Variant Curation Interface
Help Documentation - November 2017

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

REGISTRATION

1. When to Register

ClinGen curators who would like to access the production version of the ClinGen curation interfaces (https://curation.clinicalgenome.org/) will need to register for production interface (see section 2, below, on how to register). Data entered into the production interface is permanently saved, so this interface should only be used for "real" curation.

You can explore the ClinGen test/demo curation interfaces (https://curation-test.clinicalgenome.org/) without registering as a ClinGen curator (see 'Demo Login' instructions below); however we encourage those who want to explore the interface more thoroughly to register their email with us (see section below for information on how to register). We recommend curators become familiar with the interface by exploring the test interface before curating "real" evidence into the production interface.

2. How to Register

   i.   If you are a ClinGen curator, you may request an account by emailing us at clingen-helpdesk@lists.stanford.edu. The ClinGen **Variant Curation Interface** is available for public use. However, the ClinGen **Gene Curation Interface** is currently restricted to use by ClinGen curators. If you would like to collaborate on gene curation, please contact ClinGen at clingen@clinicalgenome.org.

   ii.   When you write to us please let us know the following:
      a. Your preferred email address (which you will use to log in to the interfaces)
      b. Your preferred display name (first and last name)
      c. Any affiliation you have with ClinGen

   iii.   We will write back to you to confirm that your email address has been registered and can be used for logging in to the interfaces.
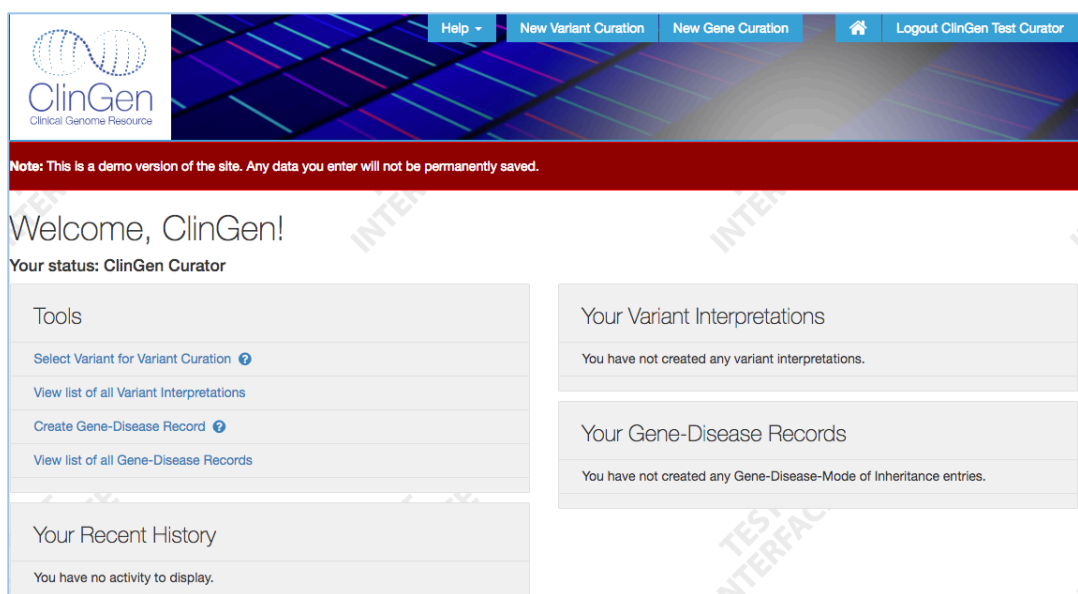
LOGGING IN

1. Demo Login

You can try out the test/demo version of the ClinGen interfaces (https://curation-test.clinicalgenome.org/) by simply clicking on the 'Demo Login' button in the header.
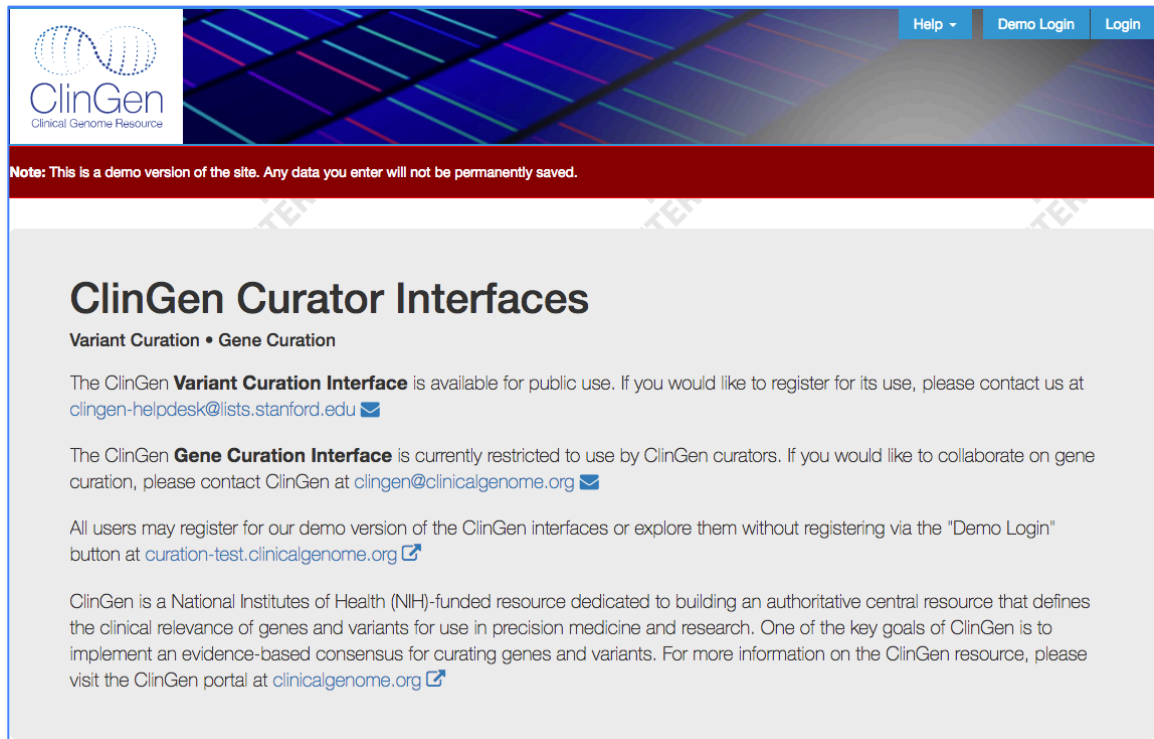

You will be logged in to the test version of the interfaces under a generic "ClinGen Curator" account.

2. ClinGen Registered User Login

In both the test (https://curation-test.clinicalgenome.org/) and production (https://curation.clinicalgenome.org/) versions of the ClinGen curation interfaces users who have registered an email address with us can login by clicking the "Login" button in the header. The Auth0 authentication system will now produce a pop-up login window.

    a.   If you are a first time user you will need to go to the "Sign Up" tab and enter your registered email address, enter your desired password, and then click "Sign Up."
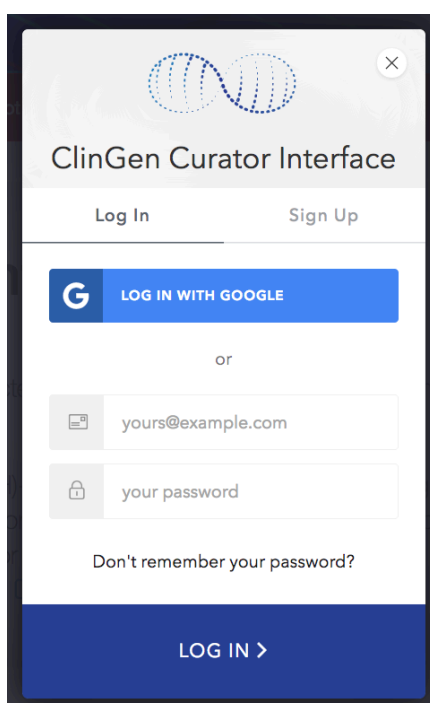
As a first time user, you will also need to be verified by Auth0. When you sign up you will be sent an email in which you need to click the link in order to verify your account. After doing this you should be able to now "log in" using your email and password.

b. If you are a returning user accessing the interfaces from a different operating system then you will see the pop-up above, in which case you should re-enter your registered email address and your selected password on the "Log In" tab and then click "LOG IN."

c. If you are a returning user accessing the interfaces from your usual operating system then your last log in details will likely be saved and you will see the pop-up shown below, in which case you only need to click on your email address to login.
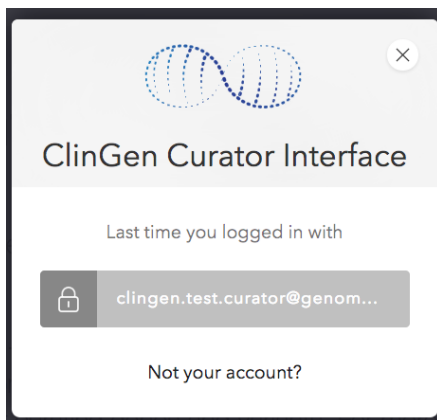
3. Google Login

You will note that one of the options on the login window is "LOG-IN WITH GOOGLE."
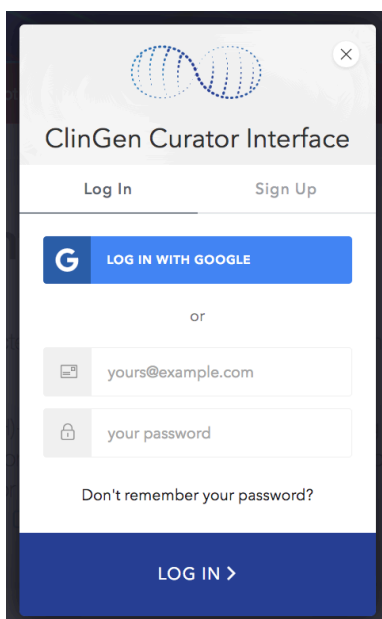
You can click this button and log in with a Google email account, however this option is only available for Google emails that have been registered as the preferred email address by a ClinGen curator. You would need to contact us if you wish to change your preferred email to a Google email address.

4. Login Troubleshooting

i. Have you registered your email address by emailing us at clingen-helpdesk@lists.stanford.edu?
ii. Have you received confirmation from us that your email address has been registered?

GENERAL NAVIGATION

1. 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" (described below) – available from all pages
- d Navigating to the online Help documentation – available from all pages
- e Navigating to "Select Variant for Variant Curation"
- f View a list of all Variant Interpretations – This list contains all the Interpretations curated to date, along with their status, creator, date created and date last edited.
- g Navigating to "Create Gene-Disease Record" (described below)
- h View a list of all Gene-Disease Records – This list contains all the Gene-Disease Records curated to date, along with their status, creator, date created and date last edited.
- i View of a curator's recent history – This section provides a chronological history of all edits made by a curator within both the Gene and Variant Curation Interfaces. A curator only views their own history. Each highlighted text is a direct link to the relevant section of the Gene or Variant Curation Interface a curator was previously curating.
- j View of a curator's current Variant Interpretation curation records – This section provides a list of edits made by a curator within the Variant Curation Interface. A curator only views their own Interpretations. Each highlighted text is a direct link to the variant a curator was previously curating.
- k View of a curator's current Gene-Disease curation records – This section provides a list of edits made by a curator within the Gene Curation Interface. A curator only views their own Gene-Disease Records. Each highlighted text is a direct link to the Gene-Disease Record a curator was previously curating.
- m. Logout – available from all pages

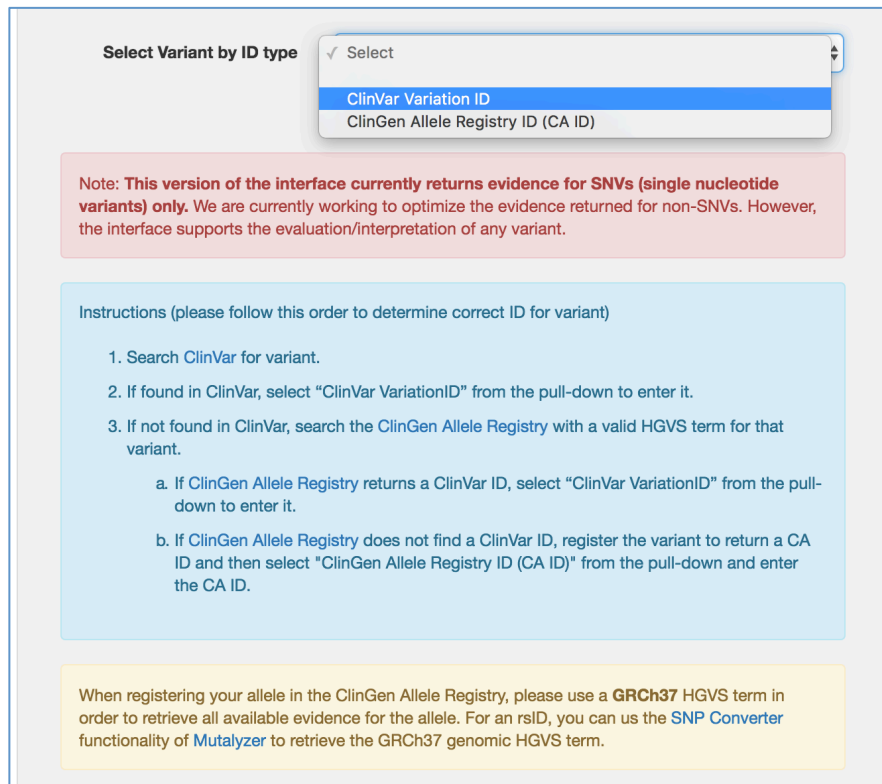## SELECTING A VARIANT FOR VARIANT CURATION

1. Begin variant curation

Select "Select Variant for Variant Curation" under the "Tools" Section
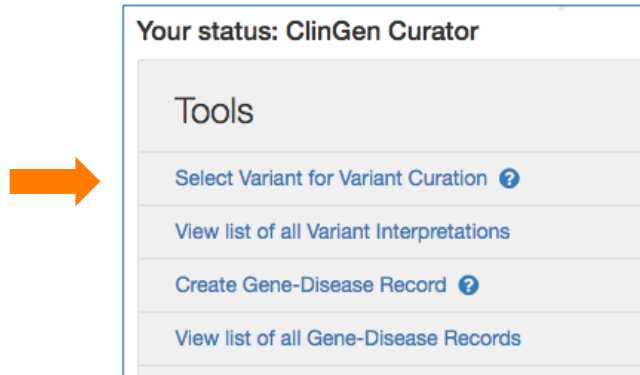
2. Select variant ID
Read instructions carefully on how to select a variant, and then choose whether you want to enter a ClinVar variant using a ClinVar Variation ID or a novel variant that you have registered with Baylor's ClinGen Allele Registry. Select "Add ClinVar ID."

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 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 arrows):

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.

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):

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 and we will be happy to assist.*

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

Add Disease

Enter a MONDO ID below. To find the desired MONDO ID:

1. Search for the desired MONDO term using the OLS MONDO ⬀ Search [Help].

2. Once you have selected the term, enter its MONDO ID (the "id" at the bottom of the "Term info" box on the right hand side of the OLS term page (e.g. MONDO:0016587 ⬀).

> e.g. MONDO:0016587

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 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

> 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)):Search HPO-Browser ⬀ *   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.

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:

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:

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. Evidence Summary – this free text box allows curators to summarize their evidence and provide a rationale for the clinical significance
j. 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