

Gene Curation Interface

Help Documentation - January 2017

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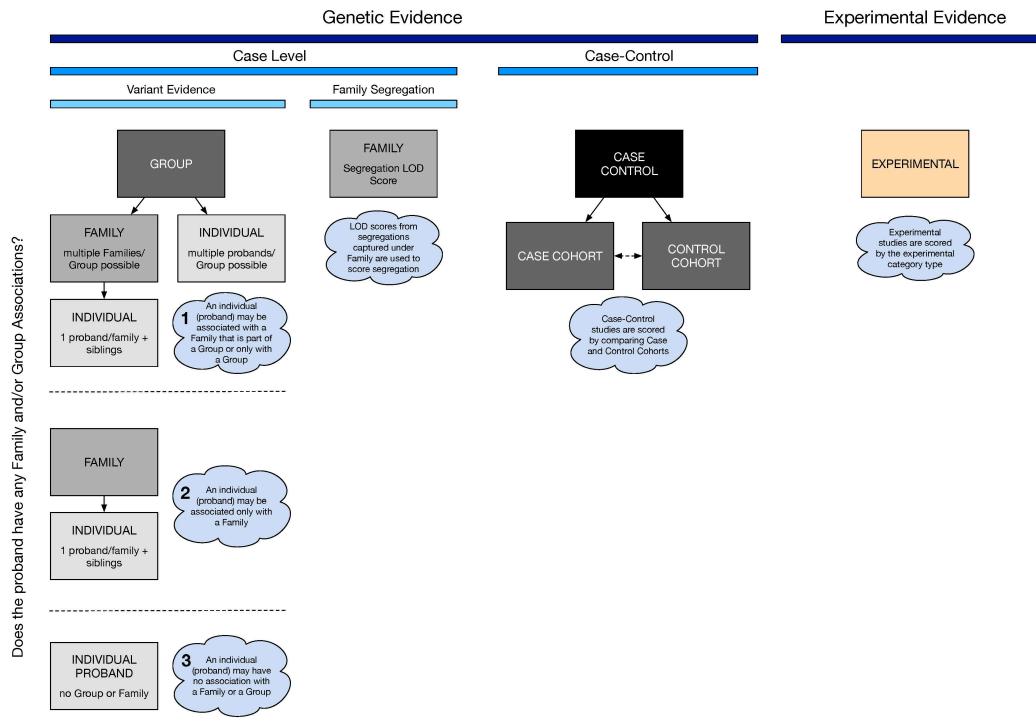
1. Curate Experimental Information

1. Scoring Table
2. Provisional Classification Table

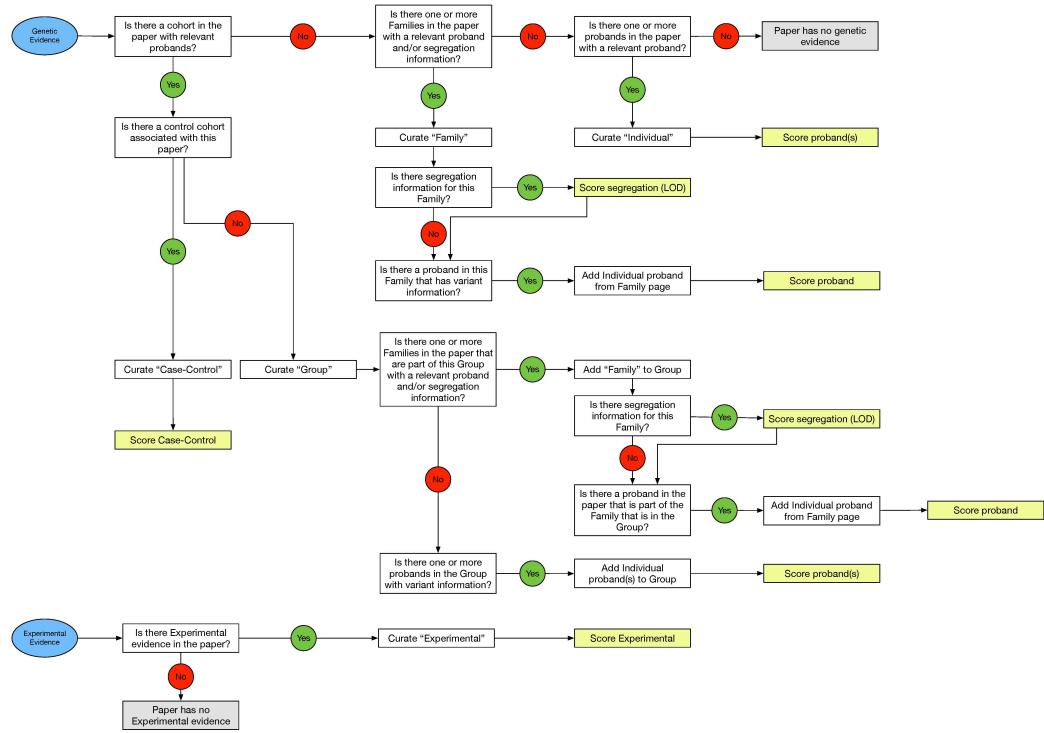
Feedback / Comments? Please email us at: clingen-helpdesk@lists.stanford.edu

OVERVIEW OF CURATION

1. Quick Reference Guide



2. Curator Workflow



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.

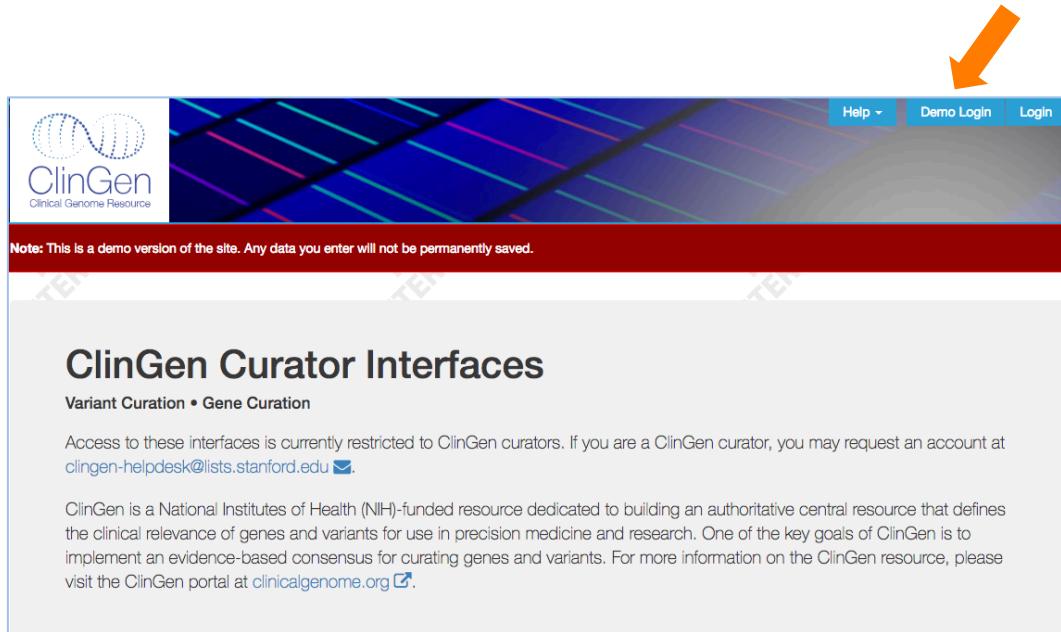
2. How to Register

- i. You may request an account by emailing us at clingen-helpdesk@lists.stanford.edu.
- ii. 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 any ClinGen CDWGs with which you are associated. Please note that if you have an email address that is associated with a Google account, you will be able to use Google to log in to the ClinGen interfaces.
- iii. We will write back to you to confirm when your email address has been registered and can be used for logging in to the interfaces (usually within 24 hours).

LOGGING IN

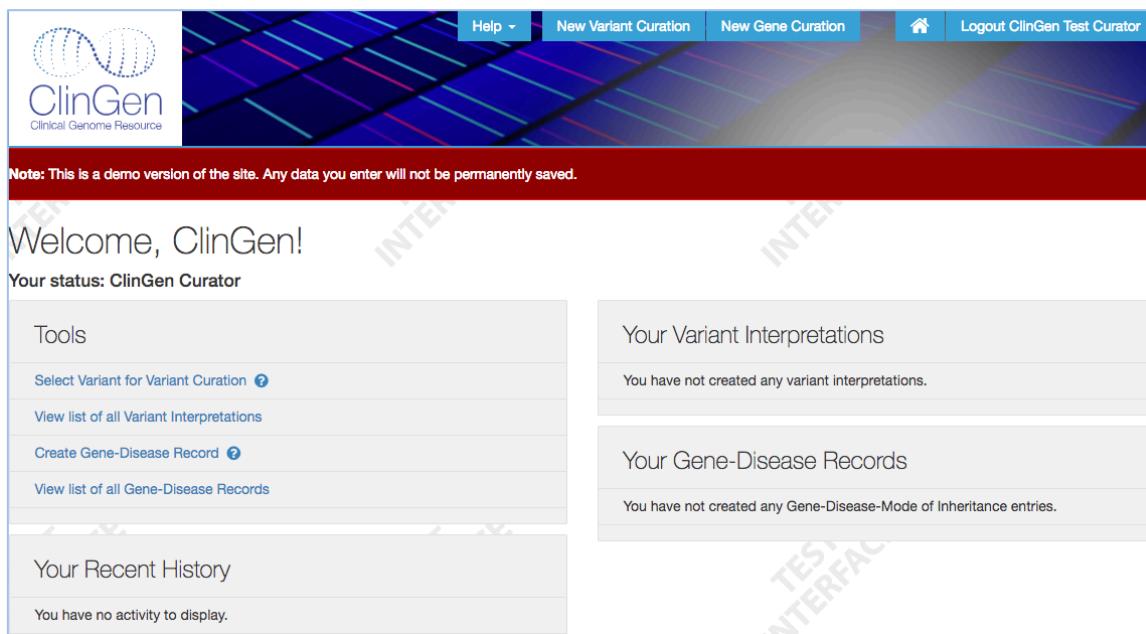
1. Demo Login

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.



The screenshot shows the ClinGen Curator Interfaces demo login page. At the top, there is a navigation bar with the ClinGen logo, a search bar, and buttons for 'Help', 'Demo Login', and 'Login'. A red note at the bottom of the page states: 'Note: This is a demo version of the site. Any data you enter will not be permanently saved.' An orange arrow points to the 'Demo Login' button.

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

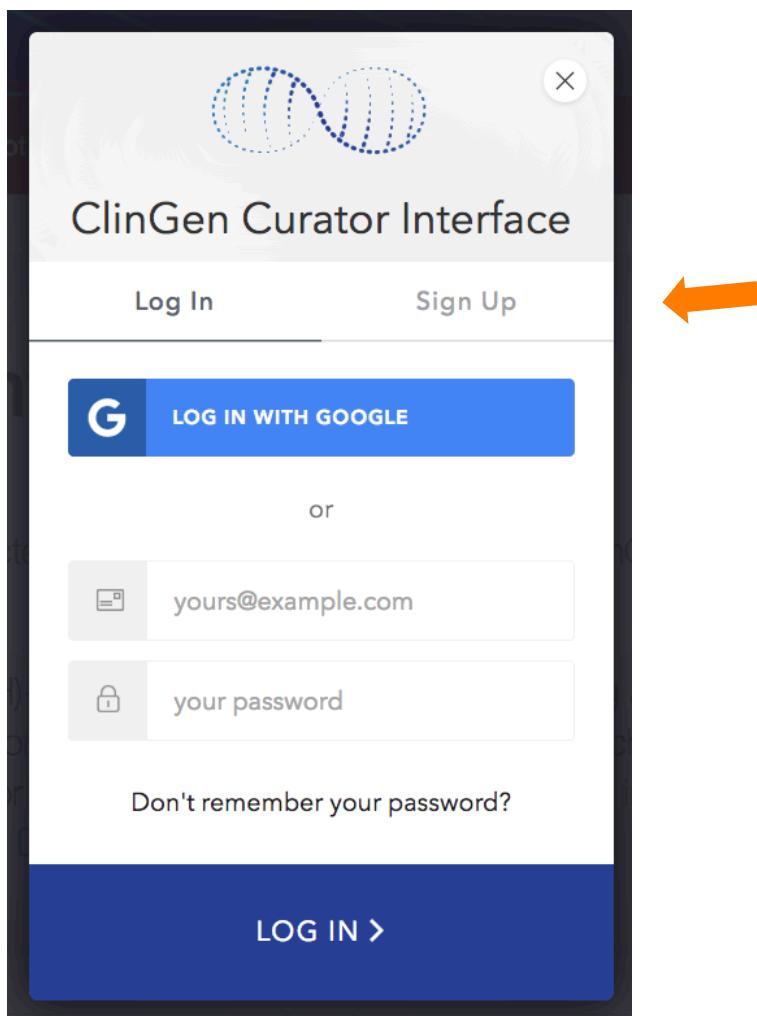


The screenshot shows the ClinGen Curator Interfaces dashboard. At the top, there is a navigation bar with the ClinGen logo, a search bar, and buttons for 'Help', 'New Variant Curation', 'New Gene Curation', and 'Logout ClinGen Test Curator'. A red note at the bottom of the page states: 'Note: This is a demo version of the site. Any data you enter will not be permanently saved.' The main content area includes sections for 'Welcome, ClinGen!', 'Your status: ClinGen Curator', 'Tools' (with links to 'Select Variant for Variant Curation', 'View list of all Variant Interpretations', 'Create Gene-Disease Record', and 'View list of all Gene-Disease Records'), 'Your Recent History' (with a message 'You have no activity to display.'), 'Your Variant Interpretations' (with a message 'You have not created any variant interpretations.'), and 'Your Gene-Disease Records' (with a message 'You have not created any Gene-Disease-Mode of Inheritance entries.').

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.

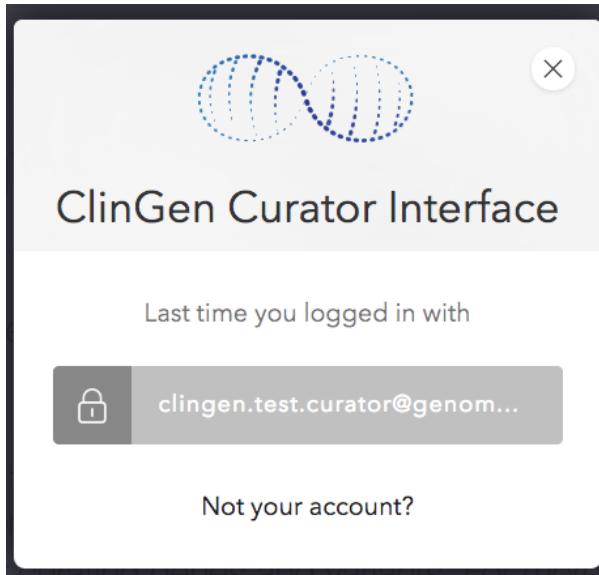
- a. If you are a first time user you will need to go to the “Sign Up” tab and enter your registered email address, enter your desired password, and then click “Sign Up.”



As a first time user, you 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 now be able to “log in” using your email and password.

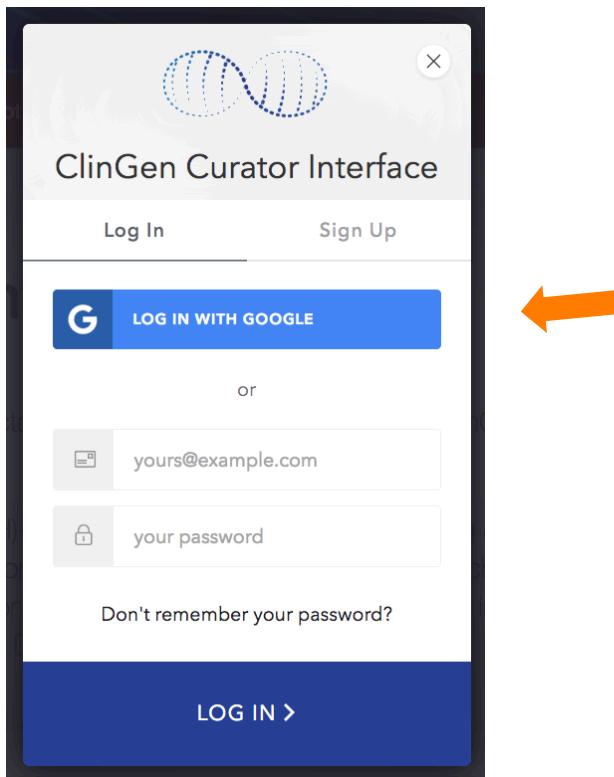
- b. If you are a returning user accessing the interfaces from a different operating system then you will see the pop-up above, in which case you should re-enter your registered email address and your selected password on the “Log In” tab and then click “LOG IN.”

- 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 emails that are associated with a Google account and 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 – Lists all Interpretations curated to date by any curator, along with each Interpretation’s status, creator, date created & date last edited.
- g Navigating to “Create Gene-Disease Record” (described below)
- h View a list of all Gene-Disease Records – Lists all Gene-Disease Records curated to date by any curator, along with each record’s status, creator, date created & 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 can only view their own history. Each highlighted text is a direct link to the relevant section of the Gene Disease Record or Interpretation.
- j View of the Interpretations created by the logged in curator. Each highlighted text is a direct link to the Interpretation.
- k View of the Gene-Disease records created by the logged-in curator. Each highlighted text is a direct link to the Gene-Disease Record.
- m Logout – available from all pages

The screenshot shows the ClinGen Test Curator interface. At the top, there's a navigation bar with the ClinGen logo, a search bar containing 'INTERPRETATION', and links for 'Help', 'New Variant Curation', 'New Gene Curation', a house icon, and 'Logout ClinGen Test Curator'. Below the navigation bar, a note says 'Note: This is a demo version of the site. Any data you enter will not be permanently saved.' The main content area is divided into several sections:

- Your Recent History (i):** Shows a list of recent additions:
 - Family FAMILY1 added to **DICER1-Achondroplasia-Autosomal dominant inheritance** for **PMID:19711917**; 2016 Dec 13, 4:47 pm
 - PMID:5555555** added to **DICER1-Achondroplasia-Autosomal dominant inheritance**; 2016 Dec 13, 4:46 pm
 - Disease **X-linked non-syndromic intellectual disability** associated with Interpretation **NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)-X-linked non-syndromic intellectual disability**; 2016 Dec 13, 4:46 pm
- Your Variant Interpretations (j):** Shows a single entry:

NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)
Disease: X-linked non-syndromic intellectual disability
Mode of Inheritance: None added
Status: Provisional
Creation Date: 2016 Dec 13, 4:45 pm
- Your Gene-Disease Records (k):** Shows a single entry:

DICER1-Achondroplasia-Autosomal dominant inheritance
Status: In Progress
Creation Date: 2016 Dec 13, 4:29 pm

CREATING A GENE-DISEASE RECORD

Note: Currently, once a Gene:Disease Record has been created, none of the selected fields (gene, disease, mode of inheritance, or adjective) can be altered for this Record. This includes adding an adjective to a Gene:Disease:Mode of inheritance record that has already been created or editing an adjective associated with a record. Please be certain you have selected the desired fields correctly from the beginning.

1. Identifying the Gene

A curator is required to identify the specific gene by entering an approved HGNC gene symbol. A link out to HGNC (www.genenames.org) is provided for a curator to look up the correct symbol for their gene.

Enter HGNC gene symbol * E.G. DICER1

Enter Orphanet ID * E.G. ORPHA15

Mode of Inheritance * Select

Select an adjective Select

Submit

2. Identifying the Disease

A curator is required to identify the specific disease by entering an Orphanet ID. A link out to Orphanet (www.orpha.net) is provided for a curator to look up the correct ID for their disease. *Please contact clingen-helpdesk@lists.stanford.edu if you are having difficulty finding an Orphanet term for the disease you are curating.*

Enter HGNC gene symbol * E.G. DICER1

Enter Orphanet ID * E.G. ORPHA15

Mode of Inheritance * Select

Select an adjective Select

Submit

3. Identifying the Mode of Inheritance

A curator is required to identify the specific Mode of Inheritance by choosing from the selection available in the pull-down.

The screenshot shows a form with fields for entering HGNC gene symbols and Orphanet IDs. Below these, a 'Mode of Inheritance' field is marked with an asterisk, with the placeholder 'Select an adjective'. A dropdown menu is open, titled 'Select', listing the following options: 'Autosomal dominant inheritance (HP:0000006)', 'Autosomal recessive inheritance (HP:0000007)', 'Mitochondrial inheritance (HP:0001427)', 'X-linked inheritance (HP:0001417)', 'Other', and 'Unknown'. An orange arrow points to the right side of the dropdown menu.

4. Selecting an Adjective (optional)

A curator can add an adjective to the Mode of Inheritance by choosing from the selection available in the pull-down.

The screenshot shows the same form as above, but the 'Mode of Inheritance' field now contains the selected value 'Autosomal dominant inheritance (HP:0000006)'. The 'Select an adjective' field is present below it. A dropdown menu is open, titled 'Select', listing the following options: 'with maternal imprinting', 'with paternal imprinting', 'sex-limited', 'with genetic anticipation', and 'primarily or exclusively de novo'. An orange arrow points to the right side of the dropdown menu.

Note: Currently, once a Gene:Disease Record has been created, none of the selected fields (gene, disease, mode of inheritance, or adjective) can be altered for this Record. This includes adding an adjective to a Gene:Disease:Mode of inheritance record that has already been created or editing an adjective associated with a record. Please be certain you have selected the desired fields correctly from the beginning.

STEPS TO BEGINNING A GENE:DISEASE CURATION

1. “Record Curation” page

This is the landing page/homepage for each Gene-Disease curation.

- a. Gene Symbol and Disease selected by a curator.
- b. Mode of Inheritance selected by a curator. If a curator selected an adjective, the adjective will appear in parentheses.
- c. “Record Curation” home – available from all pages, returns curator to this “Record Curation” page
- d. Reports last saved Summary and any Provisional Classifications for the Gene-Disease record.
- e. Generate Summary button – generates score for Gene:Disease pair based on entered evidence and ClinGen Clinical Validity Classification framework; available from most pages.
- f. Gene symbol, with links to HGNC and NCBI Gene.
- g. Disease name, with links to Orphanet and OMIM.
- h. Status of the Gene-Disease record with the name of the creator and when it was curated. This panel will update as the status of the record changes.

a SMAD3 – X-linked non-syndromic intellectual disability  **c**
b Autosomal dominant inheritance (with maternal imprinting)

Last Saved Summary & Provisional Classification
No Reported Evidence **d**

e [Generate Summary](#)

SMAD3 f HGNC Symbol: SMAD3  NCBI Gene ID: 4088 	X-linked non-syndromic intellectual f disability Orphanet ID: ORPHA777  OMIM  ID: [Add]	Status: In Progress h Creator: ClinGen Test Curator — 2017 Jan 17, 4:08 pm Participants: ClinGen Test Curator Last edited: ClinGen Test Curator — 2017 Jan 17, 4:08 pm
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[Add New PMID](#)

Add papers to this Gene-Disease Record using the Add New PMID(s) button; click on any added paper to view its abstract and begin curating evidence from that paper.

Note: The information shown is for example use only

3. Adding a PubMed article to the Gene-Disease Record

- i. To add a PubMed article to the Gene-Disease record click the “Add New PMID” button .

SMAD3 – X-linked non-syndromic intellectual disability  **c**
d Autosomal dominant inheritance (with maternal imprinting)

Last Saved Summary & Provisional Classification
No Reported Evidence

[Generate Summary](#)

SMAD3 HGNC Symbol: SMAD3  NCBI Gene ID: 4088 	X-linked non-syndromic intellectual disability Orphanet ID: ORPHA777  OMIM  ID: [Add]	Status: In Progress Creator: ClinGen Test Curator — 2017 Jan 17, 4:08 pm Participants: ClinGen Test Curator Last edited: ClinGen Test Curator — 2017 Jan 17, 4:08 pm
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[Add New PMID](#)

Add papers to this Gene-Disease Record using the Add New PMID(s) button; click on any added paper to view its abstract and begin curating evidence from that paper.

Note: The information shown is for example use only

- ii. Enter the PMID into the modal that appears and click the “Retrieve PubMed Article” button.

Add new PubMed Article

Enter a PMID *

Retrieve PubMed Article

Cancel Add Article



- iii. Based on the PMID entered the authors, title, and citation details will be auto-filled. If these details are correct then a curator can add that PMID to the Gene-Disease Record by clicking the “Add Article” button.

Add new PubMed Article

Enter a PMID *

Retrieve PubMed Article

Select "Add Article" (below) if the following citation is correct; otherwise, edit the PMID (above) to retrieve a different article.

Baumstark JS, Lee CT, Luby RJ. A new method for the determination of alpha1-protease inhibitor (alpha1-antitrypsin) phenotypes based on the formation of alpha1-protease inhibitor allele product-elastase complexes.
Biochimica et biophysica acta. 1976 Sep 28;446(1):287-300. PMID:
10000 ↗

Cancel Add Article



- iv. The PMID has now been added to the Curation Central view for that Gene-Disease Record.
- a. All articles that have been added to the record can be found in a scrollable panel on the left-hand side, with the first author, title, citation details, and PMID shown for each article. By default a newly added article will be the one selected for curation in the interface, as shown by a blue border. To select an alternative article for curation, a curator simply needs to click on that article in the left-hand panel.
- b. The central panel shows more details about the article selected by a curator, including all authors, the title, a link to PubMed, and the full abstract.
- c. An evidence curation palette on the right-hand side provides now provides access to curation resources for adding Genetic and Experimental Evidence found in the selected article.
- d. Further articles can be added to the Gene-Disease Record by clicking the “Add New PMID” button.

SMAD3 – X-linked non-syndromic intellectual disability

Autosomal dominant inheritance (with maternal imprinting)

Last Saved Summary & Provisional Classification

No Reported Evidence

Generate Summary

SMAD3 HGNC Symbol: SMAD3 NCBI Gene ID: 4088	X-linked non-syndromic intellectual disability Orphanet ID: ORPHA777 OMIM ID: [Add]	Status: In Progress Creator: ClinGen Test Curator — 2017 Jan 17, 4:08 pm Participants: ClinGen Test Curator Last edited: ClinGen Test Curator — 2017 Jan 17, 4:08 pm
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Add New PMID **d**

a
Baumstark JS et al. A new method for the determination of alpha1-protease inhibitor (alpha1-antitrypsin) phenotypes based on the formation of alpha1-protease inhibitor allele product-elastase complexes. *Biochimica et biophysica acta*. 1976 Sep 28;446(1):287-300.
PMID: 10000

b
Baumstark JS, Lee CT, Luby RJ. A new method for the determination of alpha1-protease inhibitor (alpha1-antitrypsin) phenotypes based on the formation of alpha1-protease inhibitor allele product-elastase complexes. *Biochimica et biophysica acta*. 1976 Sep 28;446(1):287-300.
PubMed

Abstract
Up until now it has been assumed that the protease-binding property of alpha1-protease inhibitor (alpha1PI) was destroyed by acid starch gel electrophoresis (pH 4.9). Analyses on acid starch gel blocks for pH and conductivity changes during and following a typical electrophoretic run showed that it was unlikely that the separating alpha1PI would be exposed to pH values lower than 6.2, and that the allele products, following the passage of the buffer front, were in an environment of constant pH(6.3), extremely low conductivity and high field strength. These results strongly suggested the likelihood that alpha1-PI would be chemically and physically unchanged as a result of exposure to acid starch gel electrophoresis. In order to test this likelihood, human serum was electrophoretically separated in acid starch gel and following electrophoresis, was immersed in 0.1 M diethylbarbiturate buffer, pH 8.6, containing 20 mug/ml of pancreatic elastase. The pH-adjusted (8.15) and elastase-impregnated starch gel layer was superimposed on hemoglobin-agar for 2.5 h at 37 degrees C followed by immersion of the hemoglobin-agar layer in 1% NaCl overnight, distilled water for 2 h, drying under filter paper and staining. The results showed zones of

Evidence for PMID:10000 **c**

Genetic Evidence

> Case Level

Group
Family
Individual

> Case-Control

Case-Control

Experimental Evidence

Experimental Data

Associated Variants

Note: The information shown is for example use only

3. Collecting Evidence

The gene curation palette on the right-hand side is the starting point for adding evidence for a selected article. To begin curation a curator clicks the ‘+’ sign next to specific type of evidence they wish to curate.

ADDING GENETIC EVIDENCE

1. Curate Group Information – to add a new Group, click the “+” on the blue bar that says “Group” (or anywhere else on that blue bar). Note: A Group represents a cohort that does not have associated control groups; for curating Case-Control information, add a “Case-Control.” (described further down in this section).

Evidence for PMID:10000

Genetic Evidence

> Case Level

- Group +
- Family +
- Individual +

> Case-Control

- Case-Control +

Experimental Evidence

- Experimental Data +

Associated Variants

The top of the landing page to Curate Group Information shows the authors, title, and citation details for the selected PubMed article in a yellow box below the header. A curator is required to enter a label for the Group, if possible using a label described in the paper.

Baumstark JS, Lee CT, Luby RJ. A new method for the determination of alpha1-protease inhibitor (alpha1-antitrypsin) phenotypes based on the formation of alpha1-protease inhibitor allele product-elastase complexes. *Biochimica et biophysica acta*. 1976 Sep 28;446(1):287-300. PMID: 10000

Curate Group Information

Group // Group EXAMPLE-GROUP-LABEL1

Group Label: * EXAMPLE-GROUP-LABEL1

Please enter a label to help you keep track of this Group within the interface - if possible, please use the label described in the paper.

The rest of the Curate Group Information page is split into relevant sections based on the type of evidence:

i. Group – Common Disease(s) & Phenotype(s)

A curator is required to enter at least one of the following to describe disease(s)/phenotype(s) common to the group:

- a) Orphanet ID(s)
- b) HPO ID(s)
- c) Phenotype free text -- Note: *the use of HPO terms whenever possible is strongly encouraged*

Group – Common Disease(s) & Phenotype(s)

Please enter an Orphanet ID(s) and/or HPO ID(s) and/or Phenotype free text (required).

Disease(s) in Common (Orphanet term): **a**

Phenotype(s) in Common (HPO ID(s)): **b**

Phenotype(s) in Common (free text): **c**

Enter phenotypes that are NOT present in Group if they are specifically noted in the paper.

NOT Phenotype(s) (HPO ID(s)):

NOT Phenotype(s) (free text):

ii. Group – Demographics

Enter information about the demographics of the group.

Group – Demographics

# males:	<input type="text"/>
# females:	<input type="text"/>
Country of Origin:	No Selection <input type="button" value="▼"/>
Ethnicity:	No Selection <input type="button" value="▼"/>
Race:	No Selection <input type="button" value="▼"/>
Age Range	
Type:	No Selection <input type="button" value="▼"/>
Value:	<input type="text"/> to <input type="text"/>
Unit:	No Selection <input type="button" value="▼"/>

iii. Group – Information

Enter information about the individuals in the group. A curator is required to enter the total number of individuals in the group.

Group – Information

Total number individuals in group: *	<input type="text"/>
# individuals with family information:	<input type="text"/>
# individuals WITHOUT family information:	<input type="text"/>
# individuals with variant in gene being curated:	<input type="text"/>
# individuals without variant in gene being curated:	<input type="text"/>
# individuals with variant found in other gene:	<input type="text"/>
Other genes found to have variants in them (HGNC  symbol):	<input type="text"/> E.G. DICER1, SMAD3



iv. Group – Methods

Enter information about the methods used to obtain genetic data for the Group.

Group – Methods

Previous Testing: No Selection

Description of Previous Testing:

Were genome-wide analysis methods used to identify the variant(s) described in this publication?: No Selection

Genotyping Method

Method 1: No Selection

Method 2: No Selection

Entire gene sequenced?: No Selection

Copy number assessed?: No Selection

Specific mutations genotyped?: No Selection

Description of genotyping method:

v. Group – Additional Information

Enter any additional information about the Group.

Group – Additional Information

Additional Information about Group:

Enter PMID(s) that report evidence about this same Group: e.g. 12089445, 21217753

Note: Any variants associated with probands that will be counted towards the Classification are not captured at the Group level - variants and their association with probands are required to be captured at the Family or Individual level. Once you submit the Group information, you will be prompted to enter Family/Individual information.

vi. Cancel/Save buttons

- a. Clicking the “Cancel” button, found at the bottom of the Curate Group Information page, will return a curator to the Record Curation page without saving any entered data.

- b. Clicking the “Save” button, found at the bottom of the Curate Group Information page, is the only way to save all the Group data added by a curator. Navigating away from this page without saving will result in the loss of any entered data.
- c. After clicking the “Save” button if any of the required fields (described above) are not filled in, then a **red text warning** will appear next to the buttons.

Please fix errors on the form and resubmit.

- Additionally, a red text warning will appear next to the required fields that need to be curated before the page can be saved.

Total number individuals in group: *

Required

2. Curate Family Information

If the Family to be entered is part of a Group already curated in this Gene-Disease Record then it can be added when prompted after saving a Group by selecting ‘Yes’ from the pull-down, and then ‘Add New Family for this Group’:

Do any of the probands or other individuals in this Group have Family Information?

Note: Family Information includes any information about a proband in the group that is part of family and any relatives of the proband (e.g. average age of onset, race, family ethnicity, etc.) and information about segregation of phenotype(s) and variant(s).

Any variant associated with a proband in a Family is captured at the Family level.

To associate segregation, variant, or any other information for a family, **Add New Family for this Group.**

If you have previously created an entry for this Family, **Return to Record Curation page** to add this Family to the newly created Group.

OR

Alternatively, It can be added directly from that Group in the curation palette on the Record page.

Evidence for PMID:10000

Genetic Evidence

> Case Level

Group +

EXAMPLE-GROUP-LABEL
ClinGen Test Curator
2017 Jan 06, 2:51 pm
[View](#) | [Edit](#)
[Add new Family to this Group](#)
[Add new Individual to this Group](#)

To add a new Family that is not associated with a Group, click the Family ‘+’ in the curation palette (or anywhere on that blue bar).

Evidence for PMID:10000

Genetic Evidence

> Case Level

Group +

Family +

Individual +

> Case-Control

Case-Control +

Experimental Evidence

Experimental Data +

Associated Variants

The top of the landing page to Curate Family Information shows the authors, title, and citation details for the selected PubMed article in a yellow box below the header. A curator is required to enter a label for the Family, if possible using a label described in the paper.

Baumstark JS, Lee CT, Luby RJ. A new method for the determination of alpha1-protease inhibitor (alpha1-antitrypsin) phenotypes based on the formation of alpha1-protease inhibitor allele product-elastase complexes. *Biochimica et biophysica acta*. 1976 Sep 28;446(1):287-300. PMID: 10000 ↗

Curate Family Information

Group EXAMPLE-GROUP-LABEL // No entry

Family Label: *

Please enter a label to help you keep track of this Family within the interface - if possible, please use the label described in the paper.

An orange arrow points to the 'Family Label' input field.

The rest of the Curate Family Information page is split into relevant sections based on the type of evidence. The first three sections are in a similar format to the same sections in the Curate Group Information:

- i. Family – Disease(s) & Phenotype(s)
- ii. Family – Demographics
- iii. Family – Methods
- iv. Family – Segregation. This section is split into two separate sections for adding information on tested individuals and LOD score respectively.

Fields for entering information on Tested Individuals within a Family. **Note: please refer to the Gene Curation SOP for help if you are uncertain how to obtain the numbers required for segregation.**

- a) For a Dominant and Recessive disease/phenotype a curator is required to enter the total number of AFFECTED individuals in the Family WITH the genotype for that disease/phenotype. *This field is required to calculate the estimated LOD score for recessive diseases.*
- b) For a Recessive disease/phenotype a curator is required to enter the total number of UNAFFECTED individuals in the Family WITHOUT the biallelic genotype for that disease/phenotype. *This field is required to calculate the LOD score for recessive diseases.*
- c) Enter the total number of segregations reported for the Family. *This field is used to calculate an estimated LOD score for dominant and X-linked diseases.*
- d) If there are any inconsistent segregations amongst the TESTED Individuals then 'Yes' should be selected from the pull-down. If not, then select 'No'.
- e) If 'Yes' is selected in the prior field then optional free text can be added here to describe the inconsistent segregations.
- f) If the Family is consanguineous then 'Yes' should be selected from the pull-down. If not, then select 'No'. If this is unknown then selected 'Not Specified'.

- g) If a pedigree was provided in the publication, then optional free text can be added here to describe the location of the pedigree within the paper.

Family – Segregation

► Tested Individuals

For Dominant AND Recessive inheritance: a Number only
Number of AFFECTED individuals *WITH* genotype? *

For Recessive inheritance only: b Number only
Number of UNAFFECTED individuals *WITHOUT* the biallelic genotype? (required for Recessive inheritance)

Number of segregations reported for this Family: c Number only
(required for calculating an estimated LOD score for Dominant inheritance)

Were there any inconsistent segregations amongst TESTED individuals? (i.e. affected individuals *WITHOUT* the genotype or unaffected individuals *WITH* the genotype?) d No Selection

please provide explanation: (optional) e

Is this family consanguineous?: f No Selection

If pedigree provided in publication, please indicate location: g e.g. Figure 3A

For entering information on a LOD Score for the Family, there are two separate scenarios based on whether the LOD score was published in the paper or not.

Published LOD Score

Select 'Yes' from the pull-down.

► LOD Score (select one to include as score):

Published LOD score?: ✓ No Selection

Include LOD score in final aggregate calculation?
Yes
No



Enter the value of the published LOD score.

➤ LOD Score (select one to include as score):

Published LOD score?:	Yes
Published Calculated LOD score:	0.72



If the entered published LOD score should be included in the final aggregate calculation then 'Yes' must be selected from the pull-down.

If the entered published LOD score should NOT be included in the final aggregate calculation then 'No' should be selected from the pull-down.

A box is provided to add free text to 'Explain reasoning' behind this decision. A further free text box allows 'Additional Segregation Information' to be entered.

➤ LOD Score (select one to include as score):

Published LOD score?:	Yes
Published Calculated LOD score:	0.72
Include LOD score in final aggregate calculation?	<input checked="" type="checkbox"/> No Selection <input type="checkbox"/> Yes <input type="checkbox"/> No
Explain reasoning:	
Additional Segregation Information:	



Estimated LOD Score

If there is no Published LOD Score then Select 'No' from the pull-down. If the required Tested Individual fields (see above) have been entered then the Estimated LOD score will be calculated automatically within the interface.

➤ LOD Score (select one to include as score):

Published LOD score?:	No
Estimated LOD score: <small>(optional, and only if no published LOD score)</small>	0.3



If the estimated LOD score should be included in the final aggregate calculation then 'Yes' must be selected from the pull-down.

If the estimated LOD score should NOT be included in the final aggregate calculation then 'NO' should be selected from the pull-down.

A box is provided to add free text to 'Explain reasoning' behind this decision. A further free text box allows 'Additional Segregation Information' to be entered.

► LOD Score (select one to include as score):

Published LOD score?:	No
Estimated LOD score: <small>(optional, and only if no published LOD score)</small>	0.3
Include LOD score in final aggregate calculation?	<input checked="" type="checkbox"/> No Selection Yes No
Explain reasoning:	
Additional Segregation Information:	



v. Family – Variant(s) Segregating with Proband

To score the proband for a Family in addition to the LOD score for the segregation, an Individual proband will need to be created including adding their associated variant(s) (see next figure).

- a. A curator is required to enter a label for the Proband, if possible using a label described in the paper. A real name should not be entered.
- b. The Orphanet ID(s) for the disease(s) associated with the Family automatically shown.
- c. Enter the Orphanet ID(s) for the disease(s) associated with the Individual.
- d. Click this button to automatically copy the Orphanet ID(s) for the disease(s) associated with the Family to the field above for the Individual.
- e. Check this box if the Individual is homozygous.
- f. Check this box if the Individual is hemizygous.
- g. Click this button to add the first variant associated with the Individual via a ClinVar ID.
- h. Click this button to add the first variant associated with the Individual via a ClinGen Allele Registry CA ID.
- i. Click this button to add a second variant (where appropriate) associated with the Individual via a ClinVar ID.
- j. Click this button to add a second variant (where appropriate) associated with the Individual via a ClinGen Allele Registry CA ID.

Family – Variant(s) Segregating with Proband

If you would like to score the proband for this family in addition to the LOD score for segregation, you need to create the Individual proband, including adding their associated variant(s). Please follow the steps below -- you will be able to add additional information about the proband following submission of Family information.

Note: Probands are indicated by the following icon:

Once this Family page is saved, an option to score and add additional information about the proband (e.g. demographics, phenotypes) will appear.

Proband Label * **a** EXAMPLE-PROBAND1

Note: Do not enter real names in this field. Please enter a label to help you keep track of this individual within the interface - if possible, please use the label described in the paper.

Orphanet Disease(s) Associated with Family: **b** ORPHA77

Orphanet Disease(s) for Individual * **c** E.G. ORPHA15

d Copy Orphanet IDs from Family

Check here if homozygous: **e**
(Note: if homozygous, enter only 1 variant below)

Check here if hemizygous: **f**

Add Variant: **g** Add ClinVar ID - or - **h** Add CA ID

Add Variant: **i** Add ClinVar ID - or - **j** Add CA ID

Adding Variants

When adding a Variant associated with an Individual via the ‘Add ClinVar ID’ or ‘Add CA ID’ buttons, a pop-up window will appear. Enter the ClinVar ID or CA ID into the window and click the ‘Retrieve from ClinVar’ or ‘Retrieve from ClinGen Allele Registry’ button respectively.

ClinVar Variant

Enter ClinVar VariationID *
37644

Retrieve from ClinVar

Enter a ClinVar VariationID. The VariationID can be found in the light blue box on a variant page (example: 139214 .

Cancel **Save**

Check the evidence retrieved for either the ClinVar ID or CA ID you have entered and once you are convinced the ID you have entered represents the correct variant, Select 'Save' to add that variant to the Individual.

The screenshot shows a web-based interface titled "ClinVar Variant". At the top, there is a field labeled "Enter ClinVar VariationID *" containing the value "10505". Below this is a blue button labeled "Retrieve from ClinVar". The main content area displays the retrieved data for VariationID 10505, which includes several HGV terms. At the bottom right of the data area are two buttons: "Cancel" and "Save". An orange arrow points to the "Save" button. The entire interface has a dark grey header bar.

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

The variants added via the ClinVar and/or CA IDs can now be seen associated with the Proband (see next figure):

- a. ClinVar Variation ID with linkout to ClinVar.
- b. ClinVar Preferred Title for the variant.
- c. Link within the Interface to 'Curate Variant Information' so that curator can enter the gene impact for that variant.
Note: A variant's gene impact must be specified in order to score the Proband.
- d. Link within the Interfaces to the 'Evidence View' in the Variant Curation Interface so that curator can view all known evidence (both programmatic and manually entered from papers) for that variant.
- e. Clear the selected variant.
- f. ClinGen Allele Registry ID with linkout to the ClinGen Allele Registry.
- g. HGV Title for the current genome build. Shown only for novel variant that cannot be found in ClinVar.

<p>ClinVar Variation ID: a 10505</p> <p>ClinVar Preferred Title: b NM_020061.5(OPN1LW):c.607T>C (p.Cys203Arg)</p> <p>Note: a variant's gene impact must be specified in order to score this proband.</p> <p>c Curate variant's gene impact d View variant evidence in Variant Curation Interface</p> <p>Clear Variant Selection: e <input type="button" value="Clear"/></p>
<p>ClinGen Allele Registry ID: f CA2289129</p> <p>Genomic HGVS Title: g NC_000003.12:g.25729211_25729214del (GRCh38)</p> <p>Note: a variant's gene impact must be specified in order to score this proband.</p> <p>Curate variant's gene impact View variant evidence in Variant Curation Interface</p> <p>Clear Variant Selection: <input type="button" value="Clear"/></p>

Once variants have been saved to a Gene Record they will appear in the Gene Record page under the header in a Gene-Disease Records Variants section. There is an individual blue box for each variant containing the name for each variant. Each box is a link to a page for curating the variant's gene impact.

<p style="text-align: center;">Gene-Disease Record Variants</p> <p>Click a variant to View, Curate, or Edit it. The icon indicates curation by one or more curators.</p> <p>NM_007294.3(BRCA1):c.536delA (p.Tyr179Serfs) NC_000003.12:g.25729211_25729214del</p>	
--	--

- vi. Family – Cancel/Save buttons
- Clicking the “Cancel” button, found at the bottom of the Curate Family Information page, will return a curator to the Record Curation page without saving any entered data.
 - Clicking the “Save” button, found at the bottom of the Curate Family Information page, is the only way to save all the Family data added by a curator. Navigating away from this page without saving will result in the loss of any entered data.
 - After clicking the “Save” button if any of the required fields (described above) are not filled in, then a **red text warning** will appear next to the buttons.

<p>Please fix errors on the form and resubmit.</p> <p><input type="button" value="Cancel"/> <input type="button" value="Save"/></p>	
---	--

- d. A red text warning will appear next to the missing required field.

› Tested Individuals

For Dominant AND Recessive inheritance: Number of AFFECTED individuals <i>WITH</i> genotype? *	Number only Required
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3. Curate Individual Information

A Proband Individual can be associated with a Family during the Curate Family Information process (as shown above). Upon saving the Family you can:

- a. Score and/or Add information about the Proband entered with the Family ('Scoring Probands' discussed later)
- b. Add a non-proband Individual to this Family.
- c. Return to Record Curation page.

An Individual entry for the proband **EXAMPLE-PROBAND1** and its associated variant(s) has been created.

You can score and add additional information about this proband, create an entry for a non-proband in this Family, or return to the Record Curation page.

Note: Individual information includes associated variant(s), phenotypes, sex, etc. For a proband, variant information can only be added or edited on the Family page as it is associated with segregation information.

a	Score / Add information about proband	Add non-proband Individual	b
c	Return to Record Curation page 		

Information about Individuals can also be entered at any time from the Curation palette on the Record Curation page (see next figure):

- a. If the Individual to be entered is part of a Group already curated in this Gene-Disease Record then it can be added from this link within that Group.
- b. If the Individual to be entered is part of a Family already curated in this Gene-Disease Record then it can be added from this link within that Family.
- c. To add a new Individual that is not associated with an existing Group or Family, click the Individual '+' in the curation palette.
- d. To Edit the Information already added for an existing Individual.

The screenshot shows a hierarchical navigation structure:

- Group**:
 - EXAMPLE-GROUP-LABEL**
 - ClinGen Test Curator
 - 2017 Jan 17, 4:28 pm
 - [View](#) | [Edit](#)
 - [Add new Family to this Group](#)
 - [Add new Individual to this Group](#) **a**
- Family**:
 - EXAMPLE-FAMILY1**
 - ClinGen Test Curator
 - 2017 Jan 17, 5:19 pm
 - Associations:
 - [EXAMPLE-GROUP-LABEL](#)
 - Variants: **2**
 - [View](#) | [Edit](#)
 - [Add new Individual to this Family](#) **b**
- Individual**:
 - EXAMPLE-PROBAND1**
 - ClinGen Test Curator
 - 2017 Jan 17, 5:19 pm
 - Associations:
 - [EXAMPLE-GROUP-LABEL](#)
 - [EXAMPLE-FAMILY1](#)
 - Variants: **2**
 - [View/Score](#) | [Edit](#) **d**

The top of the landing page to Curate Individual Information shows the authors, title, and citation details for the selected PubMed article in a yellow box below the header.

- A curator is required to enter a label for the Individual, if possible using a label described in the paper. If editing a pre-existing Individual then this Label will already be filled in but can be changed here.
- A curator must then select 'Yes' if the Individual is a proband and 'No' if the Individual is a non-proband.
- Selecting 'Yes' will make the following Orphanet ID a required field.

Baumstark JS, Lee CT, Luby RJ. A new method for the determination of alpha1-protease inhibitor (alpha1-antitrypsin) phenotypes based on the formation of alpha1-protease inhibitor allele product-elastase complexes. *Biochimica et biophysica acta*. 1976 Sep 28;446(1):287-300. PMID: 10000

Curate Individual Information

// Individual EXAMPLE-PROBAND2

If this Individual is part of a Family or a Group, please curate that Group or Family first and then add the individual as a member.

Individual Label: * EXAMPLE-PROBAND2

Note: Do not enter real names in this field. Please enter a label to help you keep track of this individual within the interface - if possible, please use the label described in the paper.

No Selection

Is this Individual a proband: *

Yes

No

Note: Probands are indicated by the following icon:

Individual – Disease & Phenotype(s)

Orphanet Disease for Individual: * E.G. ORPHA15

The Curate Individual Information page is split into relevant sections based on the type of evidence:

i. Individual – Disease & Phenotype(s)

ii. Individual – Demographics

Enter information about the demographics of the group. The ‘Sex’ of an Individual is a required field; extensive options are via a pull-down.

Individual – Demographics

Sex: *

No Selection

Male

Female

Intersex

MTF/Transwoman/Transgender Female

FTM/Transman/Transgender Male

Ambiguous

Unknown

Other

Country of Origin:

Ethnicity:

iii. Individual – Methods

iv. Individual – Associated Variant(s)

See the section ‘Adding Variants’ above, which describes how to add Variants using either a ClinVar Variation ID(s) and/or ClinGen Allele Registry CA ID(s).

v. Individual – Additional Information

vi. Individual – Score Proband

Scoring Probands

In order to score a proband, a curator must:

- Associate the proband with at least one variant in the ‘Individual – Associated Variant(s)’ section above.
- Specify the gene impact for each variant associate with the proband. To do so, the curator should click on the ‘Curate variant’s gene impact’ link under the variant.

ClinVar Variation ID: 50505

ClinVar Preferred Title: NM_001256240.1(PGAP2):c.46C>T (p.Arg16Trp)

Genomic HGVS Title: NC_000011.10:g.3811305C>T (GRCh38)

Note: a variant's gene impact must be specified in order to score this proband.

[Curate variant's gene impact](#)



After following the link, a curator is required to select the gene impact for the variant from the pull-down.

Evaluation of Pathogenicity

Select gene impact for variant:
(Note: Required for score calculation)

[View evidence](#)

No Selection
Predicted or observed null
Other variant with gene impact
Insufficient evidence for gene impact

- Each variant that has had its gene impact assessed is marked with a white box next to its variant name in the Gene-Disease Records Variants section of the Record Curation page.

Gene-Disease Record Variants

Click a variant to View, Curate, or Edit it. The icon indicates curation by one or more curators.

NM_007294.3(BRCA1):c.1669A>G (p.Thr557Ala) NM_007294.3(BRCA1):c.536delA (p.Tyr179Serfs) NM_004646.3(NPHS1):c.1234G>T (p.Gly412Cys)



- d. Upon saving the gene impact for all the variants associated with a proband, you can return to the Edit Individual Information page and will now be able to Score the proband via a pull-down selection (Score, Review or Contradicts).

Individual 🚑 — Score Proband

The gene impact for each variant associated with this proband must be specified in order to score this proband (see variant(s) and links to curating their gene impact in variant section for this Individual, above).

Select Status:

No Selection
 Score
 Review
 Contradicts

- e. The case type must then be confirmed from the pull-down. Note: The default score and range of choice if choosing a different score will change depending on this case type choice.

Individual 🚑 — Score Proband

The gene impact for each variant associated with this proband must be specified in order to score this proband (see variant(s) and links to curating their gene impact in variant section for this Individual, above).

Select Status:

No Selection
 Proband with other variant type with some evidence of gene impact
 Proband with predicted or proven null variant
 Variant is de novo

Confirm Case Information type:

Default Score:

2

Select a score different from default score:
(optional)

1

Explain reason(s) for change:
(required for selecting different score)

Note: If you selected a score different from the default score, you must provide a reason for the change here.

- f. If a curator chooses a different score from the default score then they are required to explain their reasoning in the box provided.

Default Score: 1.5

Select a score different from default score:
(optional)

Explain reason(s) for change:
(required for selecting different score)

2

Note: If you selected a score different from the default score, you must provide a reason for the change here.

A reason is required for the changed score.



4. Curate Case Control Information

To add Case-Control data to a record click on the '+' in the curation palette on the Record Curation page (or anywhere in that blue bar).

The screenshot shows the 'Evidence for PMID:10000' interface. Under the 'Genetic Evidence' section, there are three expandable categories: 'Group', 'Family', and 'Individual'. Below these, under the 'Case-Control' section, there is a single expandable category labeled 'Case-Control'. An orange arrow points to the '+' sign next to 'Case-Control', indicating where to click to add data.

The top of the landing page to Curate Group Information shows the authors, title, and citation details for the selected PubMed article in a yellow box below the header. A curator is required to enter a label for the Case-Control, the Case Cohort and the Control Cohort.

The screenshot shows the 'Case-Control Label' form. It has three main sections: 'Case-Control Label' with a value 'CASE-CONTROL' in a yellow box; 'Case Cohort' with a label 'CASE' in a white input field; and 'Control Cohort' with a label 'CONTROL1' in a yellow box.

i. Case Cohort – Disease(s) and Phenotype(s)

A curator is required to enter at least one of the following to describe disease(s)/phenotype(s) common to the Case Cohort:

- a) Orphanet ID(s)
- b) HPO ID(s)
- c) Phenotype free text

> Disease(s) & Phenotype(s)

Please enter an Orphanet ID(s)
and/or HPO ID(s) and/or Phenotype
free text (required).

Disease(s) in Common (Orphanet term):	E.G. ORPHA15 a
Phenotype(s) in Common (HPO ID(s)):	E.G. HP:0010704, HP:0030300 b
Phenotype(s) in Common (free text):	c

For the following sections, there is a split screen where Case Cohort information can be entered in the left panel and Control Cohort information can be entered in the right panel.

- ii. Case Cohort/ Control Cohort – Demographics
- iii. Case Cohort/ Control Cohort – Methods
- iv. Case Cohort/ Control Cohort – Power
- v. Case Cohort/ Control Cohort – Additional Information

For instance:

<p>> Demographics CASE</p> <p>Number of males: <input type="text"/></p> <p>Number of females: <input type="text"/></p> <p>Country of Origin: <input type="text"/> No Selection</p> <p>Ethnicity: <input type="text"/> No Selection</p> <p>Race: <input type="text"/> No Selection</p> <p>Age Range</p> <p>Type: <input type="text"/> No Selection</p> <p>Value: <input type="text"/> to <input type="text"/></p> <p>Unit: <input type="text"/> No Selection</p>	<p>> Demographics CONTROL</p> <p>Number of males: <input type="text"/></p> <p>Number of females: <input type="text"/></p> <p>Country of Origin: <input type="text"/> No Selection</p> <p>Ethnicity: <input type="text"/> No Selection</p> <p>Race: <input type="text"/> No Selection</p> <p>Age Range</p> <p>Value: <input type="text"/> to <input type="text"/></p> <p>Unit: <input type="text"/> No Selection</p>
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Then the Case-Control Evaluation section is for evaluating the evidence on the Case Control group as a whole.

- vi. Case Control Evaluation – Statistics
- vii. Case Control Evaluation – Bias Category
- viii. Case Control Evaluation – Comments
- ix. Case Control – Score

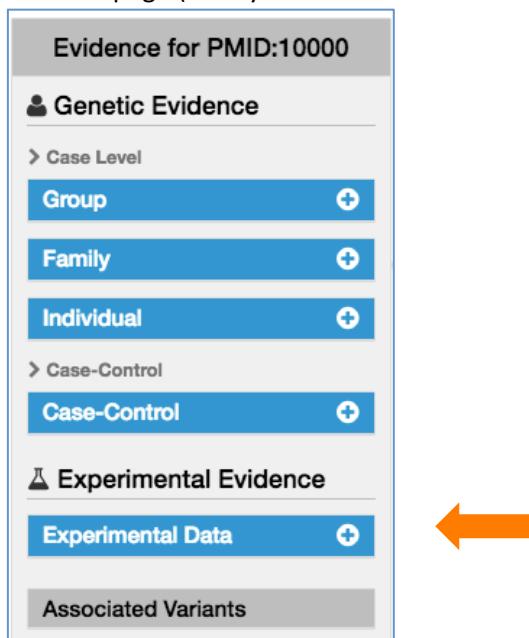
Scoring Case Control

In order to score Case Control, a curator must select a Score from the pull-down and then click Save.

The screenshot shows a user interface for scoring Case Control. On the left, there is a blue header bar with the text "Case-Control Score". Below it, a field labeled "Score:" contains the number "2". To the right of this field is a vertical dropdown menu titled "No Selection" which lists numerical values from 0 to 5. The value "2" is highlighted with a checkmark. At the bottom right of the interface is a blue "Save" button.

ADDING EXPERIMENTAL EVIDENCE

To add Experimental data to a record click on the '+' in the curation palette on the Record Curation page (or anywhere on that blue bar).



A curator is first required to select the Experiment Type from a pull-down:

Select which experiment type you would like to curate:

Experiment type: *

- No Selection
- Biochemical Function
- Protein Interactions
- Expression
- Functional Alteration
- Model Systems
- Rescue

There are six different curation experiences dependent on the Experiment Type selected by the curator.

i. Experimental – Biochemical Function (A) and (B)

The ‘Biochemical Function’ option has two separate options, A and B, provided in a pull-down.

Experiment type: * Biochemical Function

Please select which one (A or B) you would like to curate *

- A. The gene product performs a biochemical function shared with other known genes in the disease of interest
- B. The gene product is consistent with the observed phenotype(s)

No Selection

- A. Gene(s) with same function implicated in same disease
- B. Gene function consistent with phenotype(s)

Both have a number of required fields, shown with an asterisk next to the field. One of these required fields is for adding the Gene Ontology (GO) ID that best defines the function of the gene in the Record.

A. Biochemical Function

Select a GO term for this gene (view existing GO annotations for this gene [in UniProt](#) or search for a new term using [QuickGO](#)). The GO term must be from the GO aspect "Molecular Function" or "Biological Process."

Identified function of gene in this record (GO ID): * E.G. GO:0008150

Evidence for above function: *

Notes on where evidence found in paper:

Other gene(s) with same function as gene in record (HGNC [symbol](#)): * e.g. DICER1

Evidence that above gene(s) share same function with gene in record: *



Adding GO IDs

In order to aid the curator in searching for the correct GO ID, there is a link provided to the UniProt entry for the gene associated with the record. The UniProt entry lists GO terms already annotated to that gene, so first check whether there is an existing GO term that matches the function of the gene described in the paper. Alternatively, you can use the link to QuickGO to find a more representative GO term.

- a) Only choose either “Molecular Function” or “Biological Process” GO terms.
- b) Only choose manual experimental evidence, e.g. codes IDA, IMP, IGI, IPI and IEP. Other codes may be inferred, e.g. IEA which is ‘Inferred by electronic annotation,’ and therefore do not represent experimental support for the annotation.
- c) As you go down a GO tree the terms become more specific, only go down the tree as far as you feel secure in your decision.
- d) If you are not sure which specific GO term to add then go back up the tree until you find a general term that fits your knowledge. Please contact us at clingen-helpdesk@lists.stanford.edu for additional help.

Scoring Experimental Evidence

Experimental data can be scored via a pull-down selection (Score, Review or Contradicts) in Experimental Data Score sections found at the foot of every Curate Experimental Data Information page.

The screenshot shows a user interface for scoring experimental data. At the top, a blue header bar reads "Experimental Data Score". Below it, there are two main sections: "Select Status:" and "Default Score:". The "Select Status:" section contains a dropdown menu with three options: "No Selection", "Score", "Review", and "Contradicts". The "Default Score:" section shows a value of "0.5" next to a dropdown menu labeled "No Selection". Below these sections, there is a note: "Select a score different from default score: (optional)". At the bottom, there is a text input field with the placeholder text: "Explain reason(s) for change: (required for selecting different score)" and a note: "Note: If you selected a score different from the default score, you must provide a reason for the change here."

The default score and range of choice if choosing a different score will change depending on the experimental data type.

If a curator chooses a different score from the default score then they are required to explain their reasoning in the box provided.

Default Score: 0.5

Select a score different from default score:
(optional)

Explain reason(s) for change: *
(required for selecting different score)

Note: If you selected a score different from the default score, you must provide a reason for the change here.



ii. Experimental – Protein Interactions

Has a number of required fields, shown with an asterisk next to the field.

iii. Experimental – Expression (A and B)

The ‘Expression’ option has two separate options, A and B, provided in a pull-down.

Please select which one (A or B) you would like to curate *

No Selection

A. Gene normally expressed in tissue relevant to the disease
 B. Altered expression in Patients

- a) Both have a number of required fields, shown with an asterisk next to the field.
 One of these required fields is for adding an anatomical structure Ontology (UBERON) ID that best defines the organ or tissue relevant to the gene expression evidence. A link out to UBERON has been provided to aid in searching for the correct ID. Please contact us at clingen-helpdesk@lists.stanford.edu for additional help.

Search [Uberon](#) for an organ type (e.g. heart = UBERON_0015228)

Organ of tissue relevant to disease, in which gene expression is examined in patient ([Uberon](#) ID): *

E.G. UBERON_0015228

iv. Experimental – Functional Alteration

Has a number of required fields, shown with an asterisk next to the field.

Includes section for adding variant(s) associated with this data type. Simply click on “Add variant associated with Experimental data”. A pop-up window will appear whereby variants can be added via either a ClinVar VariationID or a ClinGen Allele Registry CA ID.

Experimental Data - Associated Variant(s)

If your Experimental data is about one or more variants, please add these variant(s) below

Add variant associated with Experimental data



Variants can then be added via either a ClinVar Variation ID or a ClinGen Allele Registry CA ID.

Add Variant:	Add ClinVar ID	- or -	Add CA ID
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v. Experimental – Model Systems

Has a number of required fields, shown with an asterisk next to the field.

Including selecting whether it is non-human animal or cell-culture model.

Model Systems

Non-human animal or cell-culture model?: *	No Selection ✓ Animal model Engineered equivalent
--	---

- a) If ‘Engineered Equivalent’ is selected then cell-culture type becomes a required field. This field can only accept an Experimental Factor Ontology (EFO) ID. A link out to EFO has been provided to aid in searching for the correct ID. Please contact us at clingen-helpdesk@lists.stanford.edu for additional help.

Search EFO for a cell line (e.g. HepG2 = EFO_0001187)
Cell-culture type/line (EFO ID): * E.G. EFO_0001187

Also includes section for adding variant(s) associated with this data type.

vi. Experimental – Rescue

Has a number of required fields, shown with an asterisk next to the field.

Includes section for adding variant(s) associated with this data type.

GENERATING A SUMMARY

To Generate a Summary click on the ‘Generate Summary’ found in the left upper header on each page. The Summary page contains two table: an upper automated Scoring Table, and beneath that a Provisional Classification Table.

The calculated values in these tables are generated based on the set of saved evidence that existed when the “Generate New Summary” button was clicked.

1. Scoring Table

For each specific evidence type there are the following columns:

- a. Evidence Type – brief description of types of evidence scored upon.
- b. Count - total number of scores counted for that evidence.
- c. Total Points – the total of all the scores added together for that evidence.
- d. Points Counted – the total of all the scores added together for that evidence but with any applicable upper cut-offs applied to the score. For each specific type of evidence there is a maximum number of points allowable, see the SOP for allowed max scores.

Each specific evidence type is shown in rows:

- e. Variant/proband scores, if curating an autosomal dominant disease or an X-linked disorder.
- f. Variant/proband scores, if curating an autosomal recessive disease.
- g. Case level segregation scores.
- h. Case Control scores.
- i. Genetic Evidence Total. The total number of allowable points for genetic evidence. Calculated by adding the ‘Points Counted’ for each of the genetic evidence types.
Note: Maximum points allowed for this field is 12
- j. Experimental (functional) scores.
- k. Experimental (functional alteration) scores.
- l. Experimental (functional alteration) scores.
- m. Experimental Evidence Total. The total number of allowable points for experimental evidence. Calculated by adding the ‘Points Counted’ for each of the experimental evidence types.
Note: Maximum points allowed for this field is 6.
- n. Total Points. The sum of the Genetic Evidence Total and Experimental Evidence Total.

Evidence Type			Count	Total Points	Points Counted		
Genetic Evidence	Case-Level	Variant					
a Autosomal Dominant Disease			Proband with other variant type with some evidence of gene impact	1	1		
			Proband with predicted or proven null variant	6	10		
			Variant is <i>de novo</i>	0	0		
			Two variants (not predicted/proven null) with some evidence of gene impact <i>in trans</i>	0	0		
b Autosomal Recessive Disease			Two variants in <i>trans</i> and at least one <i>de novo</i> or a predicted/proven null variant	0	0		
					0		
			c Segregation	4	7 (9.05*)		
			d Case-Control	2	4.5		
e Genetic Evidence Total					12		
Experimental Evidence	f Functional		Biochemical Functions	1	1.5		
			Protein Interactions	1	1.5		
			Expression	1	1		
	g Functional Alteration		Patient Cells	1	2		
			Non-patient Cells	0	0		
	h Models & Rescue		Animal Model	1	1.5		
			Cell Culture Model System	0	0		
			Rescue in Animal Model	0	0		
			Rescue in Engineered Equivalent	1	1.5		
i Experimental Evidence Total					6		
j Total Points					18		

* – Combined LOD Score

For Segregation Evidence, the Total Points field additionally contains the LOD score in parentheses. If the LOD score has been generated by combining multiple LOD scores then it will have an asterisk.

Segregation	4	7 (9.05*)	7
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2. Provisional Classification Table (see figure below)

- a. Genetic Evidence Total assigned points.
- b. Experimental Evidence Total assigned points
- c. Total Points
- d. Replication Over Time. Tickbox to identify whether the evidence has been replicated over time. Tick for 'Yes', leave blank for 'No'.
- e. Calculated Classification is automatically filled in based on the Total Points. The calculated classification is highlighted in blue.
Note: Required to be 'Yes' for the 'Calculated Classification' to be upgraded from To upgrade a 12-18 Total Points from a Strong to Definitive classification then 'Yes' must have been selected for Replication Over Time.
- f. Contradictory Evidence. If a Proband or Experimental evidence has been scored as Contradictory by the curator then it will have a red 'Yes', if not it will have a black 'No'.
- g. Curators can modify the Calculated Clinical Validity Classification by selecting an alternative Classification from the pull-down options.

- h. If the curator has modified the Classification then they are required to explain their reasoning here.
- i. Current Saved Provisional Classification
- j. Timestamp when current Current Saved Provisional Classification was Saved.

Gene/Disease Pair				
Assertion Criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18 points)	Replication Over Time (Yes/No)
Assigned Points	a 12	b 6	c 18	d <input type="checkbox"/>
e Calculated Classification			LIMITED	1-6
			MODERATE	7-11
			STRONG	12-18
			DEFINITIVE	12-18 & Replicated Over Time
f Contradictory Evidence?	Proband: Yes Experimental: No			
Modify Provisional Clinical Validity g Strong Classification:				
Explain Reason(s) for Change h because <div style="border: 1px solid #ccc; height: 100px; width: 100%;"></div>				
Current Saved Provisional Classification	i Strong j (2017 Jan 18, 10:29 am)			

When a curator Saves a new Provisional Classification it will now appear in the 'Last Saved Summary & Provisional Classification' banner under the header on each page.

- a. Timestamp when current Current Saved Provisional Classification was Saved.
- b. Calculated Score (and Classification) based on current saved scores.
- c. Modified Provisional Classification, based on a saved modification to classification.
- d. Click here to edit the current Provisional Classification.
- e. Click here to Generate New Summary.

RAD51C – X-linked non-syndromic intellectual disability	
Autosomal dominant inheritance (with maternal imprinting)	
Last Saved Summary & Provisional Classification Last Saved Summary Date Generated: 2017 Jan 18, 10:51 am a	
b Calculated Score (Classification): 18 (Definitive) c Modified Provisional Classification: Definitive [Edit Classification] d	
e Generate New Summary	

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