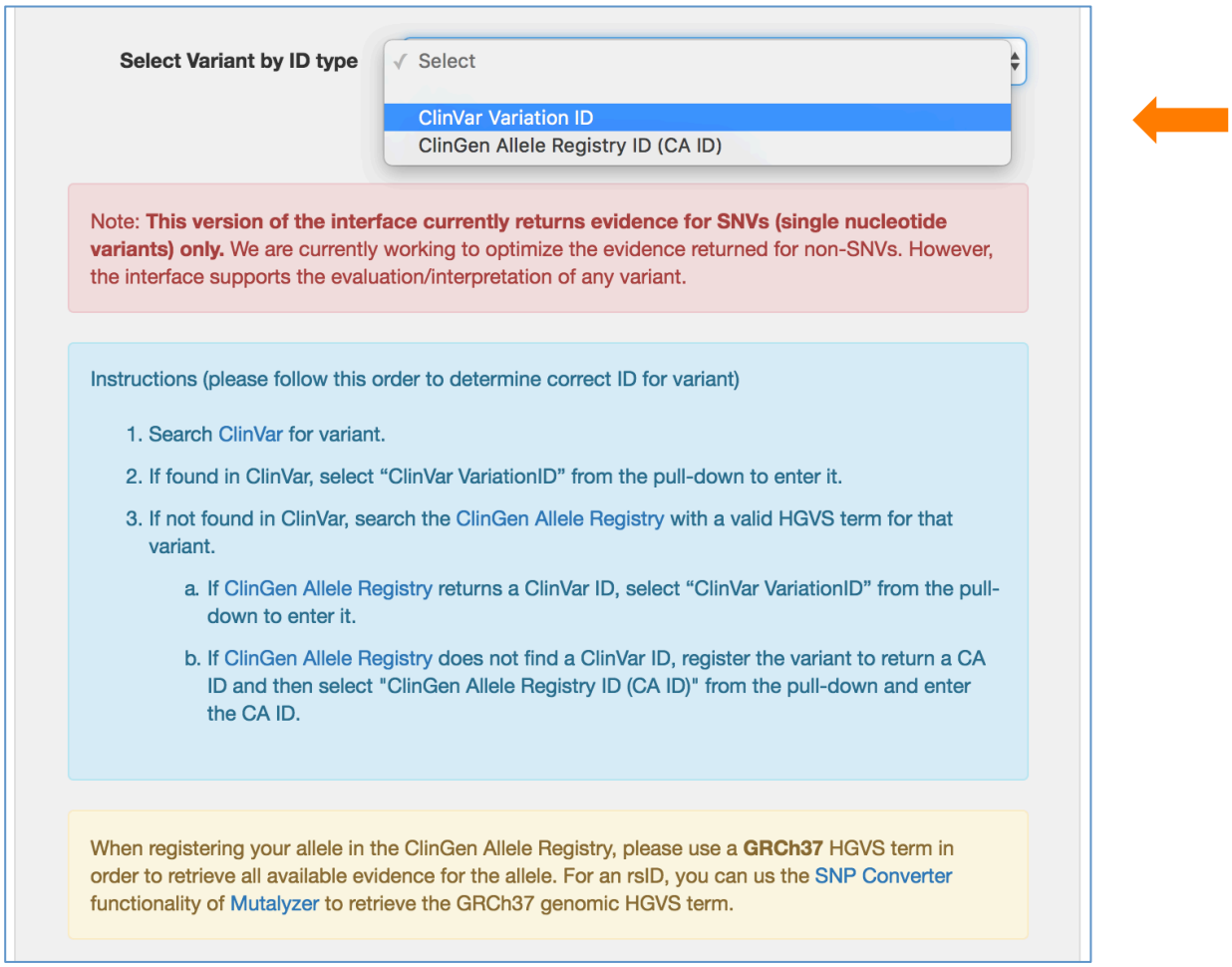
1. Begin variant curation

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

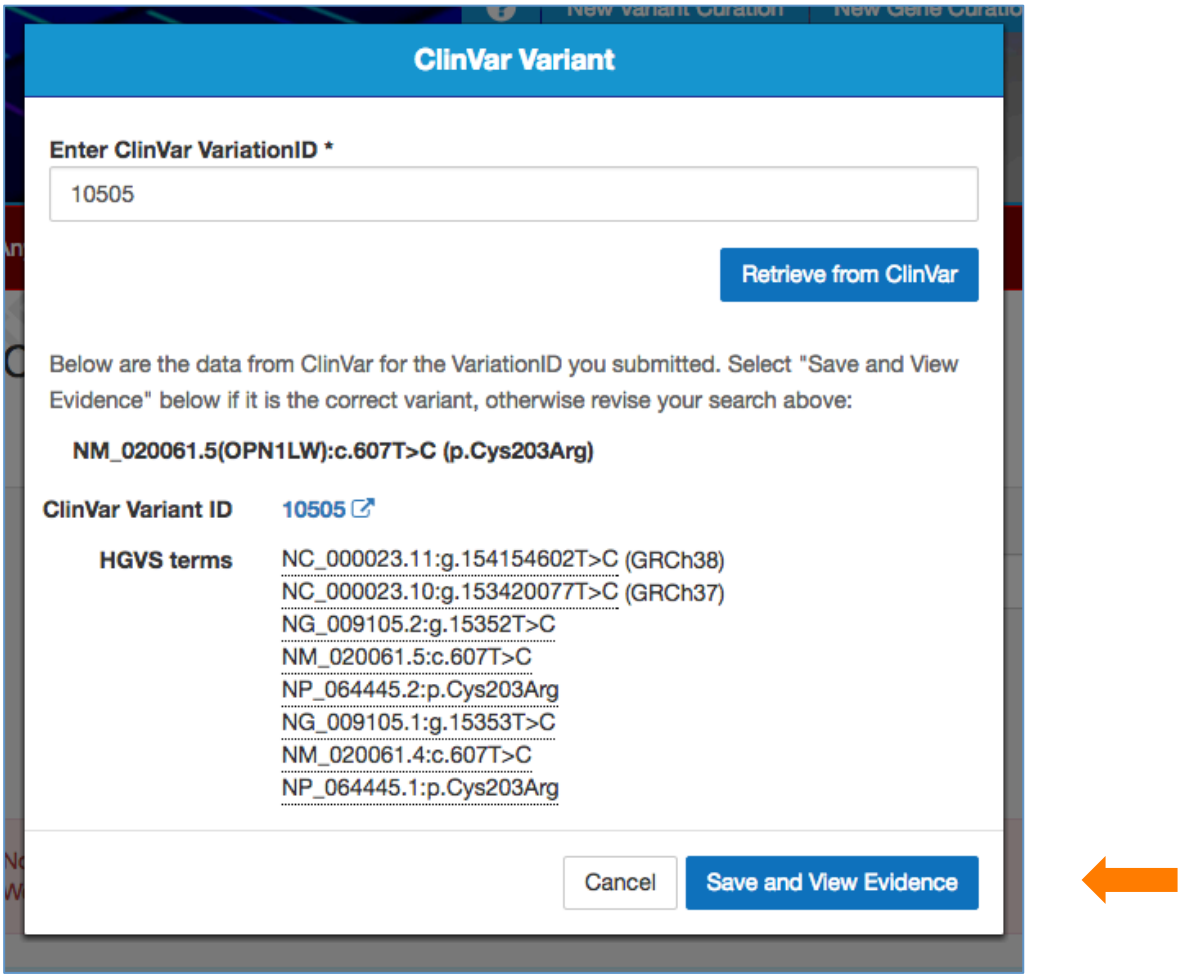


2. Select variant ID

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.”



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.”



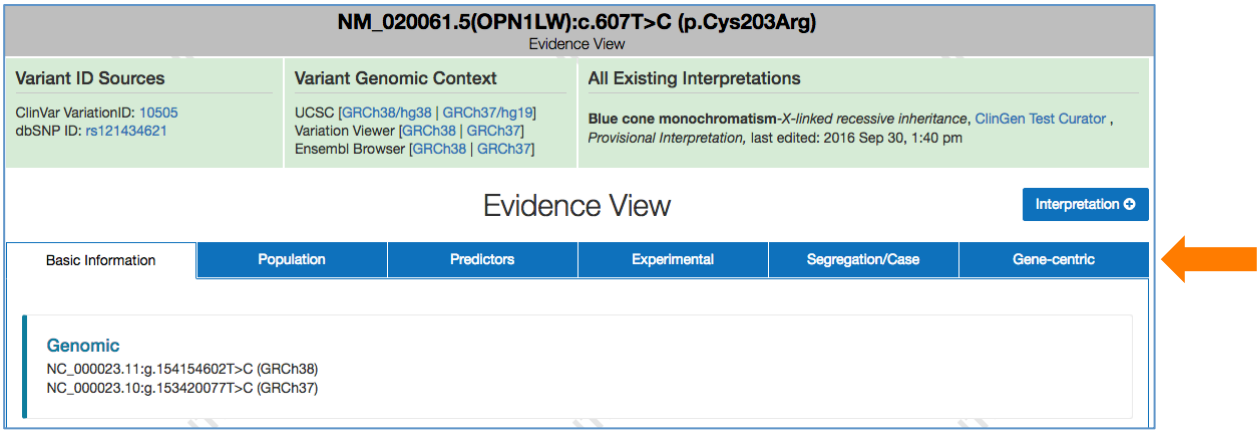
3. You will now be in the “Evidence View” for the selected variant (see next section)

GENERAL ORGANIZATION OF EVIDENCE (EVIDENCE VIEW PAGE)

1. Evidence View: Overall tab organization

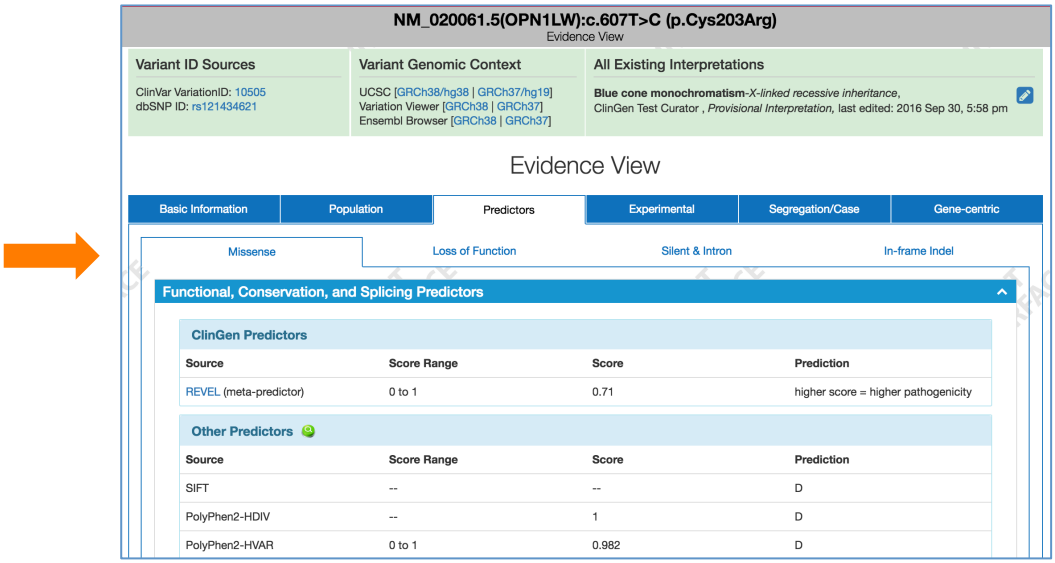
Note: The Evidence View is viewable by any logged in curator and includes both aggregated external evidence and evidence curated manually by individual curators (see "Overall Workflow" section for more details).

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.



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 the to the variant type (**Missense**, **Loss of Function**, **Silent & Intron**, and **In-frame indel**).



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.

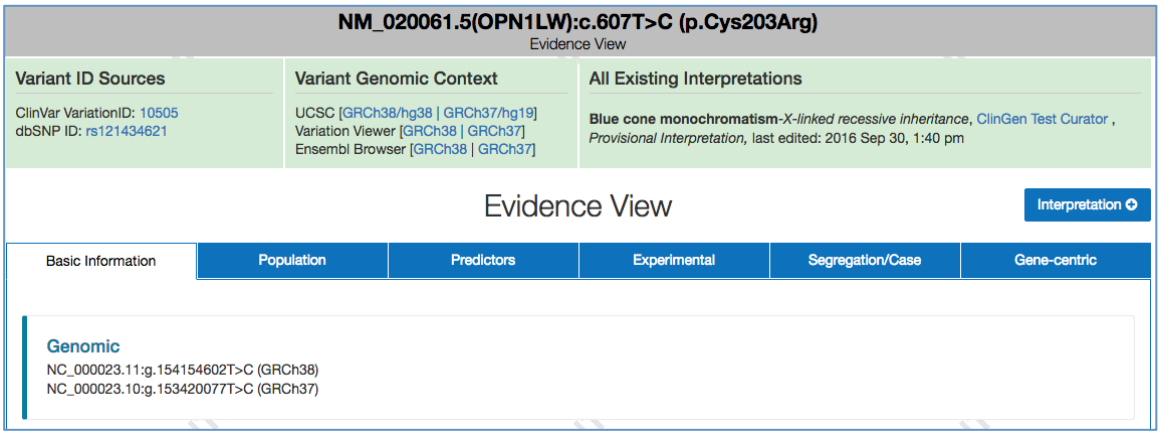
The Evidence View mode displays the following types of evidence:

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.

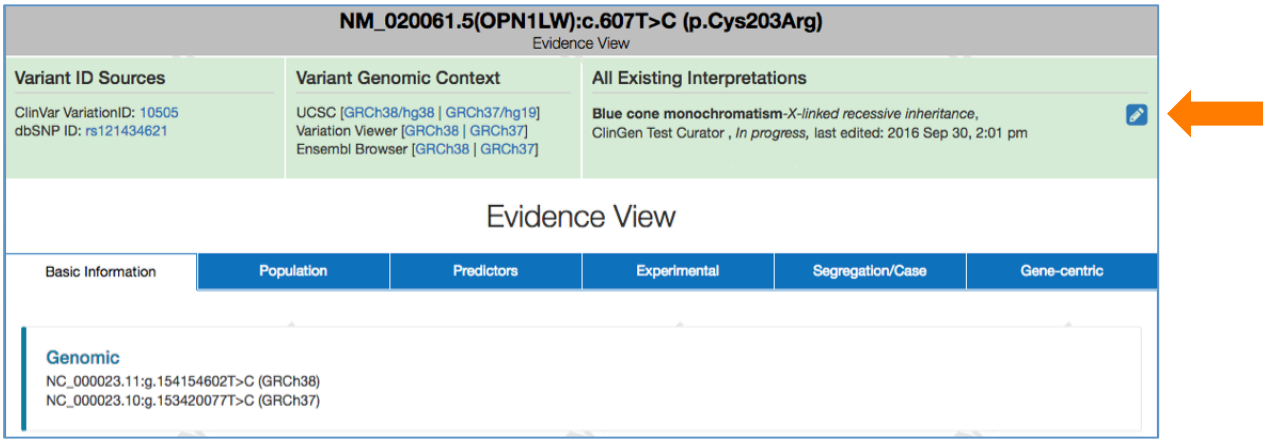
Manually curated evidence
Any evidence a curator enters for a PubMed ID (PMID) when in Interpretation mode (see next section) will be viewable by all curators in the Evidence View. Note: Evaluations (i.e. PS4 "Met") and Interpretations are specific to the curator who makes them and are not currently 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).



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.

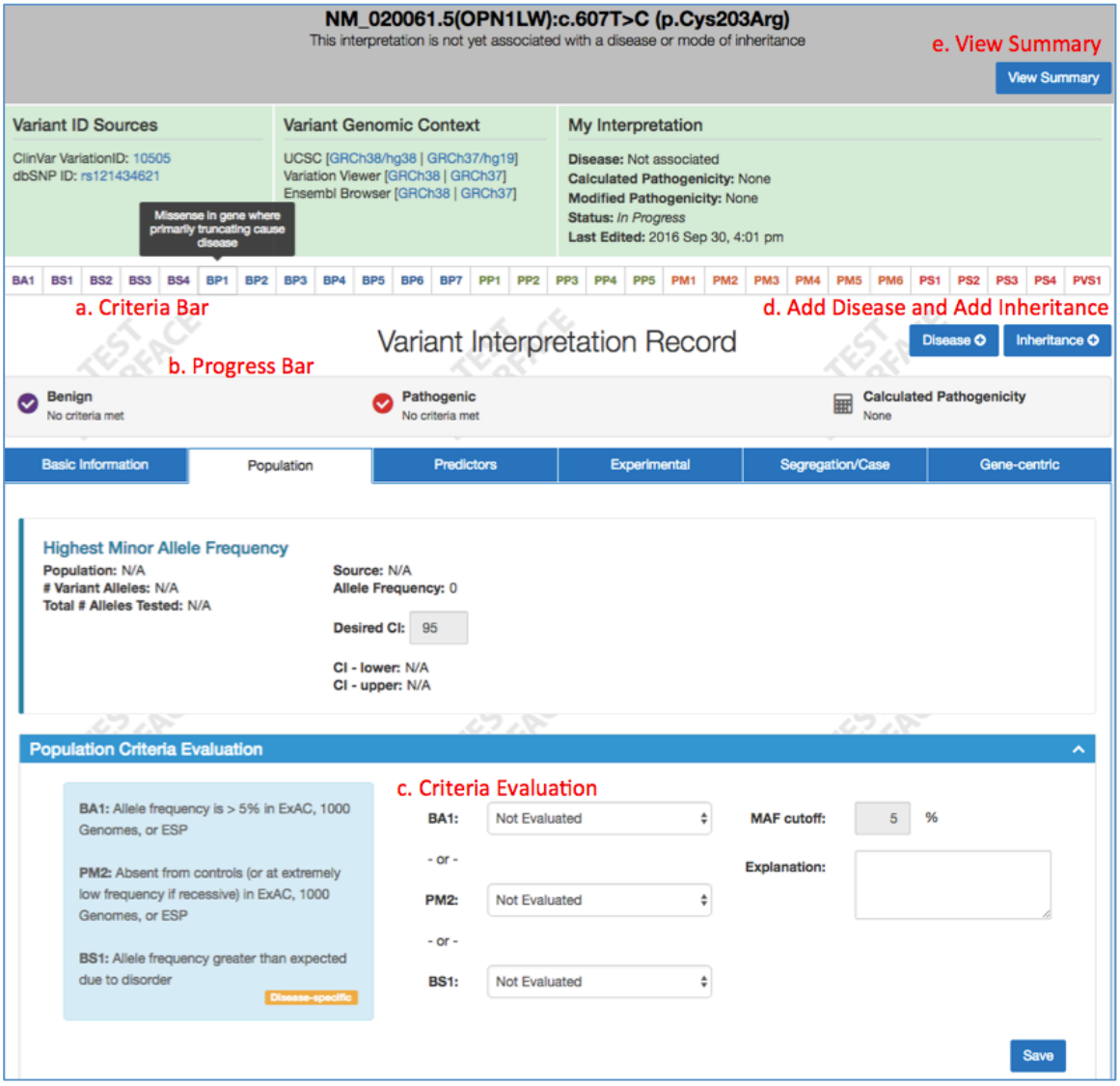


Once you click on "Interpretation +" or the pencil icon if you have previously begun an Interpretation, you will be in Interpretation mode (see next page).

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.

Once in Interpretation mode, the following will appear:

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

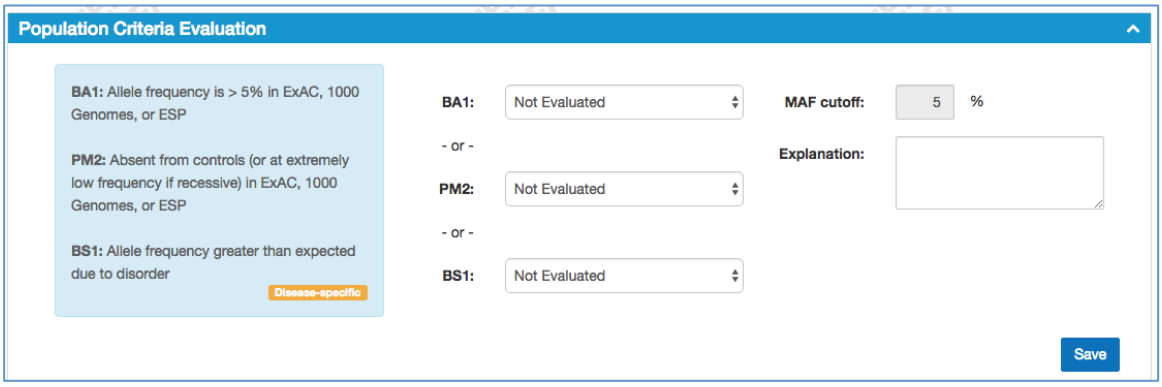


3. **Evaluation Summary/Provisional Interpretation** (Please see Evaluation Summary/Provisional Interpretation Section, p. 16)

EVALUATING CRITERIA

1. Criteria placement & organization

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



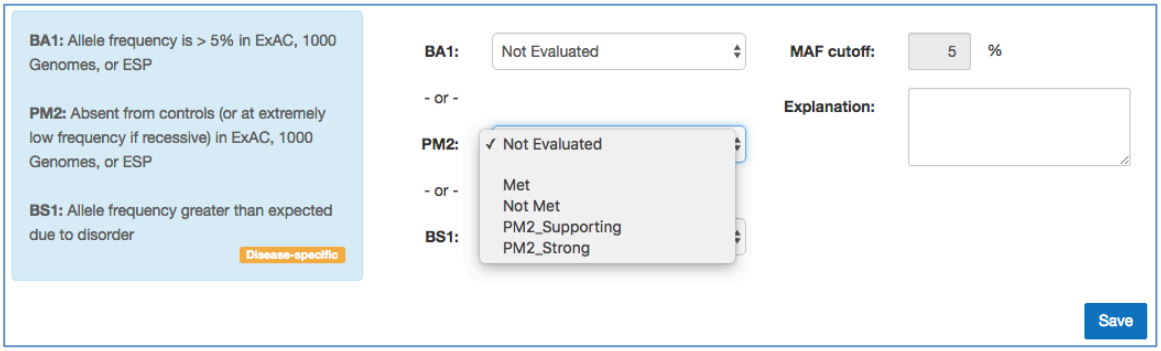
2. Criteria evaluation choices:

The pull-downs allow the following criteria evaluation choices:

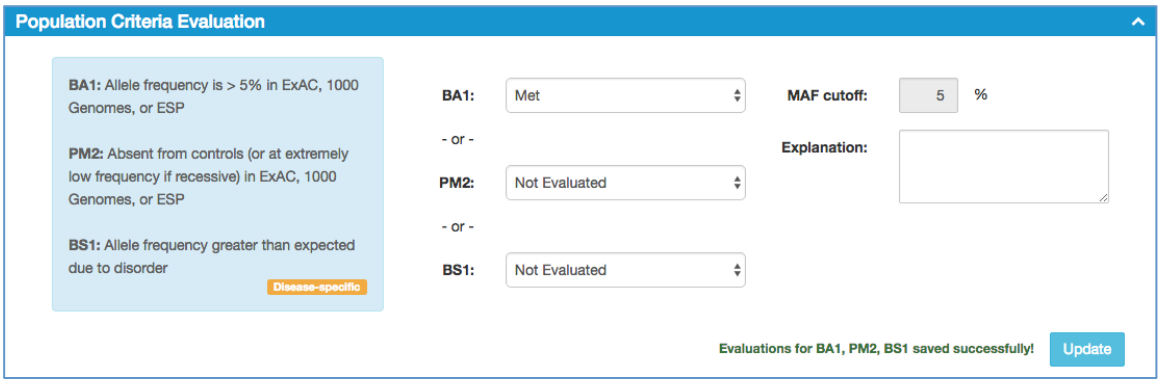
- **Not Evaluated**: The default state of an Evaluation is "Not Evaluated"
- **Met**: If the evidence supports a positive evaluation of a criterion at its original strength (e.g. PM2 = moderate strength in the pathogenic range), the curator should select "Met"
- **Not Met**: If the evidence does not 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:

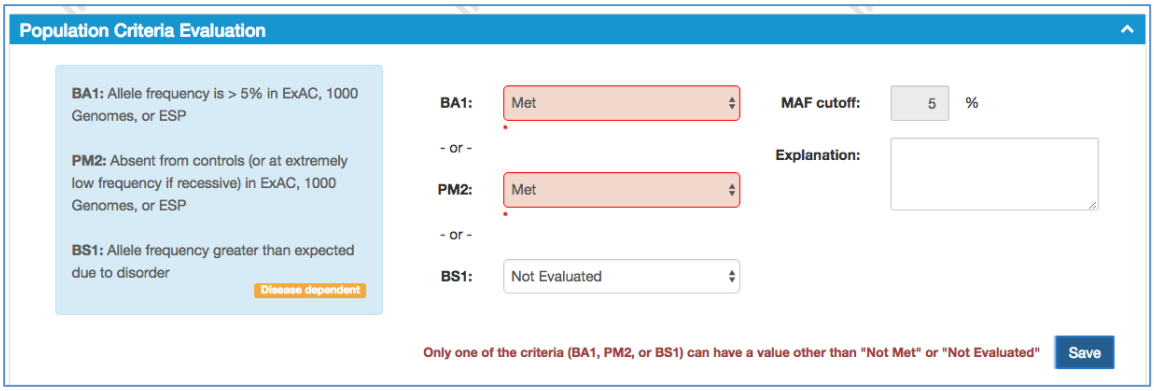
Pathogenic pull-down choices – example:



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.

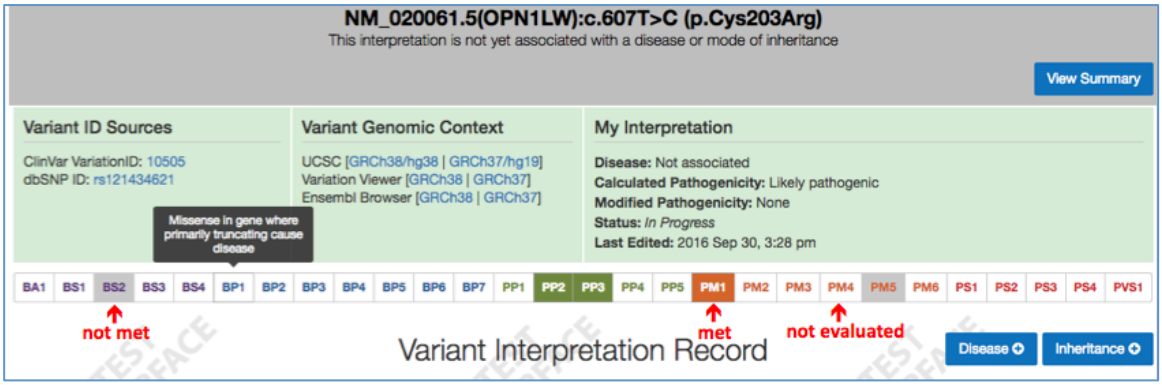


Note: When 2 (or more) criteria are opposites or cannot otherwise be “Met” at the same time, the interface will not allow “Met” to be selected for more than one of the criteria.



CRITERIA BAR

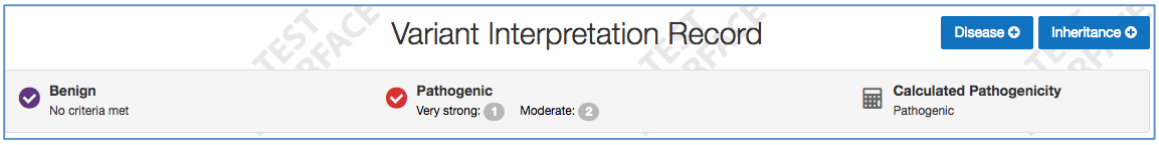
As you Save your evaluations, you will notice that the Criteria bar will indicate which criteria have been “Met” (solid color background with white criteria code), “Not Met” (grey background with colored criteria code), or remain “Not Evaluated” (white background with colored criteria code).



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:

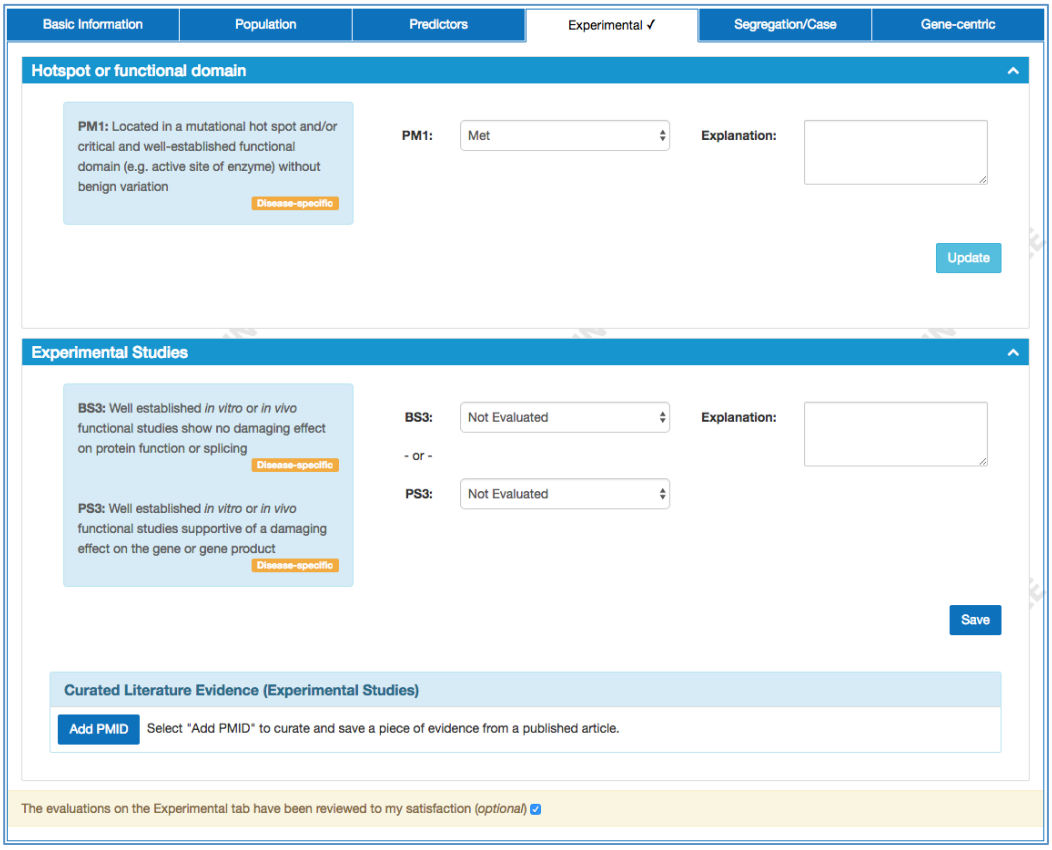


The Calculated Pathogenicity outcomes are as follows:

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:

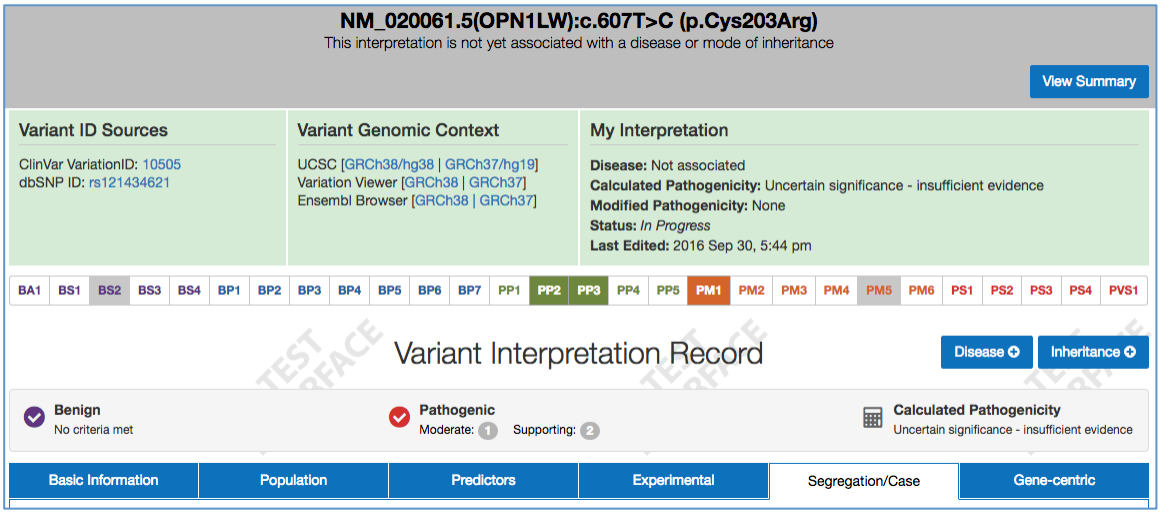


This checkbox will remain regardless of which tab you are on in the interface and can be unchecked as well:

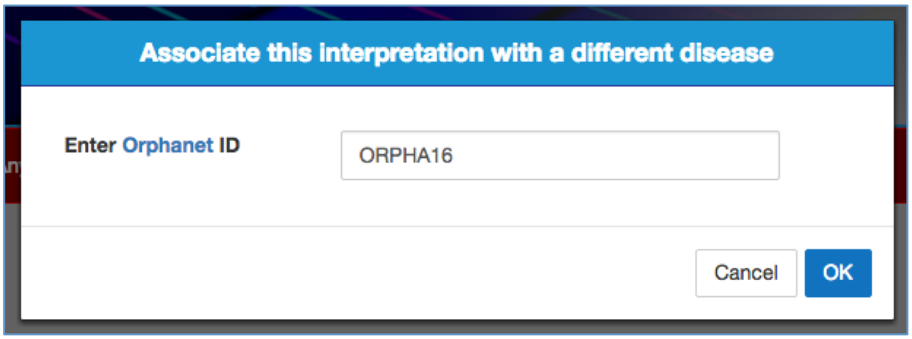
ADDING DISEASE & MODE OF INHERITANCE

1. Interpretation with Disease Association

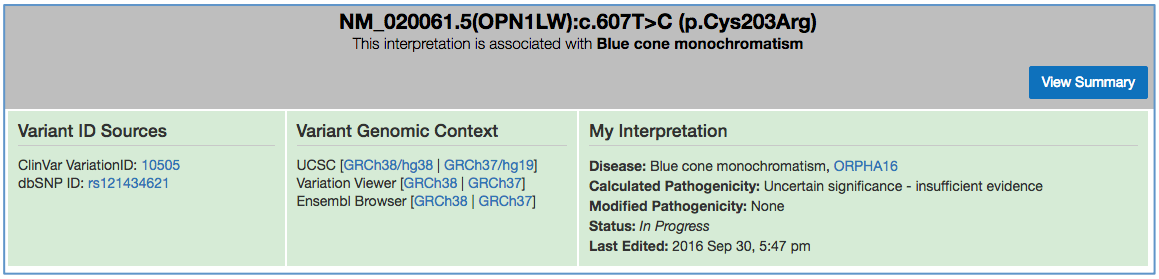
When you are ready to evaluate disease-specific criteria for your Interpretation, you can click the “Disease +” button to add the Orphanet ID for the disease. Be sure you’ve saved your evaluations before clicking this button.



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.

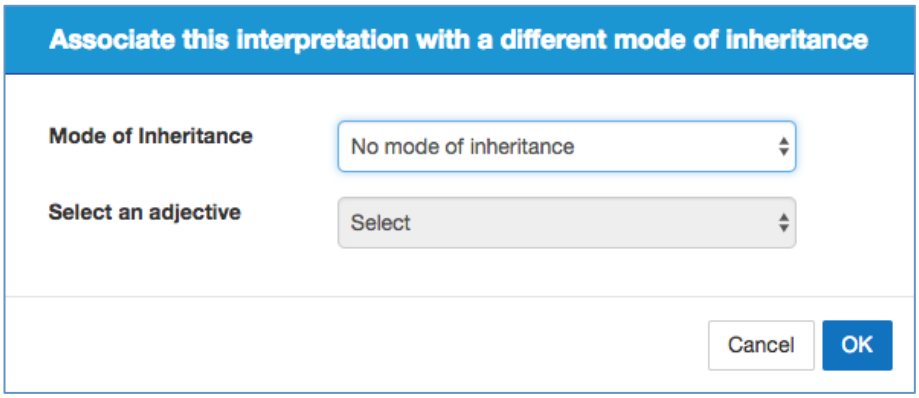


Now you will see the disease term under the variant name in the gray title area and in the green “My Interpretation’ section:

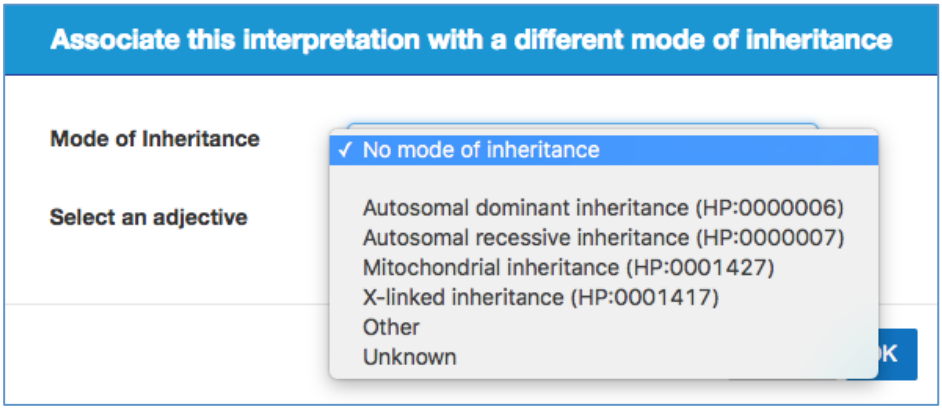


2. Interpretation with Mode of Inheritance

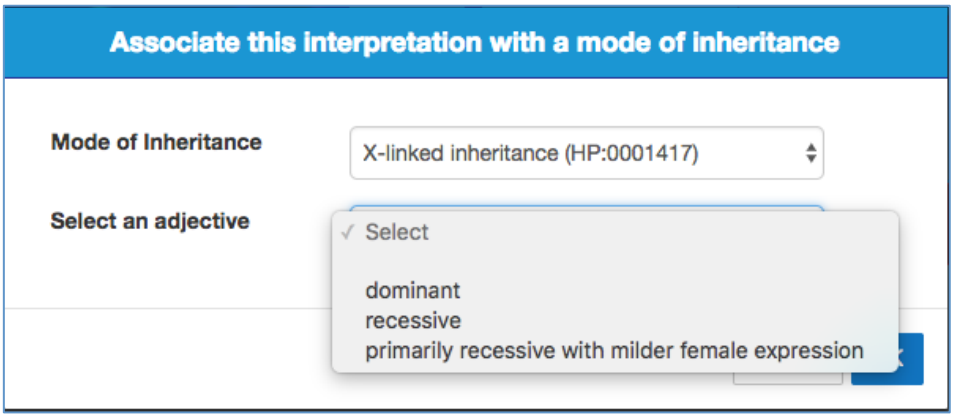
You can add the mode of inheritance by clicking the “Inheritance +” button.



Select a Mode of Inheritance:



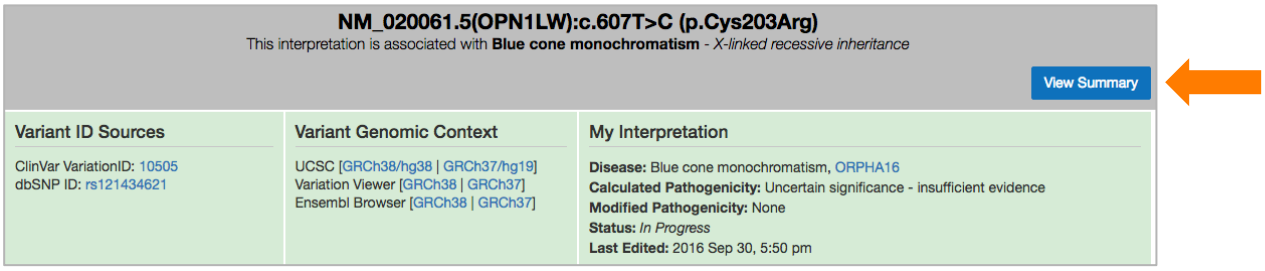
Select an adjective (the list of adjectives displayed will depend on the selected mode of inheritance):



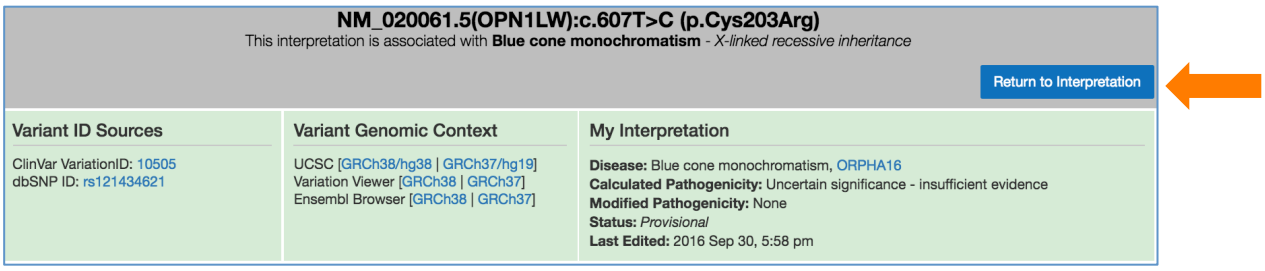
Now you will see the mode of inheritance term under the variant name in the gray title area:

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:



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”.



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	

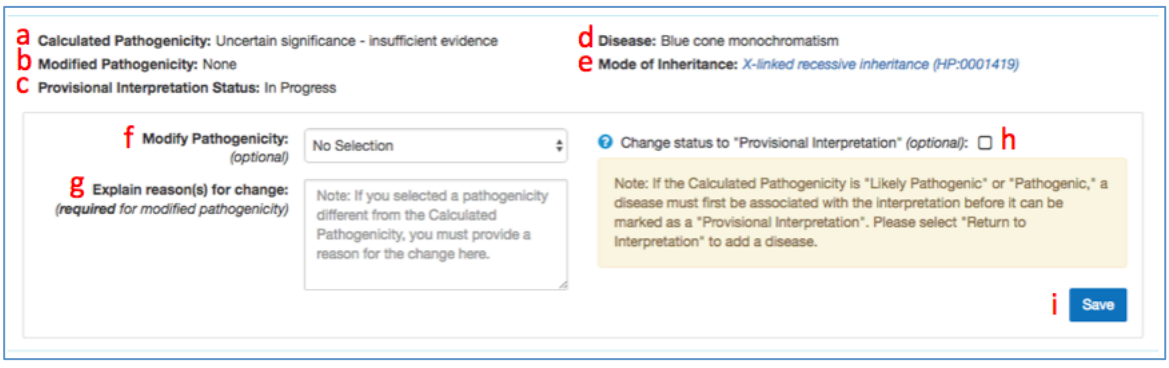
These tables summarize the evaluations made for each criterion into the following fields:

- **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:

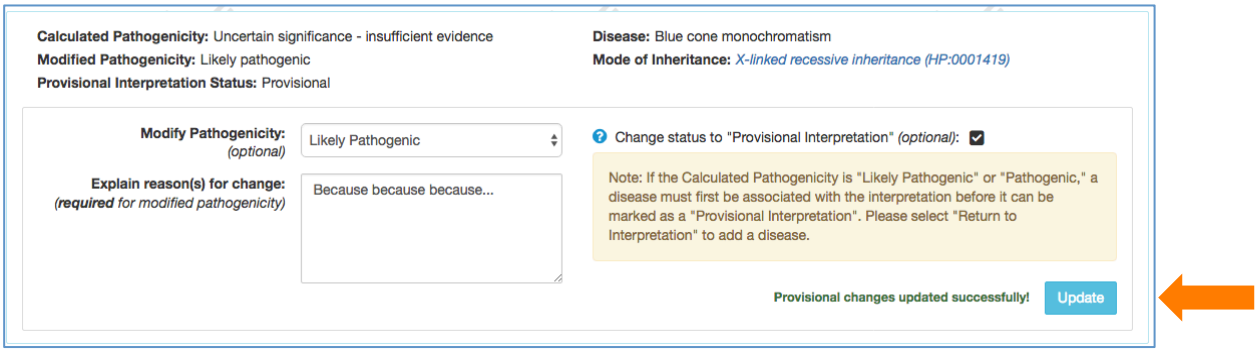
a. Calculated Pathogenicity – the pathogenicity calculated based on all the evaluations saved so far
b. Modified Pathogenicity – the pathogenicity selected by the curator
c. Provisional Interpretation Status – indicates the current status of the Interpretation
d. Disease – shows a disease where one has 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



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.



Feedback and Comments?

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