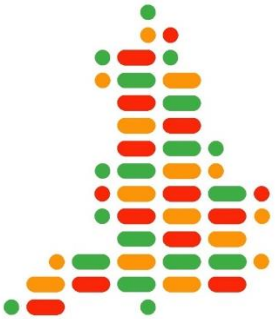
A Reviewers' Guide To PanelApp Australia



PanelApp Release 3.0.2

Reviewers' Guide V1.

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Adapted for use by PanelApp Australia by A/Prof Zornitza Stark

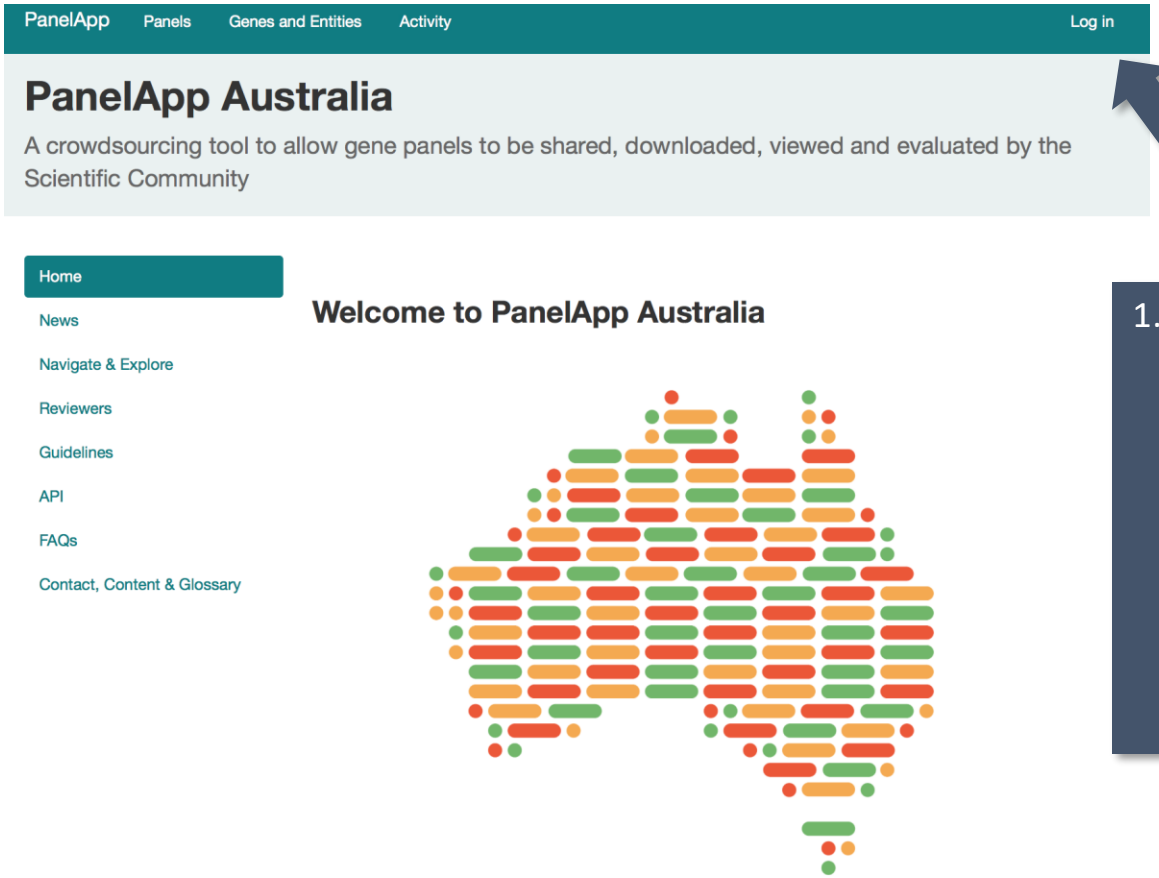
Reviewing Panels in PanelApp

- Expert review of the gene panels is sought to enable a community consensus to be reached on which genes should appear on a diagnostic-grade panel for each disorder and to keep content current in light of new gene discoveries.
- We request that reviewers have expertise in a disease area relevant to the panel they are reviewing.
- Reviewers can be based anywhere in the world, and can have an academic, clinical or diagnostic laboratory background.
- This guide highlights the key **Review** functions of PanelApp, in a series of how-to steps. The guide can be used alongside the current PanelApp handbook, which details how to browse PanelApp and leave reviews.

Guide Contents

Creating a PanelApp Reviewer Account, and Logging in

Use the top **PanelApp Toolbar** to Register as a Reviewer:



1. You can log in and register to be a reviewer using your Google account. Your account details will not be displayed when you review genes and panels

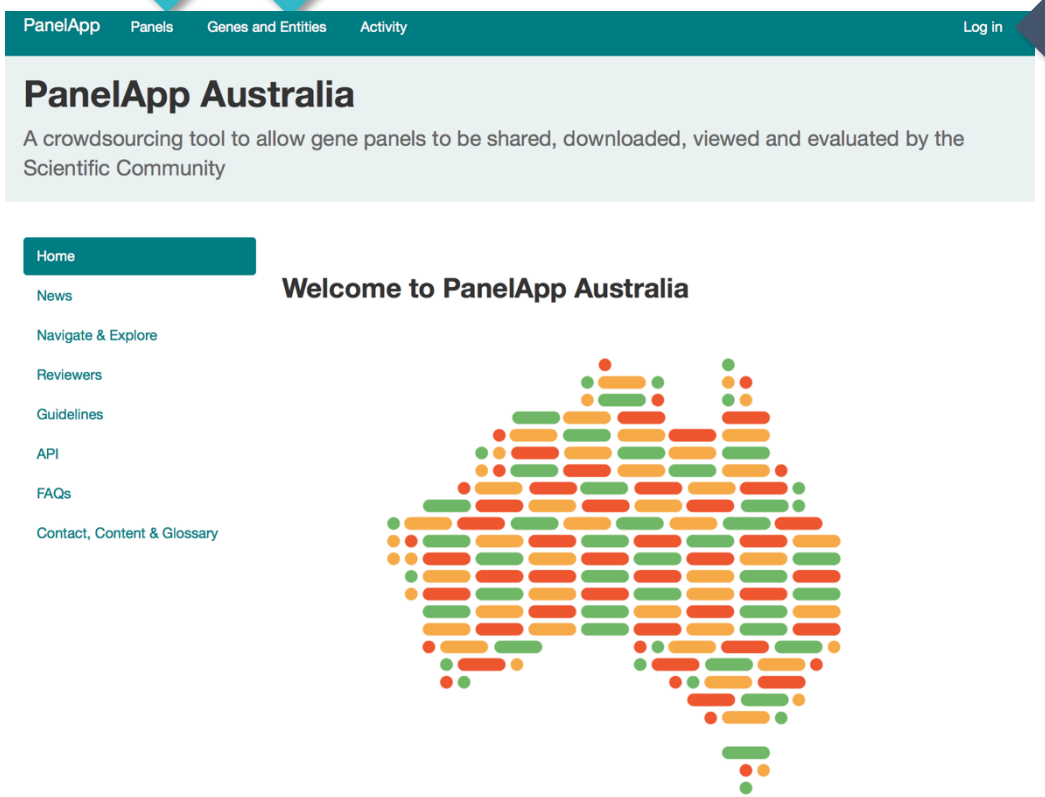
https://panelapp.agha.umccr.org

Finding your panel or gene of interest in PanelApp

Use the top **PanelApp Toolbar** to log in to your reviewer account, and search for your panel or gene of interest:

2. To leave a review on a gene, search PanelApp for a panel or gene

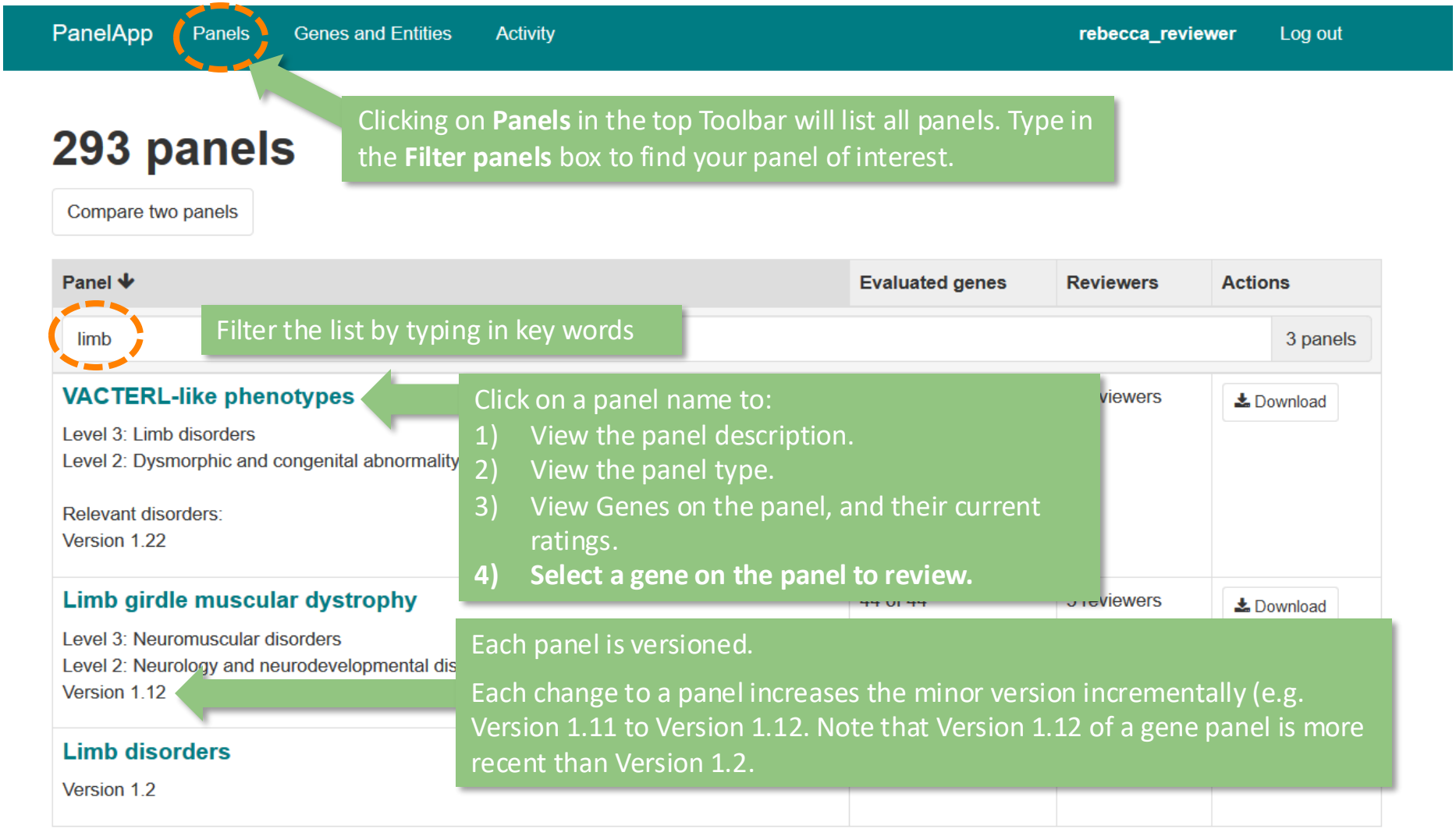
Refer to the PanelApp handbook for more details on searching.



1. Log in to your Reviewer account

You can browse PanelApp without logging in, but need to create a Reviewer account to leave ratings and comments.

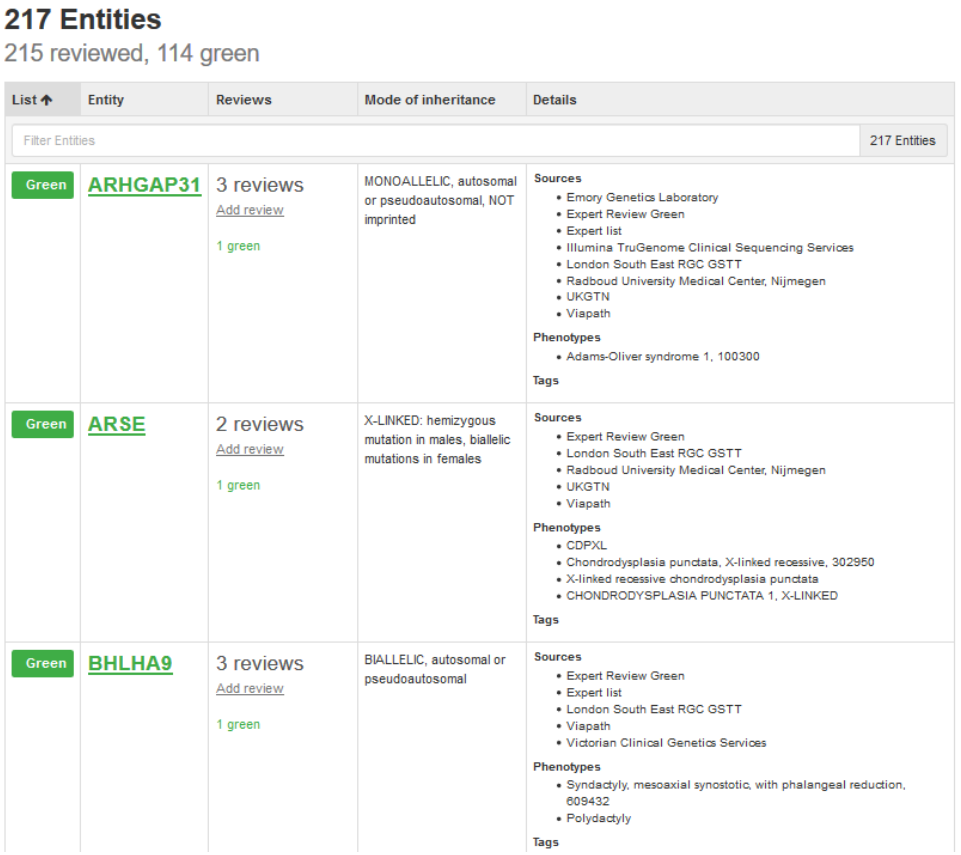
Finding a panel to review:



An overview of information captured on a PanelApp panel

Panel View in PanelApp:

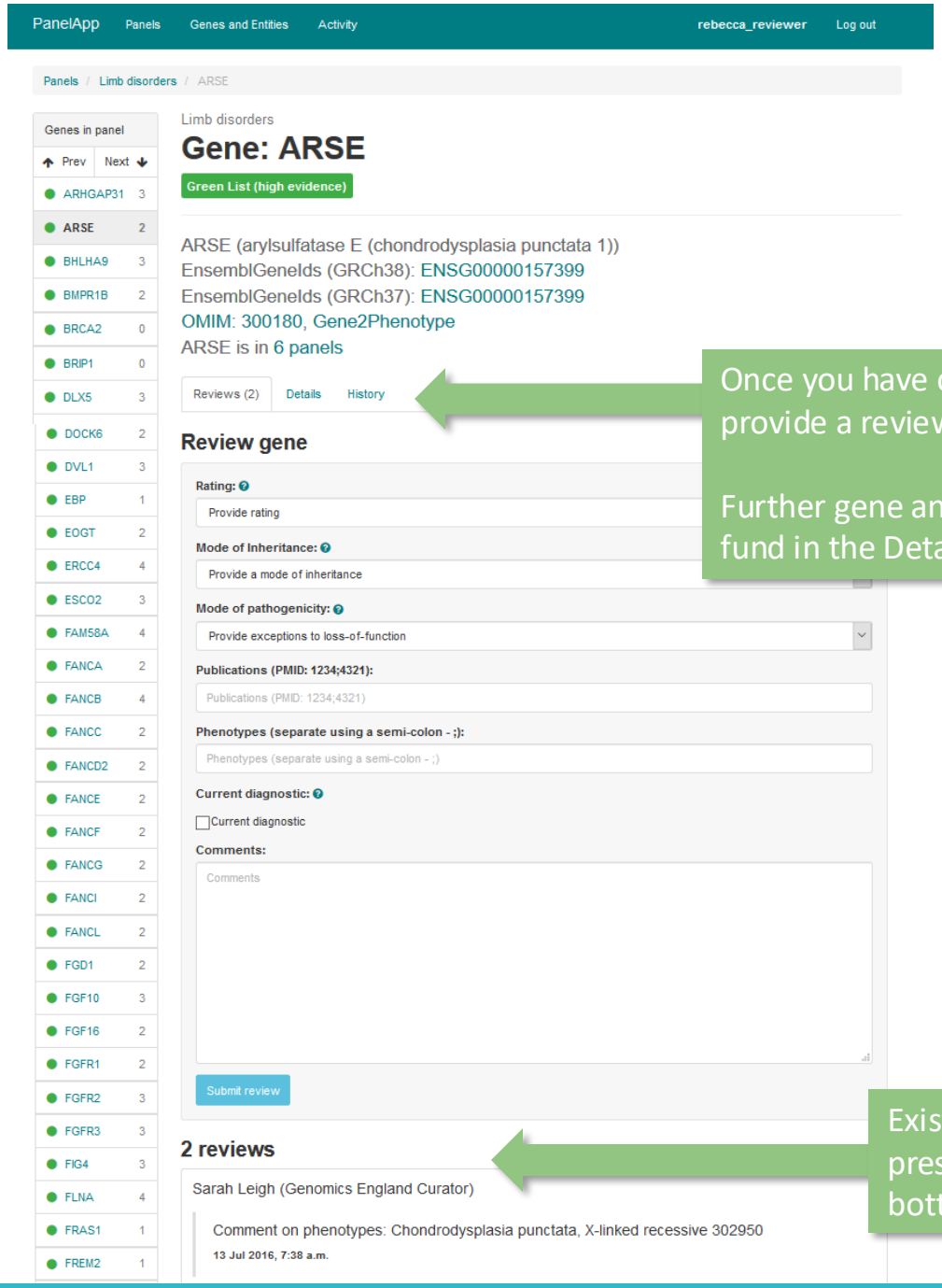
Click on a gene symbol to see further gene details, and **provide a review.**



217 Entities

215 reviewed, 114 green

List	Entity	Reviews	Mode of inheritance	Details
Filter Entities				217 Entities
Green	ARHGAP31	3 reviews Add review 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	**Sources** • Emory Genetics Laboratory • Expert Review Green • Expert list • Illumina TruGenome Clinical Sequencing Services • London South East RGC GSTT • Radboud University Medical Center, Nijmegen • UKGTN • Viapath **Phenotypes** • Adams-Oliver syndrome 1, 100300 **Tags**
Green	ARSE	2 reviews Add review 1 green	X-LINKED: hemizygous mutation in males, biallelic mutations in females	**Sources** • Expert Review Green • London South East RGC GSTT • Radboud University Medical Center, Nijmegen • UKGTN • Viapath **Phenotypes** • CDPXL • Chondrodysplasia punctata, X-linked recessive, 302950 • X-linked recessive chondrodysplasia punctata • CHONDRODYSPLASIA PUNCTATA 1, X-LINKED **Tags**
Green	BHLHA9	3 reviews Add review 1 green	BIALLELIC, autosomal or pseudoautosomal	**Sources** • Expert Review Green • Expert list • London South East RGC GSTT • Viapath • Victorian Clinical Genetics Services **Phenotypes** • Syndactyly, mesoaxial synostotic, with phalangeal reduction, 609432 • Polydactyly **Tags**



Once you have clicked on a gene symbol, you can provide a review using the **Reviews** tab.

Further gene and curation information can be fund in the Details and History tabs, respectively.

Existing reviews for the gene (where present) can be viewed at the bottom of the Reviews tab.

Understanding Gene Ratings in PanelApp

Understanding PanelApp Gene Ratings:

STOP: not enough evidence for this gene-disease; this gene should not be used for genome interpretation.

PAUSE: moderate evidence for this gene-disease association, and should not yet be used for genome interpretation.

GO: high level of evidence for this gene-disease association, demonstrates confidence that this gene should be used for genome interpretation.

- Reviewers are asked to rate genes according to this traffic light system.
- Green genes on Version 1+ panels will reflect this evidence system and can be used for genome interpretation.

Genes on a panel are classified according to a traffic light system. Genes are rated in terms of the level of evidence to support their association with the phenotypes covered by the gene panel in question.

For rare disease, the criteria for assessing the evidence were developed from a combination of the ClinGen DEFINITIVE and DDG2P CONFIRMED gene evidence levels (set out in full on the next slide). In summary:

- A diagnostic-grade (Green) rating on a panel requires evidence from **2-3 unrelated families where there is strong additional functional data** OR from 3 or more unrelated families.
- Genes that do not meet these criteria are rated as Amber (borderline) or Red (low level of evidence), and are not used for diagnostic testing.

PanelApp Criteria for Diagnostic Grade 'Green' Genes for Rare Diseases:

A. There are plausible disease-causing variants[1] within, affecting or encompassing an interpretable functional region of this gene[2] identified in multiple (3 or more) unrelated cases/families with the phenotype[3].

OR

B. There are plausible disease-causing variants[1] within, affecting or encompassing cis-regulatory elements convincingly affecting the expression of a single gene identified in multiple (3 or more) unrelated cases/families with the phenotype[3].

OR

C. As definitions A or B but in 2 or 3 unrelated cases/families with the phenotype, with the addition of convincing bioinformatic or functional evidence of causation e.g. known inborn error of metabolism with mutation in orthologous gene which is known to have the relevant deficient enzymatic activity in other species; existence of an animal model which recapitulates the human phenotype.

AND

D. Evidence indicates that disease-causing variants follow a Mendelian pattern of causation appropriate for reporting in a diagnostic setting[4].

AND

E. No convincing evidence exists or has emerged that contradicts the role of the gene in the specified phenotype.

[1]Plausible disease-causing variants: Recurrent de novo variants convincingly affecting gene function. Rare, fully-penetrant variants - relevant genotype never, or very rarely, seen in controls.

[2]Interpretable functional region: ORF in protein coding genes miRNA stem or loop.

[3]Phenotype: the rare disease category, as described in the eligibility statement.

[4]Intermediate penetrance genes should not be included.

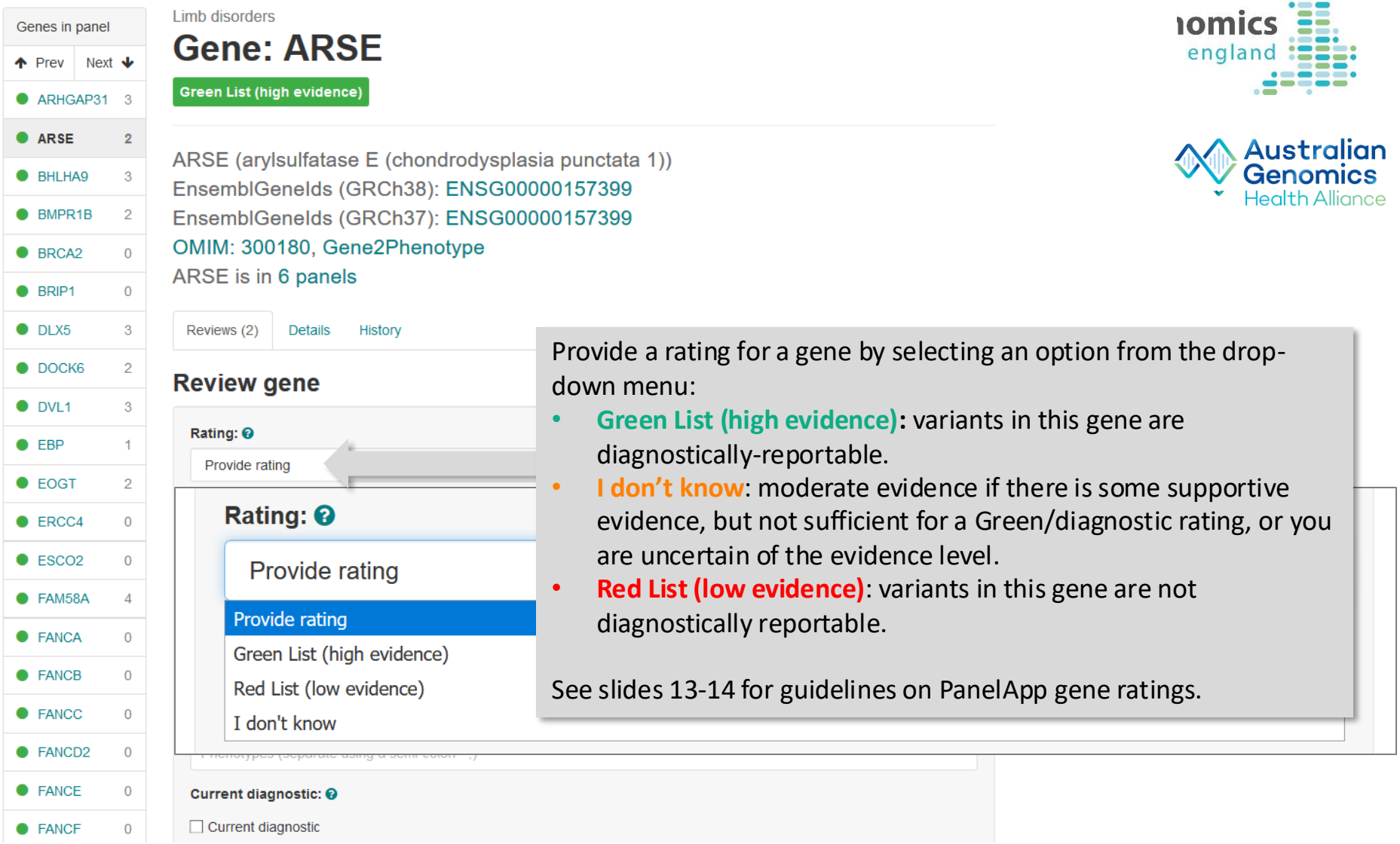
Adapted from references: PMID:28552198 and PMID: 25529582

Leaving a Review in PanelApp

When reviewing a gene please **rate** whether there is sufficient evidence for the gene to be on a diagnostic panel.

You can also **add the following fields** when reviewing, although they are not compulsory, they are useful when a curator is collating the reviews.

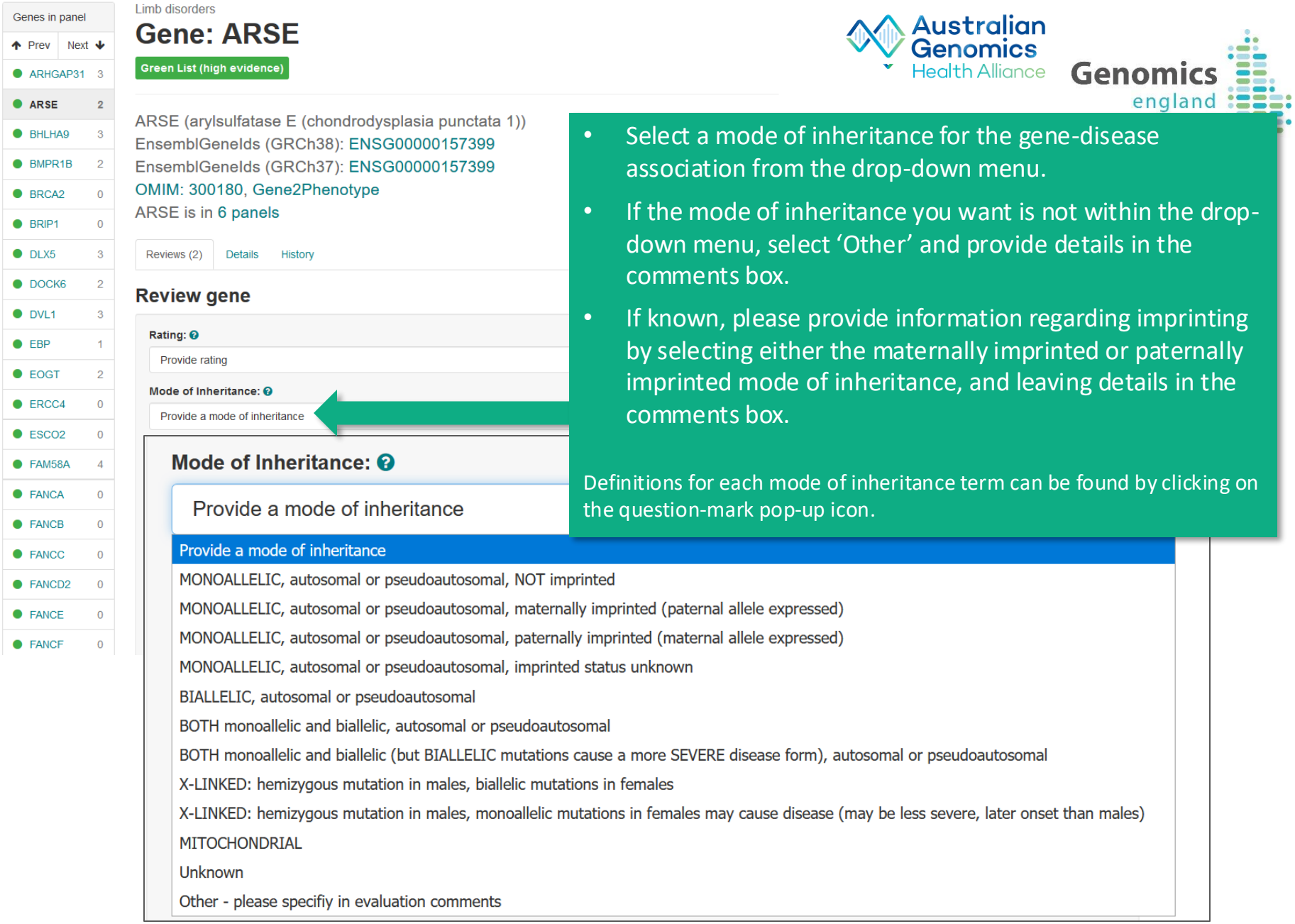
- Mode of inheritance
- Mode of pathogenicity
- Publications
- Phenotypes
- Free-text comments



Provide a rating for a gene by selecting an option from the drop-down menu:

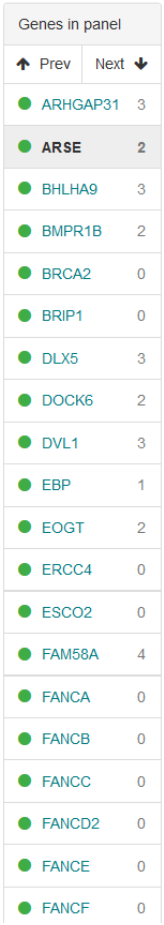
- **Green List (high evidence):** variants in this gene are diagnostically-reportable.
- **I don't know**: moderate evidence if there is some supportive evidence, but not sufficient for a Green/diagnostic rating, or you are uncertain of the evidence level.
- **Red List (low evidence)**: variants in this gene are not diagnostically reportable.

See slides 13-14 for guidelines on PanelApp gene ratings.



- Select a mode of inheritance for the gene-disease association from the drop-down menu.
- If the mode of inheritance you want is not within the drop-down menu, select ‘Other’ and provide details in the comments box.
- If known, please provide information regarding imprinting by selecting either the maternally imprinted or paternally imprinted mode of inheritance, and leaving details in the comments box.

Definitions for each mode of inheritance term can be found by clicking on the question-mark pop-up icon.



Limb disorders

Gene: ARSE

Green List (high evidence)

ARSE (arylsulfatase E (chondrodysplasia punctata 1))
EnsemblGeneIds (GRCh38): ENSG00000157399
EnsemblGeneIds (GRCh37): ENSG00000157399
OMIM: 300180, Gene2Phenotype
ARSE is in 6 panels

Reviews (2) Details History

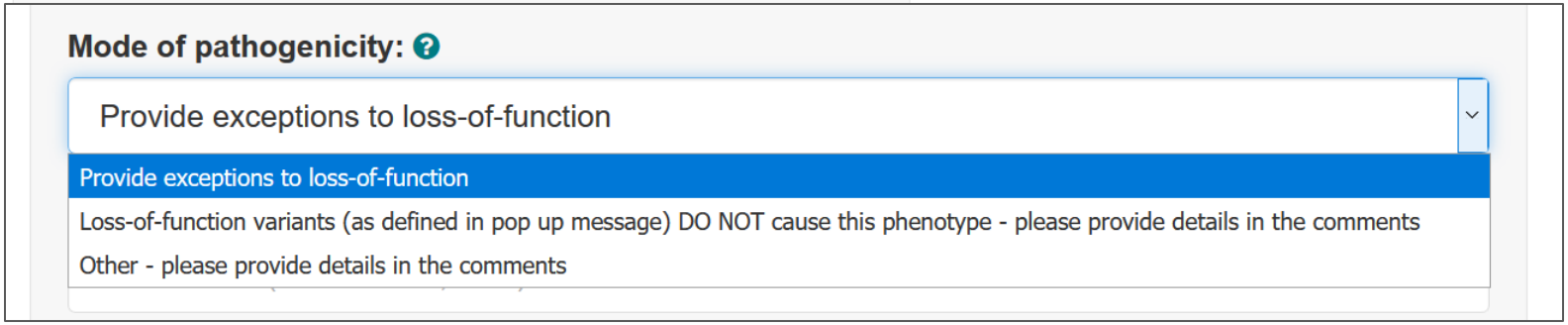
Review gene

Rating:
Provide rating

Mode of Inheritance:
Provide a mode of inheritance

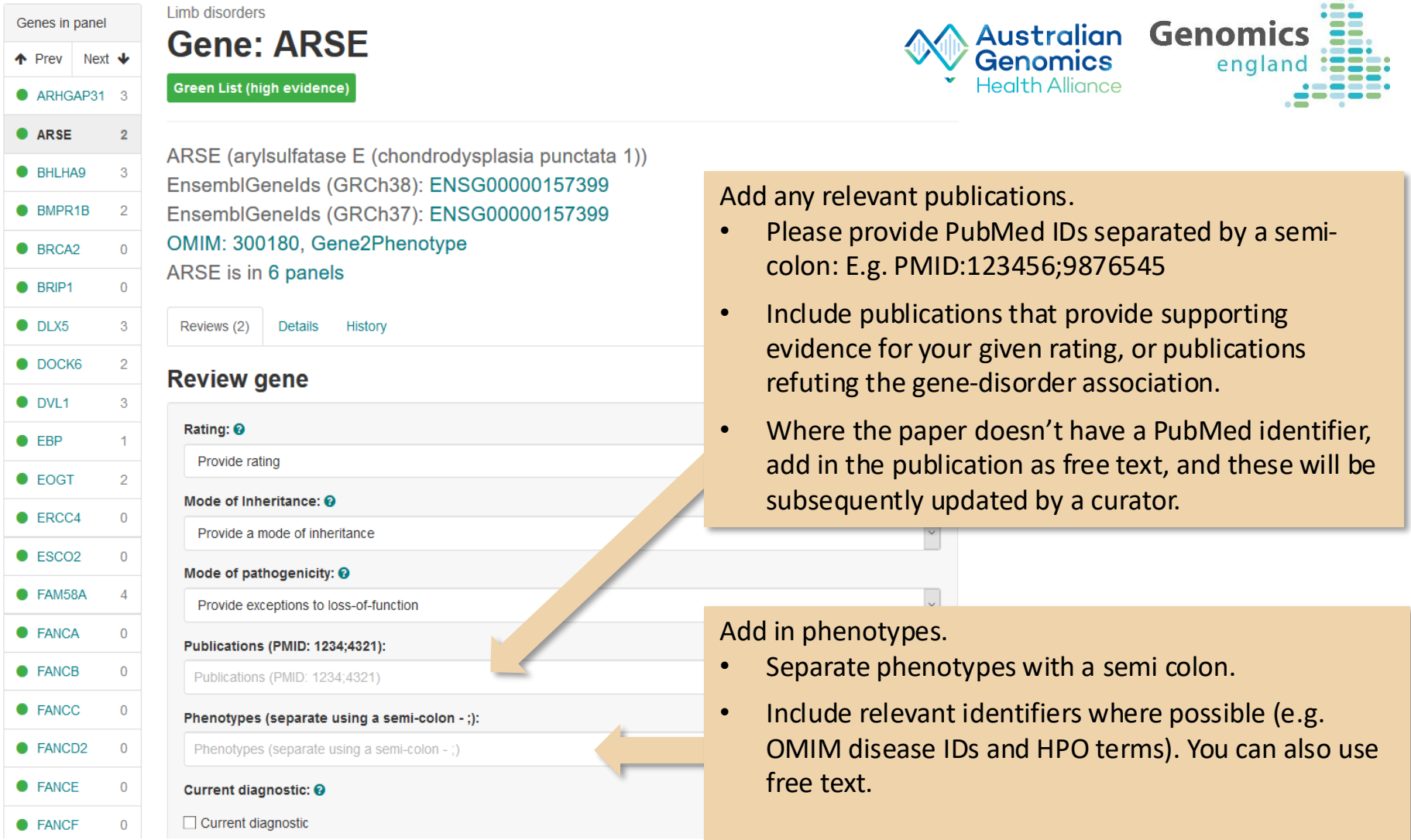
Mode of pathogenicity:
Provide exceptions to loss-of-function

- If loss-of-function variants do not cause the disease phenotype, please select an option in the mode of pathogenicity dropdown menu.
- If providing exceptions to loss-of-function, please leave a free-text comment to explain your selection (e.g. detailing literature or clinical evidence).



In PanelApp, we classify loss-of-function (high impact) variants as those with the sequence ontology (SO) terms:

- transcript_ablation
- splice_acceptor_variant
- splice_donor_variant
- stop_gained
- frameshfit_variant
- stop_lost
- Initiator_codon_variant



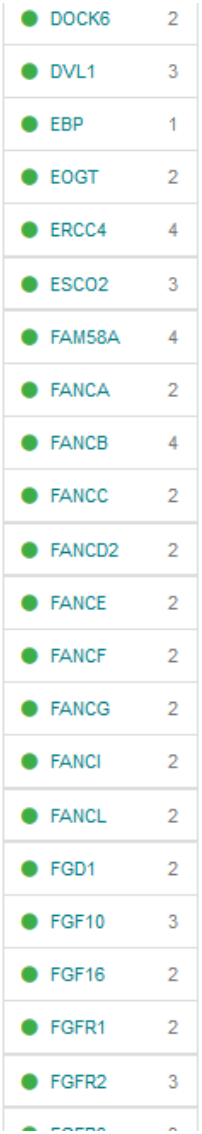
Add any relevant publications.

- Please provide PubMed IDs separated by a semi-colon: E.g. PMID:123456;9876545
- Include publications that provide supporting evidence for your given rating, or publications refuting the gene-disorder association.
- Where the paper doesn't have a PubMed identifier, add in the publication as free text, and these will be subsequently updated by a curator.

Add in phenotypes.

- Separate phenotypes with a semi colon.
- Include relevant identifiers where possible (e.g. OMIM disease IDs and HPO terms). You can also use free text.

E.g. Alport syndrome, 301050; Hearing Loss



Review gene

Rating:

Provide rating

Mode of Inheritance:

Provide a mode of inheritance

Mode of pathogenicity:

Provide exceptions to loss-of-function

Publications (PMID: 1234;4321):

Publications (PMID: 1234;4321)

Phenotypes (separate using a semi-colon - ;):

Phenotypes (separate using a semi-colon - ;)

Current diagnostic:

☐ Current diagnostic

Comments:

Comments

Submit review

If submitting the gene evaluation on behalf of a clinical laboratory, indicate whether variants in the gene are reported as part of your current diagnostic practice by checking the **Current diagnostic** box.

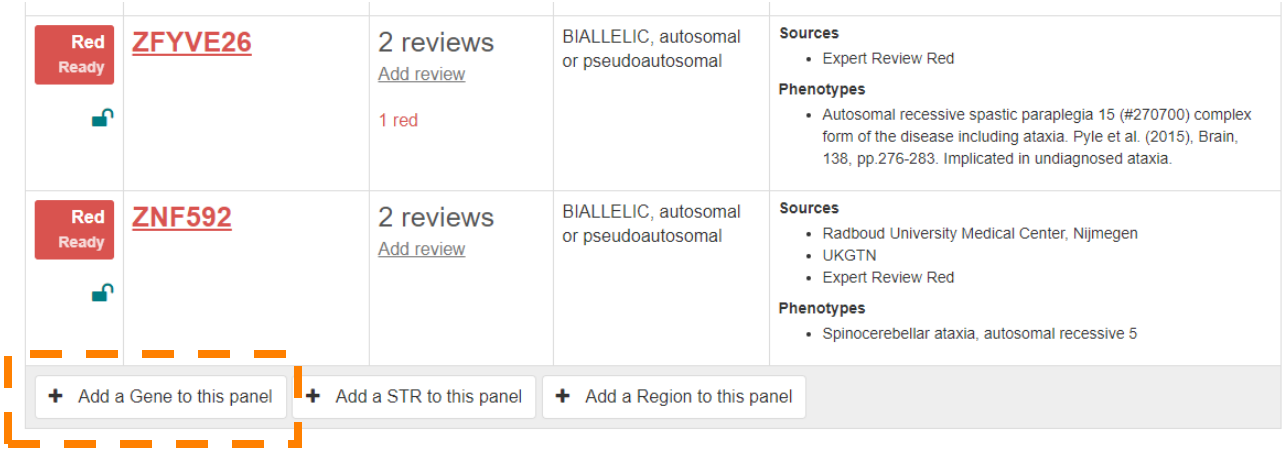
Provide justifications in the comments box to support your gene rating, particularly when changing the existing rating for a gene.

Comments will be publically visible.

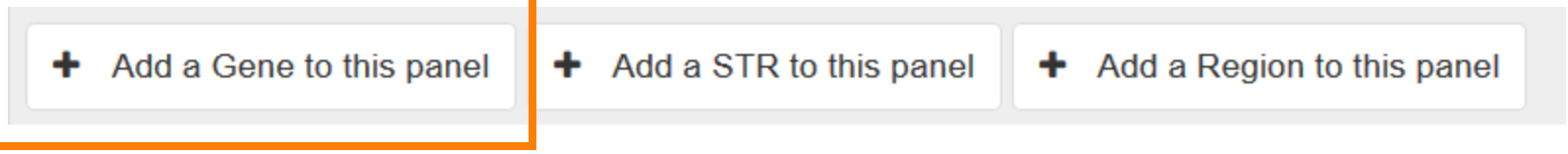
Click **Submit review** when finished.

Adding Genes to a PanelApp Panel

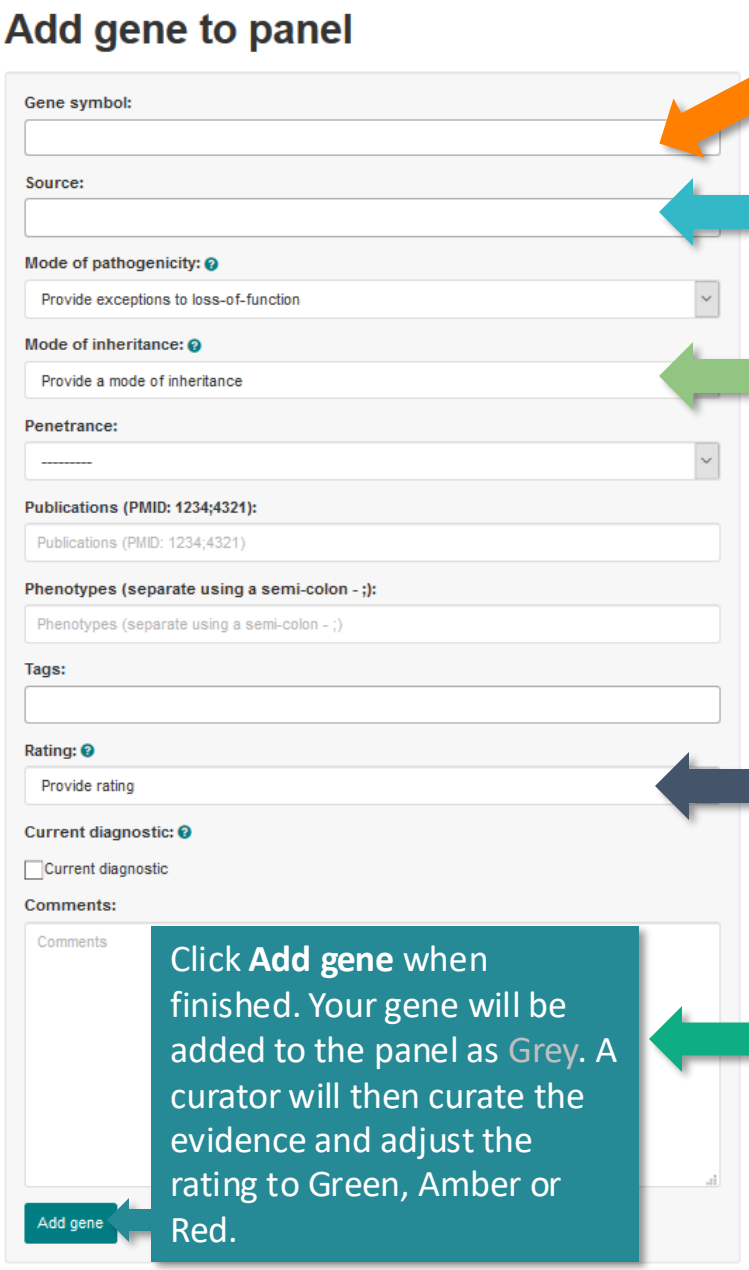
Adding a **gene** to a Panel:



If any genes are missing from a panel, you can add them using the tool bar below the Entities list:



Adding a **gene** to a panel using the **Add gene** tool



Start typing an HGNC Gene symbol into the top box to select your gene to add to a panel.

You must include a source of information for the gene:disease association. E.g. literature/Expert list.

You must provide a **Mode of inheritance** for the gene-disease association.

You can also add a **Mode of pathogenicity**, **Publications** and **Phenotypes.**

If penetrance is not complete, please denote using the drop down menu in the **Penetrance** field, and provide a comment.

Select a gene **rating** here.

The **Comments** box can be used to leave free-text information about the gene:disorder association and why the gene was added to the panel.

Comments will be publically visible.

Click **Add gene** when finished. Your gene will be added to the panel as Grey. A curator will then curate the evidence and adjust the rating to Green, Amber or Red.

View or Edit your Evaluations

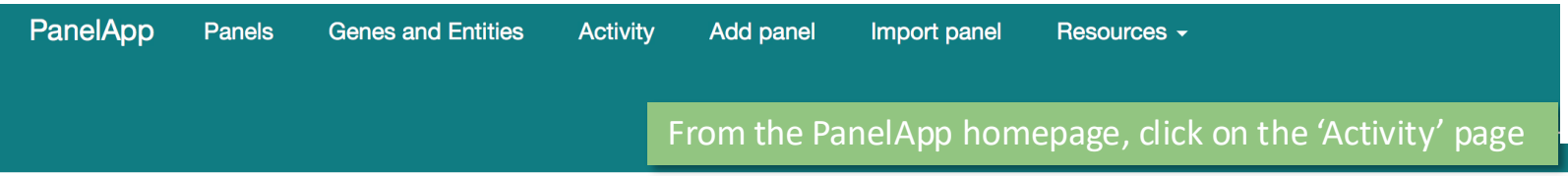
How to view or edit your Reviews:

1. From the PanelApp homepage, click on your username in the top right hand corner to view your user information and a list of your evaluations.

2. Click on the gene symbol to make changes to your evaluation, or click on the panel name to view the entire gene panel.

View Changes to Panels and new reviews

How to view updates or new reviews in PanelApp:



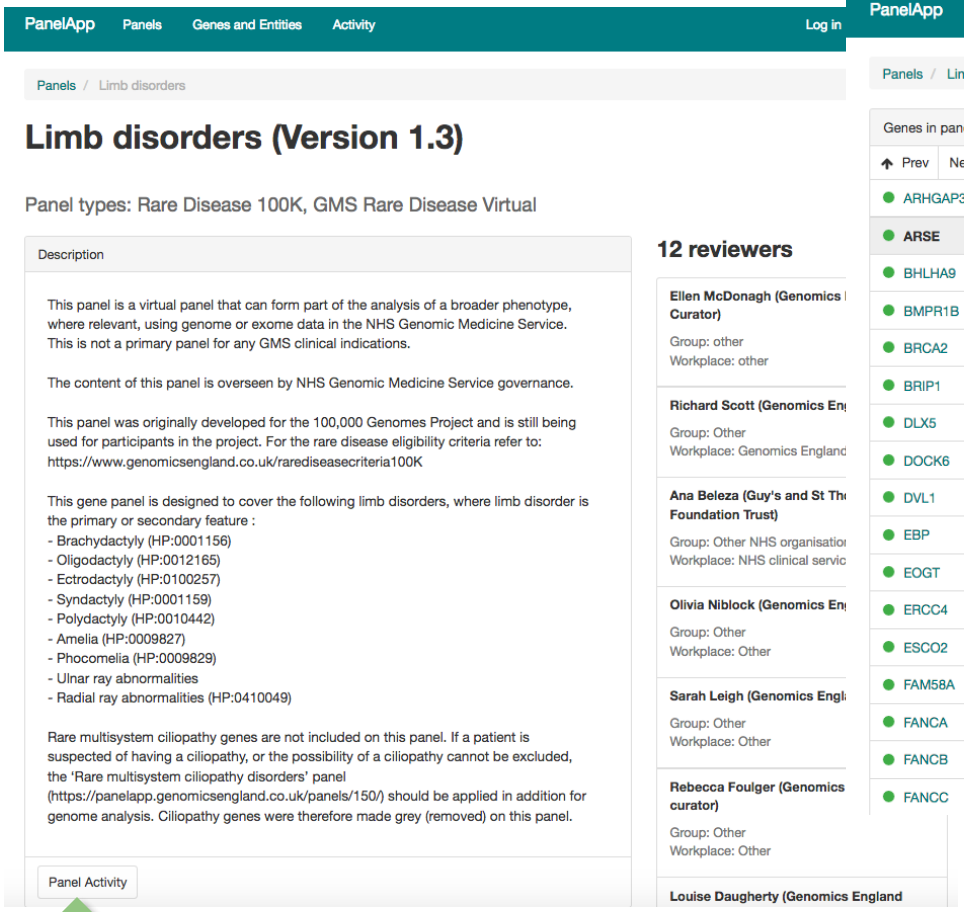
From the PanelApp homepage, click on the 'Activity' page

This will display activity for all panels in PanelApp and can be filtered for date, panel name, version, gene activity type, name of Reviewer or Curator

Activity

Date	Panel	Item	Activity
Filter activities			3000 actions
24 Nov 2019	Early onset Parkinson disease_MelbourneGenomics_VCGS v0.2	PDE8B	Zornitza Stark Marked gene: PDE8B as ready
24 Nov 2019	Early onset Parkinson disease_MelbourneGenomics_VCGS v0.2	PDE8B	Zornitza Stark Gene: pde8b has been classified as Green List (High Evidence).
24 Nov 2019	Early onset Parkinson disease_MelbourneGenomics_VCGS v0.2	PDE8B	Zornitza Stark Classified gene: PDE8B as Green List (high evidence)
24 Nov 2019	Early onset Parkinson disease_MelbourneGenomics_VCGS v0.2	PDE8B	Zornitza Stark Gene: pde8b has been classified as Green List (High Evidence).
24 Nov 2019	Early onset Parkinson disease_MelbourneGenomics_VCGS v0.1	PDE8B	Zornitza Stark gene: PDE8B was added gene: PDE8B was added to Early onset Parkinson disease_MelbourneGenomics_VCGS. Sources: Expert Review Mode of inheritance for gene: PDE8B was set to MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted

How to view updates on individual Panel or Gene pages:



From a Panel page, click on 'Panel Activity'

From a Gene page, click on the 'History' tab and then 'Filter Activity'

This will display the relevant activity can be filtered for date, version, activity type, name of Reviewer or Curator

Additional Notes for Reviewers

- Your evaluations and comments will be tagged with your name and affiliation, and are public. Your name and affiliation will appear in the list of reviewers at the top of the panel.
- The date you made your review will appear, along with the version of the panel you reviewed.
- You can make multiple comments for each gene, and edit or delete them individually.
- Changes to the rating, mode of inheritance, mode of pathogenicity and current diagnostic practice by a curator will overwrite your initial evaluation.
- Publications and phenotypes will be saved in the evaluation tool and can be added to.
- When you have reviewed a gene, you can see your review under the review tab along with any reviews from other experts.
- For your reviewed genes, a tick will appear in front of the gene in the Genes in panel list. A tick together with **You reviewed** text will also be added to the Reviewed column on the main panel page.

Acknowledgements

- We are extremely grateful to the Genomics England PanelApp team for making PanelApp open source, helping us deploy an Australian instance and for sharing documentation and expertise
- In particular, we would like to thank: Ellen McDonagh, Rebecca Foulger, Antonio Rueda-Martin, Oleg Gerasimenko and Augusto Rendon

- We are also very grateful to the Australian Genomics Program 2 team who deployed the Australian instance: Oliver Hoffman, Victor San Kho Lin and Roman Valls

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