

Variant Curation Interface

Help Documentation
August 2016 Test Release

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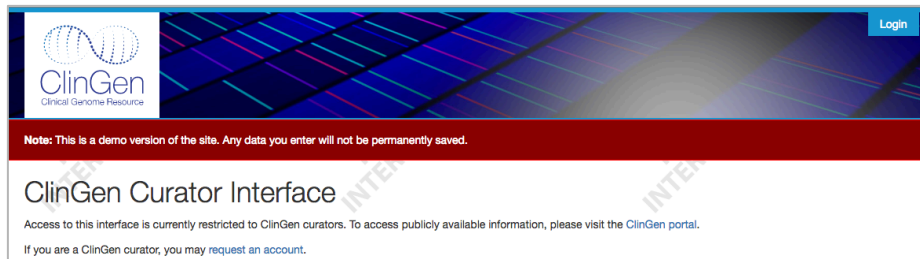
Feedback / Comments?

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

GENERAL NAVIGATION

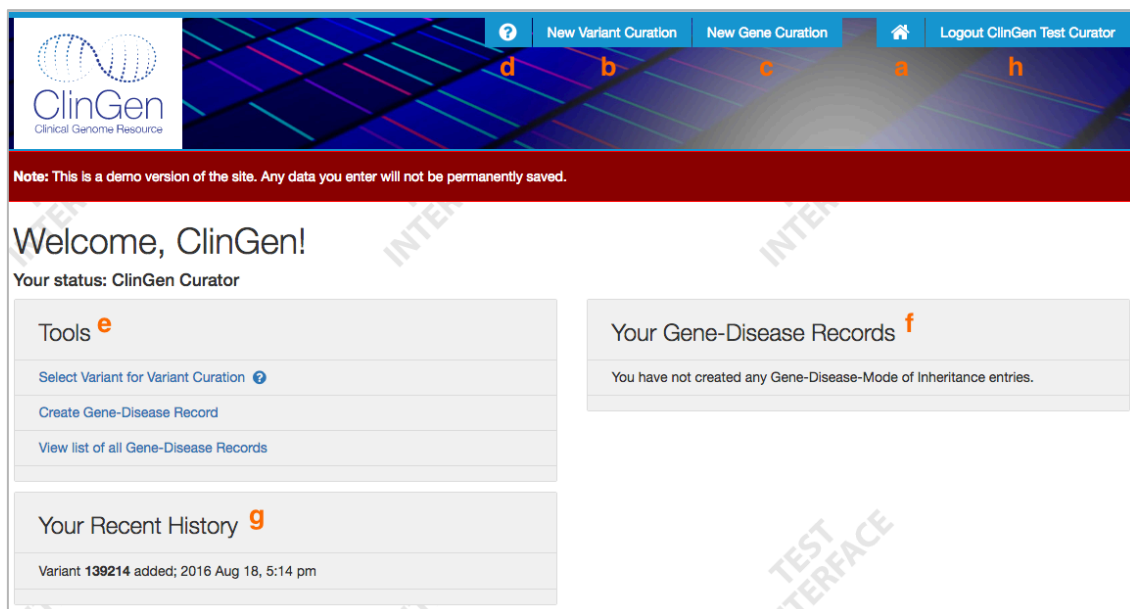
1. Logging in to the interfaces

Go to <https://variant-curation-alpha2.demo.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

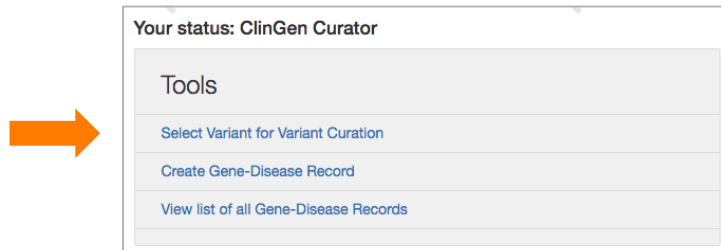
- Dashboard home – available from all pages
- Navigating to “Select Variant for Variant Curation” – available from all pages
- Navigating to “Create Gene-Disease Record” – available from all pages
- Navigating to this Help documentation online – available from all pages
- Tools – useful links
- View of your current gene-disease curation records (*variant curation records will appear in next release*)
- View of your recent history
- Logout – available from all pages



SELECTING A VARIANT FOR VARIANT CURATION

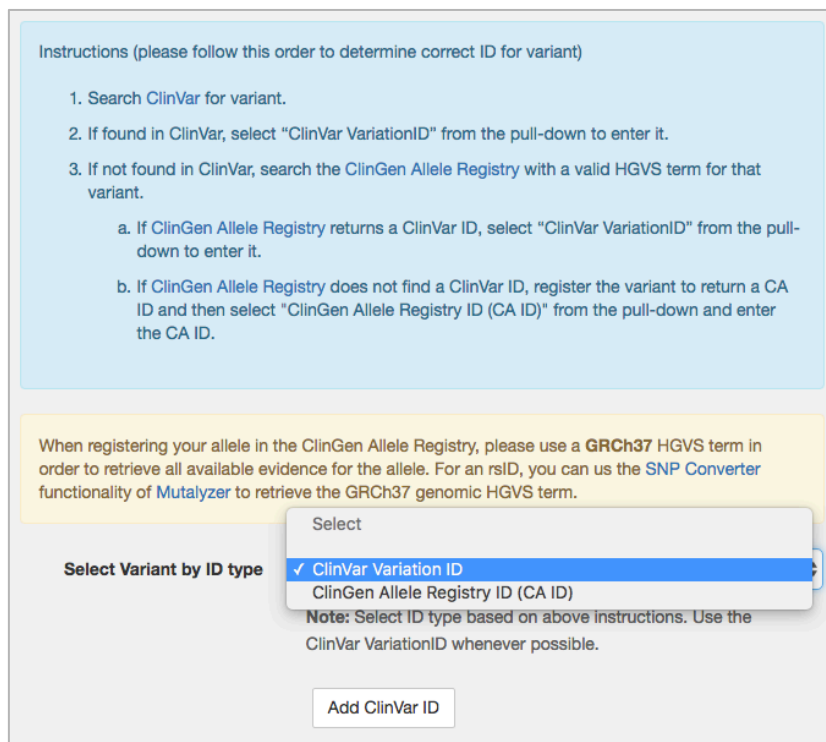
1. Begin variant curation

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 form for selecting a variant ID. At the top, there 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. Below the instructions is a yellow box with additional text: "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." Below this is a section titled "Select Variant by ID type" with a dropdown menu. The dropdown menu is open, showing three options: "ClinVar Variation ID" (which is selected and has a checkmark), "ClinGen Allele Registry ID (CA ID)", and a "Note: Select ID type based on above instructions. Use the ClinVar VariationID whenever possible." Below the dropdown is a button labeled "Add ClinVar ID". An orange arrow points from the right towards the "ClinVar Variation ID" option in the dropdown menu.

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 *

21134

[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_000271.4(NPC1):c.2324A>C (p.Gln775Pro)

ClinVar Variant ID [21134](#)

HGVS terms

- NC_000018.10:g.23541355T>G (GRCh38)
- NC_000018.9:g.21121319T>G (GRCh37)
- NG_012795.1:g.50263A>C
- NM_000271.4:c.2324A>C
- NP_000262.2:p.Gln775Pro
- NM_000271.3:c.2324A>C
- NP_000262.1:p.Gln775Pro

[Cancel](#) [Save and View Evidence](#)

3. You will now be in the “Evidence View” for your selected variant.

GENERAL ORGANIZATION OF INFORMATION AND EVIDENCE

1. Overall tab organization

Once you are in the “Evidence View only,” 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_005902.3(SMAD3):c.-28C>T
Evidence View Only

| Variant ID Sources | Variant Genomic Context | Interpretations |
|--|---|--|
| ClinVar VariationID: 139214 dbSNP ID: rs144374592 | UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37] | Other interpretations: Minyoung Choi, In Progress, (last edited 2016 Aug 17, 2:26 pm) |

Start New Interpretation

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

Genomic
NC_000015.10:g.67066127C>T (GRCh38)
NC_000015.9:g.67358465C>T (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_005902.3(SMAD3):c.-28C>T
Evidence View Only

| Variant ID Sources | Variant Genomic Context | Interpretations |
|--|---|--|
| ClinVar VariationID: 139214 dbSNP ID: rs144374592 | UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37] | Other interpretations: Minyoung Choi, In Progress, (last edited 2016 Aug 17, 2:26 pm) |

Start New Interpretation

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 | No data found | higher score = higher pathogenicity |

OVERALL WORKFLOW

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

1. Evidence View Only
2. Interpretation
3. Interpretation with Disease Association

1. Evidence View Only

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.

NM_005902.3(SMAD3):c.-28C>T
Evidence View Only

| Variant ID Sources | Variant Genomic Context | Interpretations |
|--|---|--|
| ClinVar VariationID: 139214 dbSNP ID: rs144374592 | UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37] | Other interpretations: Minyoung Choi, In Progress, (last edited 2016 Aug 17, 2:26 pm) |

[Start New Interpretation](#)

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

Genomic
NC_000015.10:g.67066127C>T (GRCh38)
NC_000015.9:g.67358465C>T (GRCh37)

2. Interpretation Mode

To begin an Interpretation in which you can evaluate the evidence according to the ACMG criteria, select “Start New Interpretation” (see arrow above). Note: if you have already begun an Interpretation for the variant and return, the button will instead say “Continue Interpretation.”

NM_005902.3(SMAD3):c.-28C>T
Evidence View Only

| Variant ID Sources | Variant Genomic Context | Interpretations |
|--|---|--|
| ClinVar VariationID: 139214 dbSNP ID: rs144374592 | UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37] | Other interpretations: Minyoung Choi, In Progress, (last edited 2016 Aug 17, 2:26 pm) |

[Start New Interpretation](#)

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

Genomic
NC_000015.10:g.67066127C>T (GRCh38)
NC_000015.9:g.67358465C>T (GRCh37)

Once you click on “Start New Interpretation,” you will be in Interpretation mode.

Once in Interpretation mode, the following will appear:

- 1) Criteria bar – scroll over a criteria to see the description of the criteria,
- 2) Interpretation Progress bar that indicates the strength of criteria met and the calculated pathogenicity
- 3) Checkbox on each tab that you can check when you have reviewed that category of evidence to your satisfaction
- 4) The criteria evaluations where you can indicate whether an individual criterion is “Met” (see page 9 of this document)
- 5) Disease-dependent criteria, which will be grayed out until a disease has been associated with the Interpretation (next step).

NM_005902.3(SMAD3):c.-28C>T
This interpretation is not yet associated with a disease

[View Summary](#)

| | | |
|---|---|--|
| Variant ID Sources ClinVar VariationID: 139214 dbSNP ID: rs144374592 | Variant Genomic Context UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37] | Interpretations My interpretations: In Progress, (last edited 2016 Aug 18, 4:02 pm) ✓ Other interpretations: ClinGen Test Curator, In Progress, (last edited 2016 Aug 18, 4:01 pm) ClinGen Test Curator, In Progress, (last edited 2016 Aug 18, 4:01 pm) |
|---|---|--|

Observed in trans with a dominant variant

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

1) Criteria Bar

Variant Interpretation Record

[Associate with Disease](#)

Benign:
 No criteria met

Pathogenic:
 No criteria met

Calculated Pathogenicity (ACMG 2015):
 None

Basic Information

Population

Predictors

Experimental

Segregation/Case

Gene-centric

Set this evidence category as complete ☐

3) Curation checkbox

Highest Minor Allele Frequency
 Population: African
 # Variant Alleles: 139
 Total # Alleles Tested: 1452

Source: ExAC
 Allele Frequency: 0.09573
 Desired CI:
 CI - lower: 0.08165
 CI - upper: 0.11195

ExAC Constraint Score
[View pLI in ExAC](#)

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
Disease dependent

4) Criteria evaluation

BA1:

- or -

PM2:

- or -

BS1:

MAF cutoff: %

Explanation:

5) Disease-dependent criteria

[Save](#)

Note that the “View Summary” button in this version is not yet functional (indicated by the yellow bar to its left).

3. Interpretation with Disease Association

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

NM_005902.3(SMAD3):c.-28C>T
This interpretation is not yet associated with a disease

[View Summary](#)

| Variant ID Sources | Variant Genomic Context | Interpretations |
|--|---|--|
| ClinVar VariationID: 139214 dbSNP ID: rs144374592 | UCSC [GRCh38/hg38 GRCh37/hg19] Variation Viewer [GRCh38 GRCh37] Ensembl Browser [GRCh38 GRCh37] | My interpretations: In Progress, (last edited 2016 Aug 18, 4:02 pm) ✓ Other interpretations: ClinGen Test Curator, In Progress, (last edited 2016 Aug 18, 4:01 pm) ClinGen Test Curator, In Progress, (last edited 2016 Aug 18, 4:01 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 [Associate with Disease](#)

| | | |
|-----------------------------------|---------------------------------------|--|
| Benign: No criteria met | Pathogenic: No criteria met | Calculated Pathogenicity (ACMG 2015): None |
|-----------------------------------|---------------------------------------|--|

Basic Information Population Predictors Experimental Segregation/Case Gene-centric

Set this evidence category as complete ☐

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 all disease-independent criteria evaluation boxes will become active and you will see the disease term under the variant name in the gray title area

NM_005902.3(SMAD3):c.-28C>T
This interpretation is associated with the disease: Aneurysm-osteoarthritis syndrome

[View Summary](#)

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, a light blue box contains three criteria: BA1 (Allele frequency is > 5% in ExAC, 1000 Genomes, or ESP), PM2 (Absent from controls...), and BS1 (Allele frequency greater than expected...), with a "Disease dependent" tag at the bottom. To the right, there are three dropdown menus for BA1, PM2, and BS1, each currently set to "Not Evaluated". Between the dropdowns are "- or -" labels. To the right of the dropdowns is a "MAF cutoff:" field with a value of "5" and a "%" symbol. Below that is an "Explanation:" text area. A "Save" button is in the bottom right corner.

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.”
- **_S, _M, _P, _VS, _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_P would be PM2 evaluated at the “supporting” (_P) level rather than its inherent level, moderate (M)). *Note: Benign criteria allow _P, _S, and _stand alone adjustments. Pathogenic criteria allow _P, _M, and _S adjustments (except for PS2, which also allows for PS2_VS).*

(See examples, next page)

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

- or -

PM2: Not Evaluated

- or -

BS1: Not Evaluated

Disease dependent

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

Disease dependent

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 Met

- or -

BS1: Not Met

MAF cutoff: 5 %

Explanation:

Evaluations for BA1, PM2, BS1 saved successfully!

Update

Disease dependent

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 notes:

If a criterion is grayed out, you will not be able to evaluate it until you associate a disease with the Interpretation (note BS1, below)

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

- or -

PM2: Not Evaluated

- or -

BS1: Not Evaluated

MAF cutoff: 5 %

Explanation:

Save

PS2 and PM4 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

PATHOGENICITY CALCULATION

As you Save your evaluation, you will notice that the Progress bar will indicate the number of criteria met according to the strength of the evaluation and whether it is 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 | | | | | | Edit Disease |
|-------------------------------|------------|---|--------------|---|--------------|--------------|
| Benign: No criteria met | | Pathogenic: Very strong: 1 Moderate: 2 | | Calculated Pathogenicity (ACMG 2015): Pathogenic | | |
| Basic Information | Population | Predictors | Experimental | Segregation/Case | Gene-centric | |

Pathogenicity outcomes:

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 top 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:

| Variant Interpretation Record | | | | | | Edit Disease |
|--|------------|---|----------------|---|--------------|--------------|
| Benign: No criteria met | | Pathogenic: Very strong: 1 Moderate: 2 | | Calculated Pathogenicity (ACMG 2015): Pathogenic | | |
| Basic Information | Population | Predictors | Experimental ✓ | Segregation/Case | Gene-centric | |
| Set this evidence category as complete <input checked="" type="checkbox"/> | | | | | | |

This checkbox will remain no matter which tab you are on in the interface and can be unchecked as well:

| Variant Interpretation Record | | | | | | Edit Disease |
|--|------------|---|----------------|---|--------------|--------------|
| Benign: No criteria met | | Pathogenic: Very strong: 1 Moderate: 2 | | Calculated Pathogenicity (ACMG 2015): Pathogenic | | |
| Basic Information | Population | Predictors | Experimental ✓ | Segregation/Case ✓ | Gene-centric | |
| Set this evidence category as complete <input checked="" type="checkbox"/> | | | | | | |

Feedback and Comments?

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