PanelApp Handbook

Version 6.6

Background & Guidance for Public Users and Reviewers for PanelApp Release V2.3.0

PanelApp Tool

Background & Guidance for Reviewers

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1 Document Purpose & Scope

The purpose of this document is to provide an overview of PanelApp, together with a step-by-step guide for users of PanelApp and reviewers of PanelApp gene panels. This includes guides about *what* information is stored, *where* to find the relevant information and *how* to leave reviews and feedback.

2 PanelApp Overview

2.1 What is PanelApp?

The Genomics England PanelApp (https://panelapp.genomicsengland.co.uk/) is a publically-available knowledgebase that allows virtual gene panels related to human disorders to be created, stored and queried. It includes a crowdsourcing tool that allows genes and genomic entities (short tandem repeats/STRs and copy number variants/CNVs) to be added or reviewed by experts from the international scientific community. Thereby providing an opportunity for the standardisation of gene panels, and a consensus to be reached on which genes have sufficient evidence for disease association. Diagnostic grade 'Green' genes and genomic entities, and their modes of inheritance, in the PanelApp virtual gene panels are used to direct the variant tiering process for the interpretation of genomes in the 100,000 Genomes Project. As panels in PanelApp are publically available, they can also be used by other group and projects. For further information, see https://www.genomicsengland.co.uk/about-genomics-england/panelapp/.

2.2 Types of Gene Panels

A **'Panel Type'** is assigned to each panel that denotes what the gene panel is utilised for. Current panel types are:

- **Rare Disease 100K**: a gene panel used for the Rare Disease programme of the 100,000 Genomes Project.

- **Cancer Germline 100K**: a gene panel used for the Germline Cancer programme of the 100,000 Genomes Project.
- **External Diagnostic Lab**: a gene panel from a diagnostic lab or other source, external to Genomics England and not directly used for genome analysis for the 100,000 Genomes Project.

2.2.1 Super panels

PanelApp also supports Super panels where a parent panel is made up of a number of child panels. Whenever a child panel is updated, the content and version of the Super panel is automatically updated. This functionality available to PanelApp Curators allows larger gene panels to be created from existing smaller panels, and keeps the Super panel up-to-date automatically.

In cases where the same gene or genomic entity is present in multiple child panels, the Super panel will display these as individual rows with links to the respective panels. The same gene or genomic entity therefore may be listed several times in the Super panel with a different rating or mode of inheritance, depending on the source child panel. The current version of each of the child panels is displayed at the top of the Super panel page. These panels will have the 'Panel Type: Super panel' once launched.

2.3 Defining and Creating PanelApp Gene Panels

For the 100,000 Genomes Project, panels are mapped to one or more recruitment categories, indicated by the gene panel name (Level 4 Title) and/or listed under 'Relevant disorders' for each panel in PanelApp.

Gene panels are created in a number of steps described in detail in Appendix A. In summary,

A. For the 100,000 Genomes Rare Disease programme:

1. **An initial gene list** is drawn up from established sources (UKGTN, Radboud UMC, Emory Genetic Laboratory and Illumina) and/or from experts in the disease area. Initial gene panels are Version 0.
2. **Expert review** of each gene is crowdsourced.
3. **Evaluation** of the reviews, further curation and consultation with the Genomics England clinical team results in a finalised gene panel.
4. **Promotion of** the panel to Version 1 allows the panel to be used in the interpretation of participant genomes.

Note that PanelApp gene panels are only used in interpretation after expert review and curation has been completed, and the panel has been promoted to 'Version 1'. Prior to this, panels are viewable and can be reviewed but the rating of genes (see Section 2.5) have not been finalised.

B. For the 100,000 Genomes Cancer Germline Project:

1. **Initial gene lists** with strong clinical evidence conferring susceptibility of clinically-relevant penetrance to the respective tumour type were submitted from the gene lists used in the interpretation pipeline. Initial gene panels are Version 0.
2. **Review, Evaluation and Promotion of the panel** as outlined in steps 2-4 above.

2.4 Entities on a Gene Panel

In addition to the analysis of genes, an interpretation pipeline for whole genome sequences has been developed and validated by Genomics England that allows short tandem repeats (STRs) and copy number variants (CNVs) to be reported. PanelApp therefore allows curation and reviews of these entities. In summary, a panel can contain the following genomic entities:

- **Gene**
- **STR** (Short Tandem Repeat). STRs can be disease-causing when a particular number of repeats is present.
- **CNV** (Copy Number Variant). PanelApp currently supports region-loss and region-gain.

Green genomic entities on a version 1+ panel will be used for genome interpretation in the 100,000 Genomes Project. For further details on the information captured for genes, STRs and CNVs, see Sections 3.3, 3.7 and 3.8.

2.5 Understanding Gene Ratings on a Version 1+ Gene Panel

We classify genes on a panel according to a traffic light system (Figure 1). Genes are rated in terms of the level of evidence to support their association with the phenotypes covered by the gene panel in question.

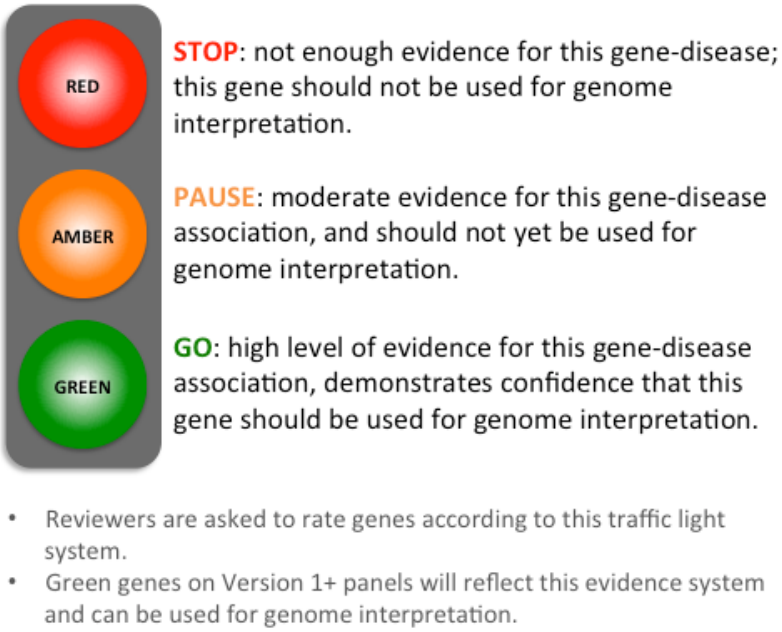

Figure 1. A traffic-light system is used to rate genes on a Version 1+ gene panel.

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 in Appendix B); a diagnostic-grade (Green) rating on a Version 1+ panel requires evidence from 3 or more unrelated families or from 2-3 unrelated families where there is strong additional functional data. Genes that do not meet these criteria are rated as Amber (borderline) or Red (low level of evidence), depending on the level of evidence, and are not used in Tiering.

For cancer germline panels, the Green genes on a Version 1+ panel are those with strong clinical evidence conferring susceptibility of clinically-relevant penetrance to the respective tumour type.

2.6 How Do I Add Genes, Genomic Entities and Reviews to a Gene Panel?

PanelApp has more than 500 registered reviewers from over 25 countries, the majority of whom are experts in rare disease diagnosis from the UK. We encourage experts to contribute their knowledge to update existing panels to help create new diagnostic-grade panels.

- To find a PanelApp gene panel of interest, see Section 3.
- For step-by-step instructions on reviewing data in PanelApp, see Section 4.
- To add genes and other entities to an existing panel, see Section 4.7.

2.7 Uses and Users of PanelApp

The diagnostic grade 'Green' genes (see Section 2.5), genomic entities, and their modes of inheritance on the Version 1+ PanelApp virtual gene panels are used to direct the Genomics England Rare Disease Tiering process. The Tiering process is to aid evaluation of Rare Disease findings by annotating variants that are plausibly pathogenic based on their segregation in the family, frequency in control populations, and effect on protein coding. Variants in diagnostic grade 'Green' genes can be tiered as Tier 1 or Tier 2.

In the Genomics England Cancer Programme, germline variants are tiered as Tier 1 if pathogenic or likely pathogenic variants are found in Green genes on the relevant cancer panel assigned based on the patient's tumour type. Tier 3 variants are rare variants reported in Green genes on a broader set of cancer panels. For Tier 1 and Tier 3 variants, clinical review and confirmation of pathogenicity are essential and should be undertaken locally. This process is explained in more detailed in the technical information available here: https://www.genomicsengland.co.uk/information-for-gmc-staff/cancer-programme/genome-analysis/

Gene panels in PanelApp can also be utilised for other projects, clinics and databases. See Appendix F for scenarios describing how PanelApp may be useful to you, depending on your role and interests.

3 Navigating PanelApp

There are several different user types of PanelApp (Table 1). You can browse the PanelApp user interface as a Public (anonymous) user without creating an account - all panels and reviewer comments are publicly visible. Individual panels of the desired version can be downloaded from the user interface or queried via WebServices (Section 3.15 and Appendix D). To provide comments or reviews for a gene panel, you will need to register as a Reviewer.

Action	Public User (Section 3.1)	Reviewer (Section 4)	Curator
View gene panels (Section 3.2)	✓	✓	✓
View gene/genomic entity information (Section 3.3)	✓	✓	✓
Download individual gene panels (Section 3.14)	✓	✓	✓
Query PanelApp API (Section 3.15)	✓	✓	✓
View reviewers' ratings and comments, and who made these (Section 3.4)	✓	✓	✓
Link to external gene sources including Ensembl, OMIM and ClinVar (Section 3.5)	✓	✓	✓
View gene/genomic entity history (Section 3.6-3.8)	✓	✓	✓
Rate genes, STRs and CNVs in a gene panel (Section 4)	X	✓	✓
Add genes, STRs and CNVs to a gene panel (Sections 4.7-4.9)	X	✓	✓
Add comments and information (e.g. publications, mode of inheritance) to a gene panel (Sections 4.3-4.6)	X	✓	✓
View a list of your own evaluations (Section 4.11)	X	✓	✓
Delete genes from a panel	X	X	✓

Change the rating of a gene/genomic entity	X	X	✓
Promote a panel to the next major version	X	X	✓
Create a panel or Super panel	X	X	✓

Table 1. The PanelApp actions available to public users, reviewers and Genomics England curators. Note that neither public users nor reviewers can delete genes from a panel.

3.1 Browsing PanelApp as a Public User

1. Go to https://panelapp.genomicsengland.co.uk/

2. If going from the https://panelapp.genomicsengland.co.uk/accounts/login/ page, select 'Browse PanelApp without logging in' to be redirected to the homepage.

3. On the homepage you can:

- Find out more about PanelApp from the left hand menu.
- Browse PanelApp through either a panel-centric, or gene and entity-centric route. Select either 'Panels' or 'Genes and Entities' from the menu at the top of the homepage (Figure 2).

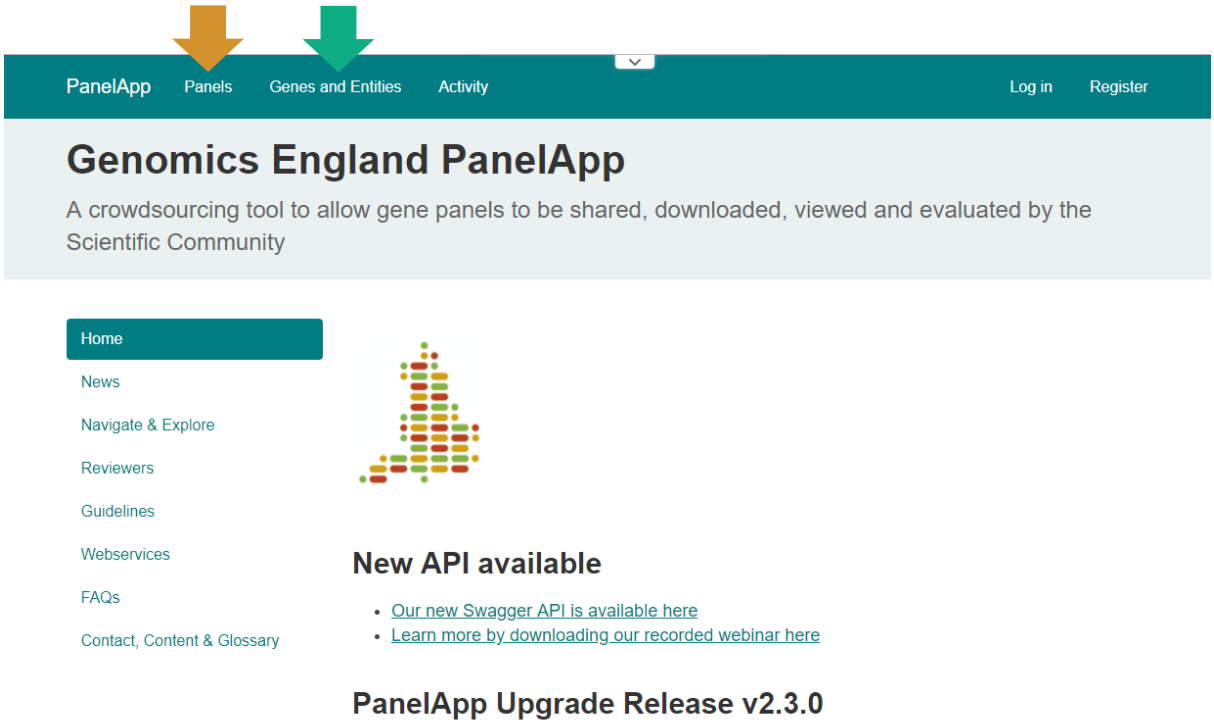

Figure 2. The PanelApp homepage. Use the top menu to navigate 'Panels' or 'Genes and Entities' within PanelApp (https://panelapp.genomicsengland.co.uk/).

3.2 Browsing Panels in PanelApp (a Panel-Centric View)

1. Click on 'Panels' in the top bar of the page (Figure 2).

A full list of panels is displayed in alphabetical order. The list can be sorted by:

- Panel name
- Percentage of Evaluated genes
- Number of Reviewers

The 'Filter panels' box allows users to find gene panels of interest, for example; by entering 'immunodeficiency', the list will be filtered to display all panels that fall under this term.

To compare two panels, click the '**Compare two panels**' button and select the panels for comparison from the drop-down menu. Once selected, click '**Compare panels**' and the genes

and their rating on each panel will be displayed. For a gene of interest select '**Compare**' to see further details regarding the gene on the two panels, including reviews.

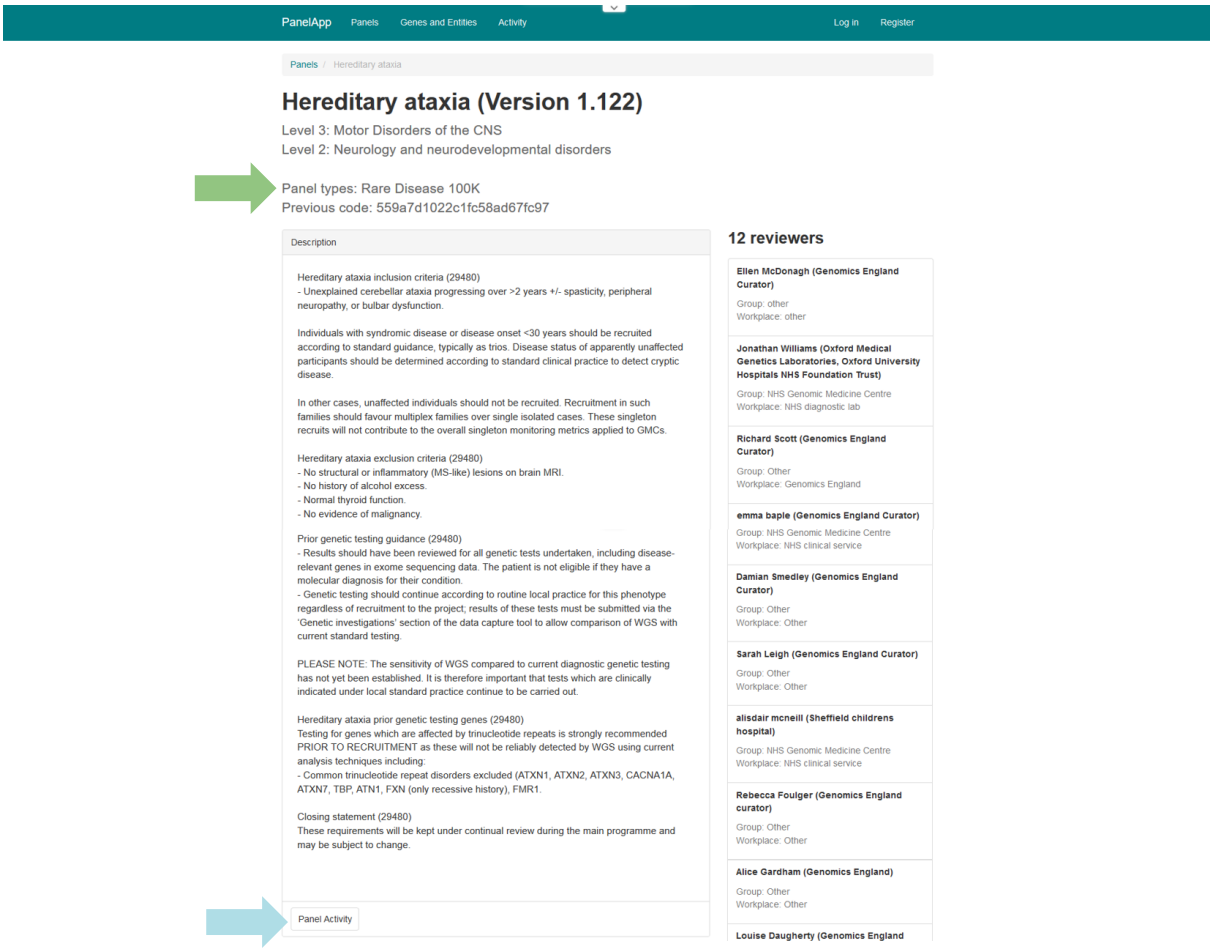

Figure 3. The gene panel for Hereditary ataxia (Level 4 title). The Panel type 'Rare Disease 100K' indicates that this panel is part of the Rare Disease programme of the 100,000 Genomes Project (green arrow). A gene panel includes a Description box detailing the eligibility statement for the rare disease category or a description of the panel. Click on 'Panel Activity' (blue arrow) to see a history of changes to the panel.

2. Click on the **gene panel** name to go to the panel, where you can

- Read the Genomics England eligibility statement for the disease displayed in the description box (Figure 3).
- View the Panel Type (Figure 3).
- View a list of the reviewers (and their affiliations) who have reviewed genes on this panel (Figure 3)
- View changes to the panel: click on the 'Panel Activity' button at the bottom of the entity list (Figure 3). Panel edits are displayed with most recent activity first. The list can be further filtered by gene/genomic region person or activity type by typing in the filter box (e.g. "new gene"). To return to the panel from the Activity view, click the panel name.
- View the list of genes and genomic entities in the panel, and their current status (Green, Amber, Red) (Figure 4).
- View mode of inheritance (if known), sources the gene was found in, and phenotypes related to the gene.
- View tags attached to genes and entities within a gene panel. These are used by curators to highlight specific information about variants in a gene, for example a 'nucleotide-repeat-expansion' tag indicates that nucleotide expansion repeat variations can cause the disorder. See Appendix E for an explanation of entity tags. From the links at the bottom of the page, you can download the whole panel or a selection of genes and other entities (see Section 3.14).

175 Entities

172 reviewed, 119 green

List	Entity	Reviews	Mode of inheritance	Details
Filter Entities				175 Entities
Green	COQ8A	3 reviews 1 green	BIALLELIC, autosomal or pseudoautosomal	Sources • Illumina TruGenome Clinical Sequencing Services • UKGTN • Expert Review Green Phenotypes • Coenzyme Q10 deficiency, Spinocerebellar Ataxia Type
Green	15q11q13 recurrent (PWS/AS) region (BP1-BP3, Class 1) Loss ISCA-37404-Loss Region	0 reviews	MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown	Sources • Expert Review Green • ClinGen Phenotypes • microcephaly • Developmental delay, muscle weakness • Mental retardation • Angelman syndrome • 176270 • Prader-Willi syndrome • 105831
Green	MRE11	3 reviews 1 green	BIALLELIC, autosomal or pseudoautosomal	Sources • Expert Review Green • Illumina TruGenome Clinical Sequencing Services • Radboud University Medical Center, Nijmegen • UKGTN Phenotypes • Ataxia-Telangiectasia-Like Disorder • Ataxia-telangiectasia-like disorder
Green	PPP2R2B_CAG STR	2 reviews 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	Sources • Expert list • Expert Review Green Phenotypes • Spinocerebellar ataxia 12 604326 Tags STR
Green	TWNK	3 reviews 1 green	BOTH monoallelic and biallelic, autosomal or pseudoautosomal	Sources • Illumina TruGenome Clinical Sequencing Services • Expert Review Green Phenotypes • Ataxia Neuropathy Spectrum Disorders (Dominant) • Spinocerebellar Ataxia, Recessive
Green	AAAS	2 reviews 1 green	BIALLELIC, autosomal or pseudoautosomal	Sources • UKGTN • Expert Review Green
Amber	COG5	1 review	BOTH monoallelic and biallelic, autosomal or pseudoautosomal	Sources • Literature • Expert Review Amber Phenotypes • Congenital disorder of glycosylation, type IIi 613612
Amber	DMXL2	1 review	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	Sources • Other • Expert Review Amber Phenotypes • Sensorineural Hearing Loss • ORPHA90636 • OMIM:612186
Amber	MVK	1 review	BIALLELIC, autosomal or pseudoautosomal	Sources • Literature • Expert Review Amber Phenotypes • Mevalonic aciduria 610377
Amber	VAMP1	4 reviews 1 green	MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown	Sources • Radboud University Medical Center, Nijmegen • UKGTN • Expert Review Amber Phenotypes • Spastic ataxia 1, autosomal dominant, 108600 Tags watchlist
Red	AARS	1 review	MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown	Sources • Expert Review Red • UKGTN
Red	ALAS2	1 review	X-LINKED: hemizygous mutation in males, monoallelic mutations in females may cause disease (may be less severe, later onset than males)	Sources • Expert Review Red • Illumina TruGenome Clinical Sequencing Services

Figure 4. A subset of genes and entities on the 'Hereditary ataxia' panel. The panel contains genes (e.g. AAAS), short tandem repeats (e.g. PPP2R2B_CAG) and CNVs (e.g. 15q11q13 recurrent (PWS/AS) region (BP1-BP3, Class 1) Loss). Short tandem repeats are labelled as 'STR' (blue arrow). CNVs are labelled as 'Region' (orange arrow). Gene information including mode of inheritance and phenotypes related to the genes or genomic entities can be viewed from this panel page (https://panelapp.genomicsengland.co.uk/panels/20/).

3.3 View Gene Information on a Panel

Click on the **gene symbol** to view information about a gene including:

- HGNC-approved name.
- Ensembl gene identifiers and a link to Ensembl.
- OMIM gene identifier and a link to OMIM.
- A link to gene information in Gene2Phenotype.
- A link to display the other panels that the gene appears on.

Further gene information is available on three separate tabs (Figure 5):

I. Reviews of the gene.
II. Details about the gene including links to ClinVar.
III. History of when the gene was added, and any changes made to the gene information.

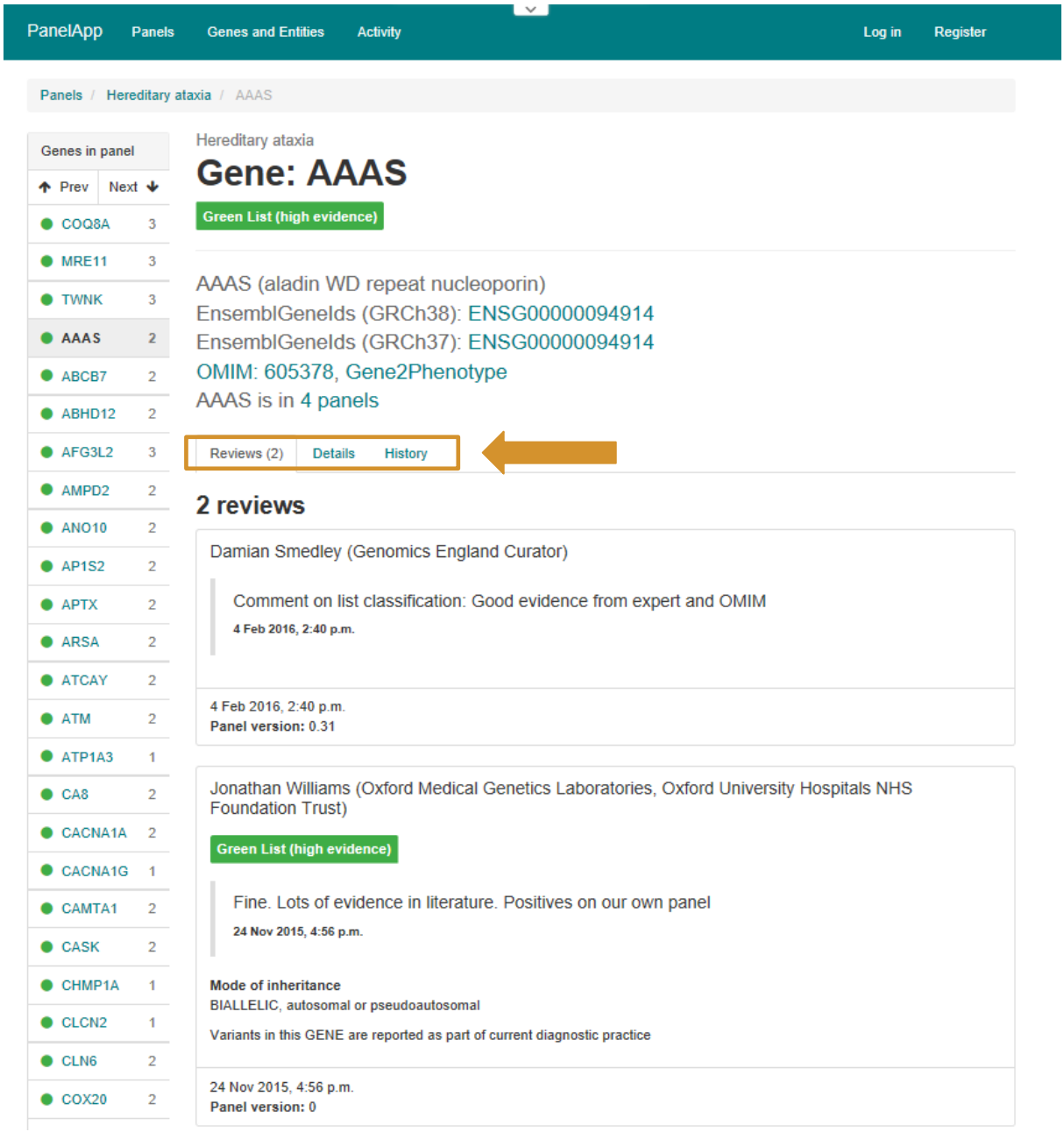

Figure 5. Each gene within a panel contains information in the 'Reviews', 'Details' and 'History' tabs (orange arrow).

3.4 View Gene Reviews using the Reviews Tab

Reviews for a gene can be accessed by different routes:

- To see the individual reviews for a given gene, click on the gene symbol and then the Reviews tab. Scroll down to view reviewer's evaluations and comments.
- If you are a reviewer, you can view your own evaluations following instructions in Section 4.11.
- A summary of reviews can also be viewed:

    - On the Panels page (https://panelapp.genomicsengland.co.uk/panels/), a summary of the number of evaluated genes, and reviewers for each gene panel is provided in the panel summaries.
    - On each individual panel page, a list of reviewers is provided on the right hand side, and the number of Red or Green reviews is shown beside each rated gene (Figures 3 and 4).

3.5 View Gene Information Using the Details Tab

The Details tab on the Gene page contains more information for that gene, including:

- Mode(s) of inheritance for that gene for the relevant disease.
- Sources in which the gene-phenotype association was reported.
- Phenotypes collected from the sources, related to the rare disease category.
- A link to the gene page in the OMIM database.
- A link to variants within this gene in the ClinVar database.
- Penetrance (the default is 'Complete penetrance', however this field allows cases of incomplete penetrance to be collected from reviewers and the literature).
- Publications related to the gene-disorder association (as links to the relevant PubMed identifier)

- The mode of pathogenicity for the gene-disorder association (if loss-of-function variants in the gene do not cause the phenotype).
- Other gene panels in PanelApp that this gene appears in.

3.6 View Gene History Using the 'History' Tab.

The history tab lists changes made to the gene information, reviews and rating (status).

3.7 View STR Information on a Panel

On the Panels page (https://panelapp.genomicsengland.co.uk/panels/), the number of STRs (if present) is displayed in the 'Evaluated genes' column. For an individual panel, STRs can be identified by their name and the 'STR' label (Figure 4). All short tandem repeats (STRs) in PanelApp are associated with a gene, and therefore the nomenclature for STRs in PanelApp is as follows: HGNC-approved gene symbol_Nucleotide repeat (e.g. PPP2R2B_CAG).

Click on the **STR symbol** on a panel to view information (Figure 6) including:

- Chromosome and genomic coordinates for the start and end of the nucleotide repeats in the reference genome for Build 37 and 38.
- The repeated nucleotide sequence.
- The maximum number of repeats that are considered non-pathogenic/normal.
- The minimum number of repeats that are considered pathogenic/disease-causing.
- OMIM, Ensembl and Gene2Phenotype information for the corresponding gene.

Further STR information is available on the **Reviews**, **Details** and **History** tabs, which hold equivalent information as provided on gene pages.

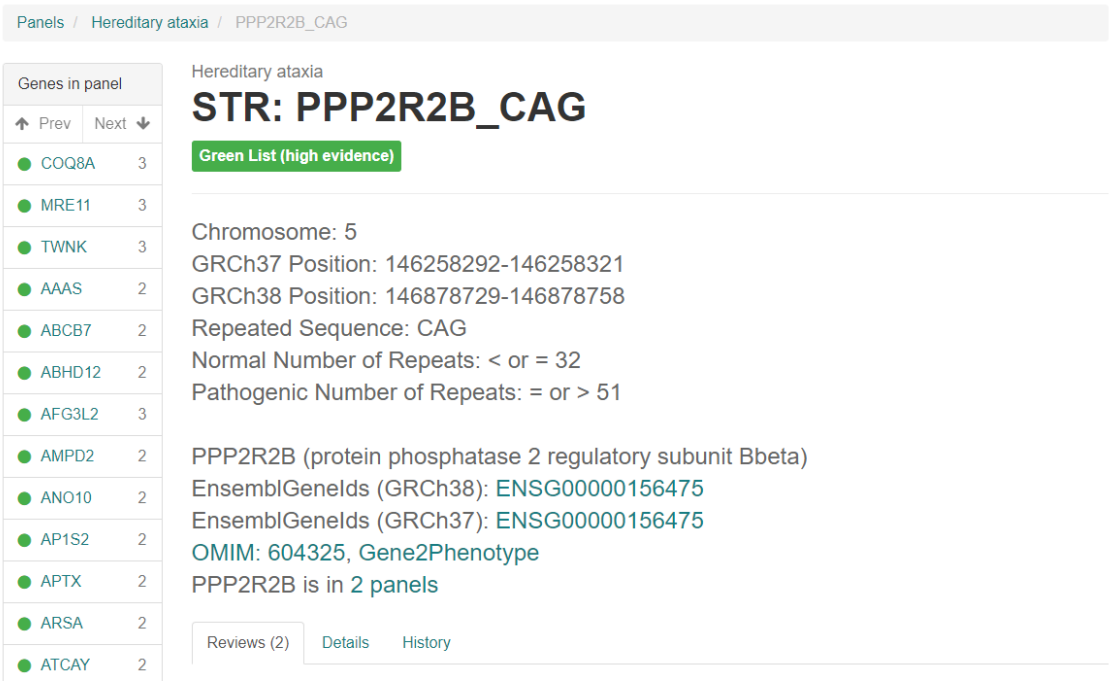

Figure 6. The annotation summary for each STR within a panel includes information about both the repeats and the corresponding gene. Further information is available in the 'Reviews', 'Details' and 'History' tabs.

3.8 View CNV Information on a Panel

PanelApp supports curation and review of genomic regions, including copy number variants (CNVs), which are integrated into the Genomics England genome analysis pipeline for rare diseases. CNVs in PanelApp originate from the curated ClinGen Dosage Sensitivity Map curated regions, available at: ftp://ftp.ncbi.nlm.nih.gov/pub/dbVar/clingen/.

On the Panels page (https://panelapp.genomicsengland.co.uk/panels/), the number of regions (if present) is displayed in the 'Evaluated genes' column. On an individual panel, CNVs can be identified by their 'ISCA' prefix, and the 'Region' label (Figure 4).

Click on a CNV symbol on the panel to view information about the CNV (Figure 7). You will be able to see:

- The CNV identifier (shown in black). This also includes whether the region is a gain or loss; the same region may be present twice on the same panel as a loss and as a gain.

- The CNV full (verbose) name (shown in grey).
- The status of the CNV (Green, Amber, Red) on the panel.
- Chromosome start and end coordinates for GRCh38. For CNVs, only GRCh38 coordinates are provided in PanelApp (unlike for genes and STRs which also display the GRCh37 details).
- The Haploinsufficiency Score (a region loss. This score is provided by ClinGen).
- The Triplosensitivity Score (a region gain. This score is provided by ClinGen).
- Variant type (CNV Loss or CNV Gain)

Note that the 'Required percent of overlap' score has a default value of 80%. This score is intended for internal use only as it relates to the Genomics England internal CNV calling algorithm, and may be different for different CNV detection methods.

Further CNV information is available on the **Reviews**, **Details** and **History** tabs, which hold equivalent information as provided on gene pages.

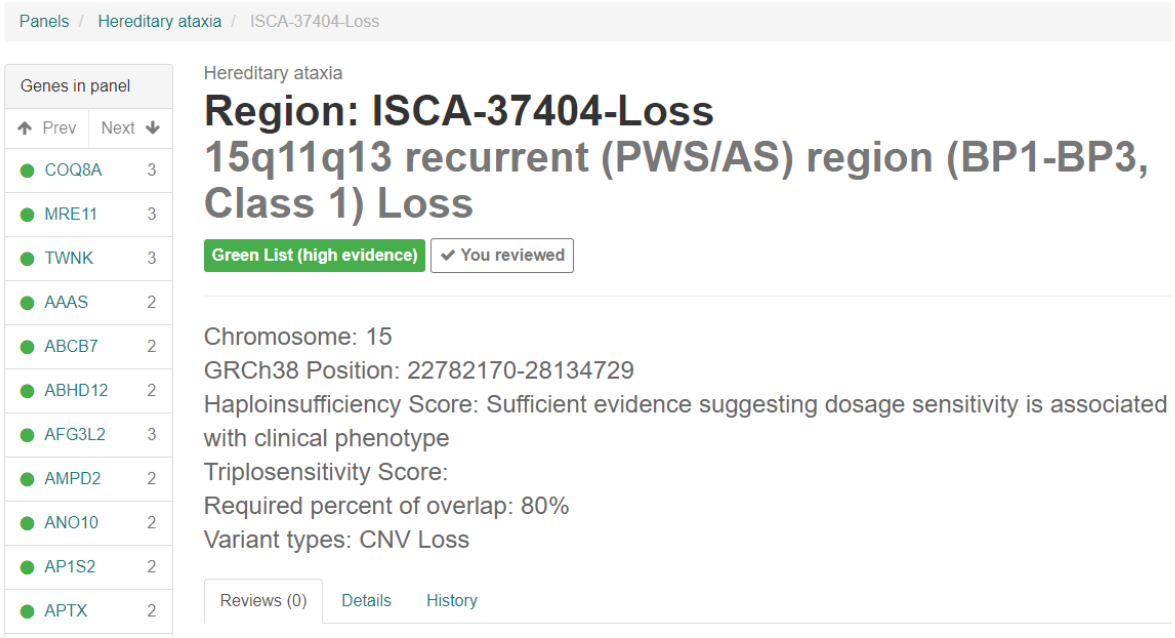

Figure 7. Each CNV within a panel contains an annotation summary, and further information in the 'Reviews', 'Details' and 'History' tabs.

3.9 Browsing Genes and Entities in PanelApp (an Entity-Centric View)

1. To browse genes, STRs and CNVs, click on 'Genes and Entities' in the top bar of the PanelApp page (Figure 2). A full list will be displayed in alphabetical order.

2. Select the gene or entity of interest, or start typing the symbol into the 'Filter genes and genomic entities' box to narrow down your selection.

3. You can filter the list to view only Genes, STRs or Regions using the checkboxes under the search box. You can also find CNVs by filtering for 'ISCA'.

3.10 View Gene Information from the 'Genes and Entities' List.

Click on a gene symbol to view information about a gene. You will be able to see:

- HGNC-approved Gene name.
- Links to OMIM and Gene2Phenotype.
- A list of all panels on which the gene occurs, and the panel version.
- The status of the gene (Green, Amber, Red) on each panel.
- The Mode of Inheritance of the gene for each disorder (if known).
- Sources in which the gene-phenotype association was found.
- The relevant phenotypes of the gene for each disorder.

From this page, you can:

- Click on the gene symbol to take you to the gene entry within the listed panel.
- Click on the panel name to view the full panel that contains that gene.

3.11 View STR Information from the 'Genes and Entities' List

If a STR appears on multiple panels it will appear multiple times in the 'Genes and Entities' List (e.g. ATN1_CAG). Click on a STR symbol from the 'Genes and Entities' list to view information about the STR and corresponding gene, and a list of panels the STR and/or gene occur on.

3.12 View CNV Information from the 'Genes and Entities' List

All CNV symbols are prefixed with 'ISCA' and end with either '-Loss' or '-Gain'. Click on a CNV symbol from the 'Genes and Entities' list to view information about the CNV, and a list of panels which contain the CNV.

3.13 View Tags from the 'Genes and Entities' List

A list of tags is displayed down the right hand side of the 'Genes and Entities' page (https://panelapp.genomicsengland.co.uk/panels/entities/). Tags are added by Genomics England Curators and highlight useful information about a gene or gene variants that may affect gene ratings, or may be useful for future curation. For example, 'founder-effect' shows that only one variant has been reported for that gene in a particular population, or a shared haplotype has been observed.

- Click on a tag name, to see a list of genes and/or entities curated with that tag.
- Click on the gene or entity name to view a table of panels containing that gene; the tag is shown in the 'Details' column.

3.14 Download a Gene Panel

The download menu is available at the bottom of each panel page. Downloads of gene panels are in .tsv format, which can be opened using a number of applications, including Microsoft Excel. Users have the option of downloading the (i) whole gene panel, (ii) only Green list, (iii)

only Amber list, (iv) Green and Amber list, or (v) only Red list. Users can also download a previous version of the panel.

The download file contains the following fields:

- Entity Name (gene name, STR name, region name)
- Entity Type (gene, str, region)
- Gene Symbol (HGNC-approved gene symbol)
- Sources (separated by ;)
- Level 4, 3 and 2 titles (E.g. specific rare disease specific, subgroup and group)
- Mode of inheritance (using PanelApp standardised terms)
- Phenotypes (as collected from all sources and reviews)
- OMIM, Orphanet, HPO terms (not currently populated)
- Publications
- Description (not currently populated)
- Flagged (default = FALSE)
- GEL status (reflects the current gene rating; 3 or 4 = Green, 2 = Amber, 1 or 0 = Red)
- User Ratings (represented as the percentage of ratings for Green;Amber;Red).
- Version (the gene panel version)
- Ready
- Mode of pathogenicity
- Ensembl ID (GRCh37)
- Ensembl ID (GRCh38)
- HGNC ID

For STRs only, the following fields will be populated:

- Position Chromosome
- Position GRCh37 start
- Position GRCh37 end
- Position GRCh38 start

- Position GRCh38 end
- STR Repeated Sequence
- STR Normal Repeats
- STR Pathogenic Repeats

For Regions (CNVs) only, the following fields will be populated:

- Region Haploinsufficiency Score
- Region Triplosensitivity Score
- Region Required Overlap Percentage
- Region Variant Type
- Region Verbose Name

3.15 Querying PanelApp via the PanelApp API

Examples for querying the PanelApp API, together with terms available to use for mode of inheritance queries, are listed in Appendix D.

A new PanelApp API (Swagger) was released in September 2018, and can be found at: https://panelapp.genomicsengland.co.uk/api/docs/. The Swagger API should be used for retrieving STRs and Regions (CNVs). It can also be used to retrieve panels and genes. For any filtered queries (e.g. retrieving genes by mode of inheritance or rating), the existing WebServices should be used (Appendix D).

Note that when querying a Super panel through The PanelApp API, all data from child panels will be returned.

4 Reviewing genes and genomic entities in PanelApp

4.1 Registering to be a Reviewer

Expert review of the gene panels is sought to enable a community consensus to be reached on which genes and genomic entities should appear on a diagnostic-grade gene panel for each disorder. We request that reviewers of the gene panels should have:

- Expertise in a disease area, genes or diagnostic genetic testing relevant to the diseases in the 100,000 Genomes Project.

A full list of the rare diseases that are part of the 100,000 Genomes Project can be found on the Genomics England website: http://www.genomicsengland.co.uk/library-and-resources/

The approved list of cancers and their eligibility criteria can be found here: https://www.genomicsengland.co.uk/information-for-gmc-staff/cancer-programme/eligibility/

Reviewers can:

- Be based anywhere in the world.
- Have an academic, clinical and/or commercial background.

To register as a PanelApp reviewer:

1. Go to: https://panelapp.genomicsengland.co.uk/accounts/login/ and select 'Register to be a reviewer' at the bottom of the page.

(If you are already browsing the PanelApp as a public user, click on the **'Register'** button in the top right hand corner of PanelApp, and you will be redirected to this Login page.)

2. Fill in the information on the Sign up page:

Username and password: These are needed to set up and sign in to your reviewer account but are not visible to the public or other reviewers in PanelApp. Please choose a username without spaces and do not use your email address as your username.

First Name, Last Name and Affiliation: To encourage openness, all gene evaluations and comments from reviewers are made public. Your full name and affiliation will be added to your reviews. By registering as a reviewer you are agreeing to this condition.

Role, Workplace and Group: These details help verify the Reviewer. Workplace and Group will be displayed on PanelApp.

Email: please use your institutional / work email address or NHS email to register if possible. This will allow us to process the reviewer request more effectively. Your confirmation of reviewer status will be sent to this email address. Your email will not be publically visible on PanelApp.

3. Submit your request by clicking 'Register'.

After registering, you will be sent an email requiring you to verify your email address by visiting a link provided in the email; note that the link expires in 3 days. **Please click on this link to enable your registration to be processed**. Your application will then be reviewed by a Genomics England Curator within 48 hours. If accepted, you will be sent a confirmation email and then you can log in to PanelApp to provide reviews on panels. While your application is being processed, you can still browse PanelApp as a public user.

4.2 Signing in as a Reviewer

Once registered as a reviewer, to sign-in go to https://panelapp.genomicsengland.co.uk/accounts/login/

If you have forgotten your password, you can reset your account by selecting 'I forgot my password', then enter the same email you registered with and select 'Request new password'.

Please contact panelapp@genomicsengland.co.uk if you have any issues signing in or have any questions regarding reviewing.

4.3 Instructions for Review of Genes and Genomic Entities on PanelApp

We welcome reviews for genes, STRs and CNVs. Once logged in as a reviewer (see Section 4.2), search for the panel, gene or genomic entity that you would like to review or comment on, by browsing PanelApp as described in Section 3.

We request that reviewers read the details regarding the panel in the description box. For the rare diseases this will be the eligibility statement for the 100,000 Genomes Project (where available, see Figure 3). The description provides information on the phenotype inclusion for the panel. Please also review Section 2.5 to gain an understanding of the rating system for rare disease and cancer germline panels.

4.4 Instructions for Review of Genes on PanelApp

- Click on each gene in the panel and provide a review using the 'Reviews' tab. Please leave feedback for each gene on a panel, specifically:
- Provide a rating
    - Green: high evidence, clinically-actionable or diagnostically-reportable pathogenic or likely pathogenic variants.
    - Red: low evidence, variants that are not clinically actionable.
    - Amber : moderate evidence if there is some supportive evidence, but not sufficient for a green rating.

- Guidelines for reviewers for the evidence required for a gene to be rated as 'Green/high evidence' for rare disease panels are available from the PanelApp homepage (on the **Guidelines** tab), and are detailed in this document in Appendix B.
- Provide a mode of inheritance for the gene-disease association from the drop-down menu.
    - Definitions for the terms are provided in the (?) pop-up box, within this document (See Appendix E) and on the PanelApp homepage within the **Contact, Content & Glossary** tab.
    - If the mode of inheritance you want to add is not within the drop down menu, or you know of more than one mode of inheritance pattern, different modes of inheritance for specific phenotypes, or other scenarios, please select 'other' and provide details in the comments box. Please provide information regarding imprinting, if known.
- Add relevant phenotypes.
    - Where possible, please add phenotypes using standardised OMIM, Orphanet or HPO terms and codes relevant to the rare disease category (level 4 title). The phenotypes shown in PanelApp are largely those collected from the sources, with relevance to the panel.
    - Separate phenotypes using a semi-colon e.g. Agammaglobulinemia 7, autosomal recessive, 615214; SHORT syndrome, 269880.
- Add relevant publications.
    - Please provide PubMed IDs separated by a semi-colon, in the format 1234;4321. Include publications that provide supporting evidence for your given rating e.g. published family pedigree studies supporting the gene-phenotype association, or publications showing a lack of an association between the gene and phenotype.
    - If the publication does not have a PubMed ID (e.g. a recently-accepted article), please include details in free-text and these will subsequently be updated by a Curator.

- If loss-of-function variants do not cause the disease phenotype, please select an option in the mode of pathogenicity dropdown menu and provide further details as a comment.
    - Loss-of-function variants are defined as variants with the sequence ontology (SO) terms; **transcript_ablation**, **splice_acceptor_variant**, **splice_donor_variant**, **stop_gained**, **frameshift_variant**, **stop_lost**, **initiator_codon_variant** (see Appendix E).
    - An example where loss-of-function variants are not relevant is for the *PCSK9* gene in hypercholesterolemia (PMIDs:12730697; 15654334).
- Provide justifications in the comments box to support your gene rating, particularly when changing the existing rating for a gene. Include information such as the age of disease onset, penetrance, and details of clinical practice.
    - The comments box can also be used to provide comments intended to activate community debate.
- 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 '*Clinical diagnostic'* box.
- Add any missing genes using the 'Add a Gene to this panel' button found at the bottom of the gene list. See Section 4.8 for further details.

4.5 Instructions for Review of STRs on PanelApp

- Click on the STR in the panel and provide a review using the 'Reviews' tab.
- Provide a rating (Green, Amber or Red).
- Add a mode of inheritance, and relevant phenotypes and publications, as outlined for a Gene review (Section 4.4).
- Provide justifications in the comments box to support your STR rating. Include information such as premutation and repeat number.

- If submitting the STR evaluation on behalf of a clinical laboratory, indicate whether STR repeats are reported as part of your current diagnostic practice by checking the '*Current diagnostic'* box.
- Check the box if interruptions in the repeated sequence are reported as part of standard diagnostic practice in your laboratory/clinic.
- You can add any missing STRs using the 'Add a STR to this panel' button found at the bottom of the gene panel. Alternatively, contact us at panelapp@genomicsengland.co.uk. See Section 4.9 for further details.

4.6 Instructions for Review of CNVs on PanelApp

- Click on the CNV in the panel and provide a review using the 'Reviews' tab.
- Provide a rating (Green, Amber or Red).
- Add relevant phenotypes and publications, as outlined for a Gene review (Section 4.4).
- Provide a mode of inheritance for the CNV-disease association from the drop-down menu.
    - For all autosomal CNVs, except those where the gene is associated with an autosomal recessive phenotype, choose 'MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown' mode of inheritance
    - For X-linked CNVs, use 'X-LINKED: hemizygous mutation in males, monoallelic mutations in females may cause disease'.
- Provide justifications in the comments box to support your CNV rating, particularly when changing the existing rating of a CNV.
- If submitting the CNV evaluation on behalf of a clinical laboratory, indicate whether the region is reported as part of your current diagnostic practice by checking the '*Current diagnostic'* box.
- You can add any missing CNVs using the 'Add a Region to this panel' button found at the bottom of the gene panel. Alternatively, contact us at panelapp@genomicsengland.co.uk. See Section 4.9 for further details.

4.7 How to Add a Gene or Genomic Entity to a Panel

Scroll down to the bottom of the gene panel where there are options to add a gene, a STR or a region to the panel (Figure 8).

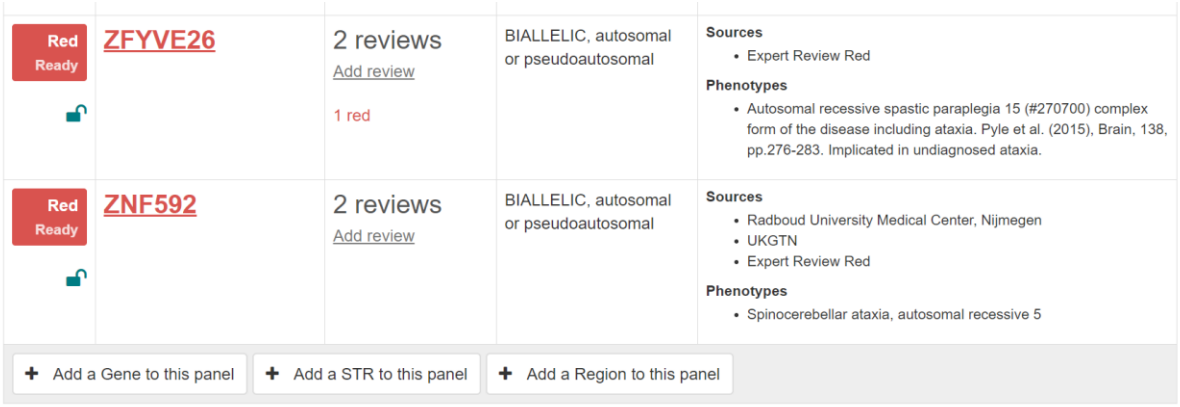

Figure 8. Reviewers and Curators can add Genes, STRs and Regions to a panel using the tool buttons at the bottom of the genes and entities list.

Once a gene, STR or CNV has been added to a panel, it will appear at the bottom of the list in Grey to indicate that it was submitted by a reviewer. The rating will change (to Green, Amber or Red) when evaluated by a Genomics England Curator and/or Clinical Fellow.

4.8 Adding a Gene to a Panel

- To add a gene to the panel, click on the 'Add a Gene to this panel' button.
    - Start to type the gene symbol in the 'Gene symbol' box.
    - An automated list of HGNC-approved gene symbols and corresponding gene name will appear.
    - Select the relevant gene from the list.
    - To check the HGNC-approved gene symbol for a gene or a list of genes, use the symbol checker tool (http://www.genenames.org/cgi-bin/symbol_checker).

- To add the source, select: Expert Review, Literature, or Research from the drop down menu, depending on which is most suitable.
    - Choose '**Expert Review**' as a source if you test for this gene as part of current clinical practice in the diagnosis of the relevant rare disease category. Using the evaluation tool, please rate the gene 'Green List (high evidence)' and check the 'Current diagnostic' checkbox. Provide a short explanation in the comments as to why this gene is important to add to the panel.
    - Chose '**Literature'** or '**Expert Review'** as the source if the gene is well established in the disease area. Please rate the gene 'Green List (high evidence)' and add publications to support the addition of this gene. Please also provide a short explanation in the comments box as to why this gene is important to add to this panel.
    - Choose '**Research'** as the source if the gene is still in research phase, and requires further evidence before it can be used in diagnosis, for example a gene you have identified in your own research. Adding such genes to the panel is useful to encourage the submission of further evidence from other reviewers. You should rate these genes as 'Red List (low evidence)'. Please provide a short explanation in the comments box for why you think it is important to add.
- Add Mode of Inheritance, Publications and Phenotypes as outlined above, and where applicable, select 'loss-of-function variants in this gene do not cause the phenotype' (Mode of pathogenicity).
- If penetrance is not complete, please denote using the drop down menu and provide a comment.
- Provide a rating and comments as to why the gene was added to the list.
- Click 'Add gene'.

If you have a number of genes that you wish to add to a panel, please contact us at panelapp@genomicsengland.co.uk, and a Curator can assist in uploading the genes to a panel.

4.9 Adding a STR or CNV to a Panel

There is a set of minimal information that is required when adding in an STR or CNV to PanelApp, including genomic co-ordinates and chromosome information, in addition to PanelApp naming conventions for these entities. Therefore, please contact the PanelApp curation team if you have an STR or CNV that you would like to add to the panel, at: panelapp@genomicsengland.co.uk.

4.10 Additional Notes for Reviewers

- Your evaluation and comments will be tagged with your name and affiliation, and are public. In addition, 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 or genomic entity, and edit or delete them individually.
- Changes to the rating, mode of inheritance, mode of pathogenicity and current diagnostic practise using the gene evaluation tool will overwrite your initial evaluation.
- Publications and phenotypes will be saved in the evaluation tool and can be added to; please note that if you delete what has been saved in these boxes, your original submissions of publications and phenotypes will be overwritten.
- When you have reviewed a gene or genomic entity, 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 'Reviews' column on the main panel page.

If a curated set of known-pathogenic variants is available for this gene-phenotype, please contact us at panelapp@genomicsengland.co.uk.

4.11 View or Edit your Evaluations

From the PanelApp homepage, click on your username button in the top right hand corner to view your user information and a list of your evaluations. Click on the gene or genomic entity name to make changes to your evaluation, or click on the panel name to view the entire gene panel.

5 Contact information

For enquiries related to PanelApp, to give feedback or suggestions or to submit gene lists, please email: panelapp@genomicsengland.co.uk.

For enquiries regarding the 100,000 Genomes Project please contact the Service - details of how are provided here: https://www.genomicsengland.co.uk/contact-us/

To cite PanelApp, please use: Genomics England PanelApp; https://panelapp.genomicsengland.co.uk (date accessed), and provide the name and version of the gene panel(s) used when applicable. Please also let us know by emailing panelapp@genomicsengland.co.uk.

We are interested in how the community is utilising PanelApp - please let us know by emailing panelapp@genomicsengland.co.uk.

6 Frequently Asked Questions

6.1 Why gene panels?

The finalised 'Green' genes on a Version 1+ gene panel will be used in the tiering of variants in order to aid clinical interpretation of the genomes sequenced as part of the 100,000 Genomes Project. As the virtual gene panels are publically accessible, they are also available for the scientific and clinical community.

6.2 Why are you asking experts to review the gene panels?

The aim is to utilise expertise and knowledge from the scientific community to establish consensus gene panels (a defined Green list) for each rare disease category.

6.3 As an expert reviewer, how do I rate the genes?

Genes included in a Genomics England gene panel for a rare disease category (Green list) should fit the criteria outlined in the gene panel guidelines (see Appendix B). For step-by-step instructions on rating genes, see Section 4.

6.4 Review Scenarios

For the congenital hearing impairment (profound/severe) panel:

a. A gene is proven to cause syndromic hearing loss but has not to date been proven to manifest with non-syndromic hearing loss. The level 3 title for the panel is 'Non-syndromic hearing loss' Should it be included in the panel?

> Yes; we feel that these genes should be included because a variant in this gene is likely to be relevant to this individual (for example highlighting additional medical features that should be looked for) and should therefore be reported in the genome interpretation.

b. A gene is proven to cause hearing loss, but not congenital profound/severe hearing loss. Should it be included in the panel?

> Yes, we feel that these genes should be included because a variant in this gene is likely to be relevant to this individual (even if only partially explaining the phenotype) and should therefore be reported in the genome interpretation.

6.5 Who will be able to access the gene panels?

Anyone can view, download or query the gene panels. In addition, registered reviewers can evaluate genes on the gene panels and provide comments.

6.6 Will the gene panels change?

Gene panels may change over time as knowledge accumulates and Curators become aware of new evidence. This includes:

- The addition of new genes and genomic entities.
- Rating changes to existing genes or addition of gene information.
- Panels may also be merged or split as appropriate, and Super panels may be created made up of two or more child panels.

Each change to a panel increases the minor version (E.g. Version 1.0 to Version 1.1). Previous versions of a gene panel can be downloaded using the tool available at the bottom of a gene panel page or by querying the PanelApp API (see Section 3.15).

The PanelApp '**Activity**' tab (displayed from the PanelApp home page) displays the last 3000 key changes to all panels. This can be filtered using the filter icon (funnel) to select the panel or date you would like to view. Filter this further by typing in the 'Filter activities' box. The 'History' tab for each gene on a gene panel records changes to gene information, and the 'Panel Activity' tool button, at the bottom of the panel description box, displays all changes for that panelGene reviews are also added with a date-stamp for tracking.

Gene panels <Version 1 are viewable and can be reviewed. Once expert reviews have been collected and evaluated internally by Genomics England Curators, Version 1 of the gene panels are released. Version 2 panels will be launched when significant changes have been made to Version 1 panels.

6.7 What is recorded when I make my reviewer evaluation?

When you are logged in as a reviewer, any information you enter using the gene evaluation or new gene tool will be recorded. Your reviewer name (made up of your first name, last name and affiliation used when you registered to be a reviewer) will be attached to ratings and evaluations. To encourage openness, all gene evaluations and comments you make as a reviewer will be open to anyone to see (the public and other reviewers). The date, time and version of the panel when these actions were carried out is also recorded.

6.8 Am I able to change my reviewer evaluations?

As a reviewer, you can log in to PanelApp using your log in details, and view and/or edit your evaluations at any time. To make changes to your evaluations, see Section 4.11.

6.9 Who will be assessing the evaluations?

The evaluations will be viewed by Genomics England Curators using internally established rules, and consultation with Genomics England clinicians.

6.10 How will reviews be assessed/conflicting reviews resolved?

A set of rules has been established to define different scenarios in order to have a pragmatic review evaluation process. The Validation & Feedback GeCIP (Genomics England Clinical Interpretation Partners) Domain was involved in establishing this process. Comments regarding changes to a gene rating are viewable in PanelApp for transparency via the '**Reviews**' tab.

6.11 Can I send the link to others so that they can review/download panels?

Please distribute the PanelApp URL or gene panel URLs to those within the Scientific Community; anyone can view and download the gene panels. We also encourage those with expertise to register as reviewers. We are interested in how the community is utilising PanelApp - please let us know by emailing panelapp@genomicsengland.co.uk.

Please note; if someone else logs in with your review log in details, any evaluations made will over-ride yours, and comments will not be distinguished as being from more than one user. You are therefore responsible for any changes and comments made under your reviewer name.

6.12 When I register to be a reviewer, where are my details kept and who has access?

Information added during the registration process is stored internally and only utilised for uses related to PanelApp and will not be passed to third parties. Your first name, last name, affiliation, Workplace and Group will be visible to the public. Your role may be used to display the demographics of PanelApp reviewers.

You can view your account information by clicking on the "Logged in as: …" button in the top right hand corner of the screen. Please contact panelapp@genomicsengland.co.uk to make any changes to your user information.

6.13 Where can I keep up to date with major changes or news regarding PanelApp?

- Follow @PanelAppTeam or @GenomicsEngland #PanelApp on Twitter.
- Select the 'Activity' page from the top menu for the latest key updates to panels.
- Go to the PanelApp home page, https://panelapp.genomicsengland.co.uk and click the **News** tab.
- News items may also be displayed on the Genomics England website – for more information see https://www.genomicsengland.co.uk/about-genomics-england/panelapp/.

6.14 Can I submit my own gene panels?

We welcome submission of panels of genes from experts for the rare diseases covered in the 100,000 Genomes Project. Please submit gene panels by sending an email to panelapp@genomicsengland.co.uk.

7 Key Changes in PanelApp 2.3.0

7.1 New and Improved Functionality in PanelApp 2.3.0

- When registering as a reviewer, further checks are performed: namely an email is sent to verify your email address.
- Each panel now has a **Panel Type**, which appears on the panel page. This helps distinguish which project the gene panel is utilised for (Section 2.2).
- Support for short tandem repeats (STRs) has been added to PanelApp.
- Support for copy number variants (CNVs) has been added to PanelApp.
- PanelApp can now support Super panels. This allows Genomics England Curators to create a parent panel made up of a group of child panels. Any information updated on a child panel will also be updated on the Super panel.
- Improved recording and searching of changes to panels
    - Clicking on the new '**Panel Activity**' button found under the panel description box shows the latest activity on this panel. This can be further filtered e.g. by gene or genomic region, person or activity type by typing in the filter box.
    - The 'Activity' page, which logs changes to all PanelApp panel can now be filtered to select the panel or date you wish to view. This can be filtered further by typing the activity type, gene or person (Curator or Reviewer) in the filter box.
- A new PanelApp API (Swagger) is available at: https://panelapp.genomicsengland.co.uk/api/docs/

8 Appendices

Appendix A: Gene Panel Curation Protocol

Creation of an Initial Gene Panel for a Rare Disease

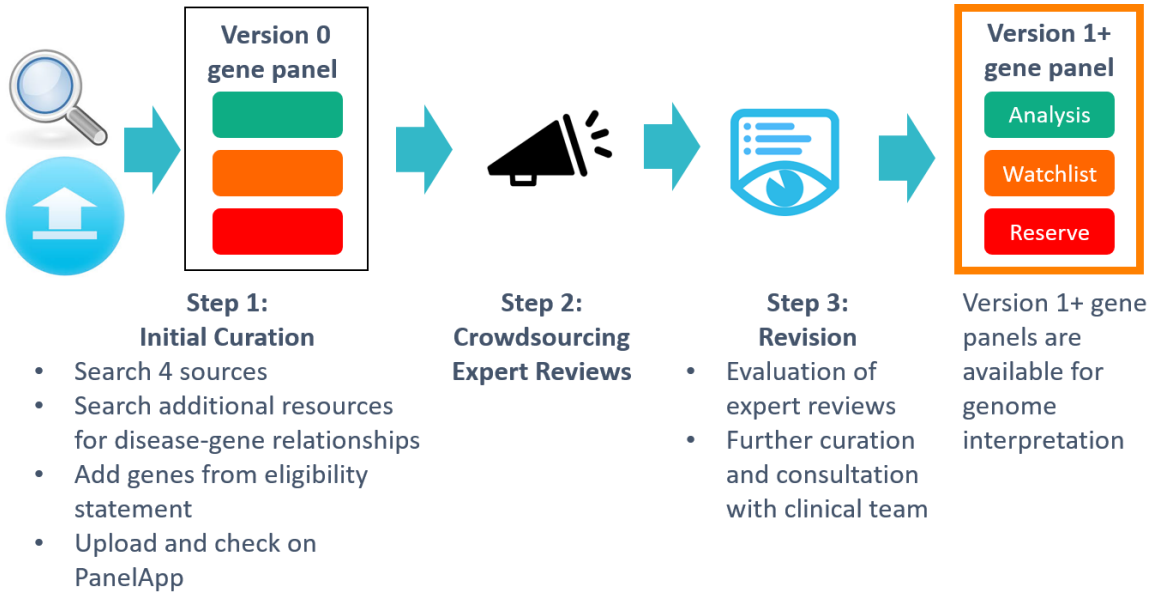

Figure 9. The curation process from initial establishment of a Version 0 gene panel for the Rare Disease programme of the 100,000 Genomes Project, expert review and subsequent revision to form a Version 1 panel.

For each approved rare disease category within the 100,000 Genomes Project, an initial virtual gene panel is created by a Genomics England Scientific Curator. Each of the following four sources is manually searched for key relevant phenotypic words (e.g. disease category and/or key phenotypes mentioned in the eligibility statement or additional sources summarising the disorder): Radboud University Medical Center, Illumina TruGenome Predisposition Screen, Emory Genetics Laboratory and UKGTN. Genes identified in this way are added to the panel. In addition, genes are added to the panel from gene lists provided by experts in particular disease areas, and genes mentioned in eligibility criteria for disease recruitment for the

100,000 Genomes Project. Curation of scientific publications and other key sources may also be performed to contribute to the gene panel (Table 2).

Source displayed in PanelApp	Source Name and URL	Details
Illumina TruGenome Clinical Sequencing Services	Illumina TruGenome Predisposition Screen: www.illumina.com/clinical/illumina_clinical_laboratory/trugenome-clinical-sequencing-services.html#tps	4 sources used in the initial establishment of gene lists. Genes are given an initial ranking (Green, Amber, Red) depending on how many of these four sources the gene appears on
Emory Genetics Laboratory	www.egl-eurofins.com	
UKGTN	United Kingdom Genetic Testing Network: https://ukgtn.nhs.uk/	
Radboud University Medical Center, Nijmegen	https://order.radboudumc.nl/en/genetics/lab-information/exome-panels	
Expert List	n/a	Gene lists submitted from an expert in the disease area
Eligibility statement prior genetic testing	http://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/rare-disease-eligibility-criteria/	Prior genetic testing required/advised on the Genomics England Eligibility Statement for each disorder
Eligibility statement exclusion criteria	http://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/rare-disease-eligibility-criteria/	The gene was included in the exclusion criteria within the eligibility statement
Literature	PubMed: www.ncbi.nlm.nih.gov/pubmed	Genes are sourced from peer-reviewed published articles
Other	OMIM (Online Mendelian Inheritance in Man): https://omim.org/	Used for some phenotype, gene, or mode of inheritance information. Links to OMIM gene pages are provided in PanelApp
Other	Orphanet: www.orpha.net/consor/cgi-bin/index.php	Used for some phenotype, gene, or mode of inheritance information
Other	Gene2Phenotype: www.ebi.ac.uk/gene2phenotype	Used for some phenotype, gene, or mode of inheritance information. Links to Gene2Phenotype gene pages are provided in PanelApp
Other	NIH Genetics Home Reference: https://ghr.nlm.nih.gov/	Used for some phenotype, gene, or mode of inheritance information
Other	ClinVar: www.ncbi.nlm.nih.gov/clinvar	Links to ClinVar are provided in PanelApp to aid evaluation of the evidence for an association between the gene and phenotype
ClinGen	ClinGen Home & Gene Validity Classification	ClinGen gene panels can be used to revise and re-evaluate PanelApp gene panels. CNVs on panels also originate from the curated ClinGen Dosage Sensitivity Map

Other	HGNC, HUGO Gene Nomenclature Committee: www.genenames.org	Used to check gene names in order to establish the correct HGNC-approved symbol
Expert Review Green/Amber/Red	n/a	Indicates the rating assigned by a reviewer
BRIDGE study Tier 1 gene	n/a	BRIDGE consortium Tier 1 genes from NIHR BioResource – Rare Diseases Study (NIHRBR-RD)
Victorian Clinical Genetics Services	https://www.vcgs.org.au/	Clinical Genetic Service in Victoria, Australia. Used to revise and re-evaluate PanelApp gene panels.

Table 2. Key sources used in gene panel curation. There may be additional Sources from individual groups (e.g. EUROPAC on the Pancreatitis panel).

For the creation of other gene panels, for example for pertinent germline genes for the cancer programme within the 100,000 Genomes Project, genes are identified from a variety of sources, which will be indicated within the 'Source' section in PanelApp and publications for each gene.

Genes are uploaded to the PanelApp website to create an initial 'version 0' gene panel. Each gene in a version 0 panel will automatically be given an initial level of confidence, based on the number of the 4 sources (Radboud, Illumina, Emory, and UKGTN) that the gene was mentioned in, as indicated by the traffic light system:

- **Green** = highest level of confidence; a gene from 3 or 4 sources.
- **Amber** = intermediate; a gene from 2 sources.
- **Red** = lowest level of confidence; 1 of the 4 sources or from other sources.

Crowdsourcing Expert Review

Once a panel has been created (Version 0+), review of the evidence and clinical utility for each gene is sought from the international clinical and scientific community from those with

relevant expertise. Once registered as a reviewer, experts can utilise the reviewer tool within PanelApp to provide their rating of a gene (see Section 4).

Revision of the Gene Panel to Establish a List of High-Level Evidence Genes for Genome Interpretation

Based on the expert reviews and additional evidence from other sources (Table 2), Genomics England Curators with clinical input evaluate the gene panel, based on criteria outlined in Appendix B, so that the genes and their ratings reflect a community consensus.

Once completed, the revised panel is promoted to the next major version – i.e. Version 1. The list of Green (high confidence) genes on this revised panel have a high level of evidence (diagnostic-grade) for implication in disease causation, and are used within the 100,000 Genomes Project Bioinformatics pipeline for prioritisation of genetic variants. The Amber (moderate level of evidence) and Red (low level of evidence) genes on each panel will be maintained as lists of genes that are not currently be used in clinical reporting. These genes may be of interest for research purposes, and may be promoted to Green if more evidence for the gene-disease association arises. Gene panels (Version 0 and Version 1+) on PanelApp are dynamic, so genes can be added to the panel by Reviewers or Curators, and gene ratings may be changed by Curators as new evidence arises. These genes may be utilised to prioritise tier 3 variants. Substantial revisions of the panel result in the panel increasing to the next major version (e.g. a Version 1 panel will be promoted to version 2).

Appendix B: 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) 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.*

References:

[a] https://www.clinicalgenome.org/site/assets/files/5967/gene-validity_classification.pdf and **Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework developed by the Clinical Genome Resource**, PMID:28552198.

[b] https://decipher.sanger.ac.uk/ddd#ddgenes and **Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data.** PMID: 25529582.

Appendix C: Genomics England Gene Panel Principles for Rare Diseases in the 100,000 Genomes Project

- A conservative list of Green genes, STRs and CNVs of known clinical utility and scientific validity is required.
- The Green list on a panel should be a conservative (diagnostic grade) set of genes and genomic entities that out of the whole genome should be examined first, as variants within the genes are most likely to cause/explain the disease phenotype. We acknowledge that the panel will therefore be missing genes that have been reported in association with the disease/phenotype but where the level of proof has not reached that required for them to enter use in a diagnostic setting. Variants that have passed the standard filtering criteria but are not within the gene panel for the relevant disease category will be assigned to a separate tier (Tier 3).
- Genes included on a panel may have been screened in a patient previously (for example, may be included within prior-genetic testing before recruitment to the 100,000 Genomes Project); however, variants of interest in genes not well covered by exome sequencing or missed by other methods may be detected by whole genome sequencing and should be included.
- A single gene or genomic entity may appear in multiple gene panels.
- Genes may also be associated with additional phenotypes not indicated in the gene panel.
- The gene panels will be updated as we learn from new published evidence, clinical information, and the 100,000 Genomes Project participant data.

Appendix D: Example PanelApp API queries, and terms available for Mode of Inheritance queries

Query Description	Query Example
Get a list of the panel names	https://panelapp.genomicsengland.co.uk/WebServices/list_panels/ https://panelapp.genomicsengland.co.uk/api/v1/panels/
Get a list of panels in the Rare Disease programme of the 100K Genomes Project	https://panelapp.genomicsengland.co.uk/api/v1/panels/?type=rare-disease-100k
Get information about individual panels using the panel name (last version of the panel by default)	https://panelapp.genomicsengland.co.uk/WebServices/list_panels/?Name=Hereditary%20ataxia https://panelapp.genomicsengland.co.uk/api/v1/panels/Hereditary%20ataxia/
Get individual panels using the panel identifier (last version of the panel by default)	https://panelapp.genomicsengland.co.uk/WebServices/get_panel/559a7d1022c1fc58ad67fc97 https://panelapp.genomicsengland.co.uk/api/v1/panels/20
Select a specific version of a panel (version=X.X)	https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Hereditary%20ataxia/?version=1.0 https://panelapp.genomicsengland.co.uk/api/v1/panels/Hereditary%20ataxia/?version=1.0
Get a list of all CNVs (Regions)	https://panelapp.genomicsengland.co.uk/api/v1/regions
Get a list of all STRs	https://panelapp.genomicsengland.co.uk/api/v1/strs/
Filter Green entities on a panel by level of confidence	https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Hereditary%20ataxia/?LevelOfConfidence=HighEvidence
Filter Green and Red genes by level of confidence	https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Hereditary%20ataxia/?LevelOfConfidence=HighEvidence,LowEvidence
Filter the genes by biallelic mode of inheritance	https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Hereditary%20ataxia/?LevelOfConfidence=HighEvidence,LowEvidence&modesOfInheritance=biallelic
Search for panels by gene	https://panelapp.genomicsengland.co.uk/api/v1/genes/BTK https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/

Search for a gene in one panel	https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?panel_name=Intellectual%20disability&format=json
Search by a gene, and pull out information only when it is rated Green	https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?&LevelOfConfidence=HighEvidence&format=json
Search by gene from a particular source (e.g. UKGTN)	https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?&Evidences=UKGTN&format=json
Search for all genes in a panel	https://panelapp.genomicsengland.co.uk/WebServices/search_genes/all/?panel_name=Intellectual%20disability&format=json
Specify the genome build with either GRch37 (default) or GRch38 as a value. Ensembl IDs will be returned for the specified assembly version: GRch37 version 82 or GRch38 version 90 if they exist in the database.	https://panelapp.genomicsengland.co.uk/WebServices/search_genes/AKT2/?panel_name=Regional%20overgrowth%20disorders&assembly=GRch38
Get a list of recent panel activity (displays the last 3000 activities)	https://panelapp.genomicsengland.co.uk/api/v1/activities/

Queries for genes and panels can be made using the existing WebServices or the new API. Queries for STRs, CNVs and panel activity should be made using the new API. Queries involving filtering should be made using the existing WebServices.

Available Filters

PanelApp Mode of Inheritance	WebServices Query
MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	"monoallelic_not_imprinted"
MONOALLELIC, autosomal or pseudoautosomal, maternally imprinted (paternal allele expressed)	"monoallelic_maternally_imprinted"
MONOALLELIC, autosomal or pseudoautosomal, paternally imprinted (maternal allele expressed)	"monoallelic_paternally_imprinted"
MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown	"monoallelic"
BIALLELIC, autosomal or pseudoautosomal	"biallelic"
BOTH monoallelic and biallelic, autosomal or pseudoautosomal	"monoallelic_and_biallelic"
BOTH monoallelic and biallelic (but BIALLELIC mutations cause a more SEVERE disease form), autosomal or pseudoautosomal	"monoallelic_and_more_severe_biallelic"

X-LINKED: hemizygous mutation in males, biallelic mutations in females	"xlinked_biallelic"
X-LINKED: hemizygous mutation in males, monoallelic mutations in females may cause disease (may be less severe, later onset than males)	"xlinked_monoallelic"
MITOCHONDRIAL	"mitochondrial"
Unknown	"unknown"

ModeOfPathogenicity : comma separated list of modes of pathogenicities, one of the following values:

- loss_of_function
- other

Penetrance : comma separated list of penetrance values, one of the following:

- unknown
- Complete
- Incomplete

LevelOfConfidence : comma separated list of confidence levels, one of the following:

- HighEvidence (green)
- ModerateEvidence (amber)
- LowEvidence (red)

Evidences: comma separated list of evidences, one of the following:

- radboud_university_medical_center_nijmegen
- illumina_trugenome_clinical_sequencing_services
- emory_genetics_laboratory
- ukgtn
- other
- export_list
- export_review
- literature
- eligibility_statement_prior_genetic_testing
- research

Appendix E: Glossary

Eligibility statement

Eligibility statements for each of the rare diseases and cancers have been written and can be found on the Genomics England website (https://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/, https://www.genomicsengland.co.uk/information-for-gmc-staff/cancer-programme/eligibility/). The aim of the eligibility statements is to provide guidance to clinicians regarding the patients most likely to benefit from the opportunity of diagnostic whole genome sequencing and who are therefore eligible for recruitment into the Genomics England Rare Diseases and Cancer Programme. Each eligibility statement has been informed by at least one clinician specialising in the field and represents a significant effort on the part of the community.

Each eligibility statement is composed of the following key information:

1. The sub-category (Level 3) and disease (Level 4) titles.

2. Inclusion criteria – the clinical features, characteristics or investigations that probands with a given disease must have in order to be eligible for recruitment.

3. Exclusion criteria - the clinical features, characteristics or investigation findings that participants with a given disease must not have in order to be eligible for recruitment.

4. Prior genetic testing – this sets out both in general terms, and where appropriate more specifically, the genetic testing which participants with a given disease must have performed prior to recruitment.

The relevant eligibility statement is provided in the gene panel *description* box for each rare disease and Cancer programmes where available. For some gene panels, no eligibility statement is available at the current time. These include disorders within the Pilot study that

were not taken to the main phase of the programme, or panels encompassing a broader set of diseases.

Level 4 panel title, Level 3 title, Level 2 title

These terms refer to the rare disorder categories and titles e.g. Arrhythmogenic Right Ventricular Cardiomyopathy (level 4 title) is a disease under the Cardiomyopathy sub-category (level 3 title), within Cardiovascular disorders (level 2 title).

Entity

A gene, short tandem repeat (STR) or region (CNV) on a gene panel.

STR

Short Tandem Repeat. These have 'Entity type: str' in PanelApp.

CNV

Copy Number Variant. These have 'Entity type: region' in PanelApp.

Gene symbol

The HGNC-approved symbol for the gene.

Gene description

The HGNC-approved name for the gene.

GEL Status

The current gene rating:

- 3 or 4 = Green = highest level of confidence
- 2 = Amber = intermediate level of confidence
- 1 or 0 = Red = lowest level of confidence

The 4 sources used in the initial establishment and ratings of genes are listed in Appendix A:

Mode of inheritance

Standardised terms were used to represent the gene-disease mode of inheritance, and were mapped to commonly used terms from the different sources. Below each of the terms is described, along with the equivalent commonly-used terms.

MONOALLELIC, autosomal or pseudoautosomal, not imprinted: A variant on one allele of this gene can cause the disease, and imprinting has not been implicated.

MONOALLELIC, autosomal or pseudoautosomal, maternally imprinted (paternal allele expressed): A variant on the paternally-inherited allele of this gene can cause the disease, if the alternate allele is imprinted (function muted).

MONOALLELIC, autosomal or pseudoautosomal, paternally imprinted (maternal allele expressed): A variant on the maternally-inherited allele of this gene can cause the disease, if the alternate allele is imprinted (function muted).

MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown: A variant on one allele of this gene can cause the disease. This is the default used for autosomal dominant mode of inheritance where no knowledge of the imprinting status of the gene required to cause the disease is known. Mapped to the following commonly used terms from different sources: autosomal dominant, dominant, AD, DOMINANT.

BIALLELIC, autosomal or pseudoautosomal: A variant on both alleles of this gene is required to cause the disease. Mapped to the following commonly used terms from different sources: autosomal recessive, recessive, AR, RECESSIVE.

BOTH monoallelic and biallelic, autosomal or pseudoautosomal: The disease can be caused by a variant on one or both alleles of this gene. Mapped to the following commonly used

terms from different sources: autosomal recessive or autosomal dominant, recessive or dominant, AR/AD, AD/AR, DOMINANT/RECESSIVE, RECESSIVE/DOMINANT.

BOTH monoallelic and biallelic (but BIALLELIC mutations cause a more SEVERE disease form), autosomal or pseudoautosomal: A variant on one allele of this gene can cause the disease, however a variant on both alleles of this gene can result in a more severe form of the disease/phenotype.

X-LINKED: hemizygous mutation in males, biallelic mutations in females: A variant in this gene can cause the disease in males as they have one X-chromosome allele, whereas a variant on both X-chromosome alleles is required to cause the disease in females. Mapped to the following commonly used term from different sources: X-linked recessive.

X linked: hemizygous mutation in males, monoallelic mutations in females may cause disease (may be less severe, later onset than males): A variant in this gene can cause the disease in males as they have one X-chromosome allele. A variant on one allele of this gene may also cause the disease in females, though the disease/phenotype may be less severe and may have a later-onset than is seen in males. X-linked inactivation and mosaicism in different tissues complicate whether a female presents with the disease, and can change over their lifetime. This term is the default setting used for X-linked genes, where it is not known definitively whether females require a variant on each allele of this gene in order to be affected. Mapped to the following commonly used terms from different sources: X-linked dominant, x-linked, X-LINKED, X-linked.

MITOCHONDRIAL: The gene is in the mitochondrial genome and variants within this can cause this disease, maternally inherited. Mapped to the following commonly used term from different sources: Mitochondrial.

Unknown: Mapped to the following commonly used terms from different sources: Unknown, NA, information not provided.

Other - please specify in evaluation comments: For example, if the mode of inheritance is digenic, please indicate this in the comments and which other gene is involved.

Sources

The source of the gene-phenotype information is provided. The sources are summarised in Appendix A.

Phenotypes

Phenotypes collected from the sources are provided where possible and include phenotypes and disease names together with the MIM identifier.

OMIM

A link to the gene page on OMIM is provided to give reviewers quick access to gene-disease information.

ClinVar Variants

A link to the gene page on ClinVar is provided for quick access to information regarding variants within the gene that are associated with different conditions.

Penetrance

This is set as a default to "complete". Reviewers can provide information regarding the penetrance during their gene evaluations (Section 4.4).

Publications

Publications that provide evidence linking this gene to this disorder, or provide evidence disputing a role for a gene in a disease.

Mode of pathogenicity

For each gene in a gene panel in PanelApp, it is assumed that loss-of-function variants (see Appendix E) in this gene can cause the disease/phenotype unless an exception to this rule is known. In PanelApp, we are collecting information regarding exceptions to this rule.

Sequence Ontology (SO) Terms and Descriptions

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

SO ID	Name	Definition
SO:0001893	transcript_ablation	A feature ablation whereby the deleted region includes a transcript feature.
SO:0001574	splice_acceptor_variant	A splice variant that changes the 2 base region at the 3' end of an intron.
SO:0001575	splice_donor_variant	A splice variant that changes the 2 base region at the 5' end of an intron.
SO:0001587	stop_gained	A sequence variant whereby at least one base of a codon is changed, resulting in a premature stop codon, leading to a shortened transcript.
SO:0001589	frameshift_variant	A sequence variant which causes a disruption of the translational reading frame, because the number of nucleotides inserted or deleted is not a multiple of three.
SO:0001578	stop_lost	A sequence variant where at least one base of the terminator codon (stop) is changed, resulting in an elongated transcript.
SO:0001582	initiator_codon_variant	A codon variant that changes at least one base of the first codon of a transcript.

Gene History/Genomic Entity History

A record of when the gene or genomic entity was added to the panel in PanelApp and additional key changes to gene information.

Tags

Attached to a gene or genomic entity within a gene panel by a Curator. Tags highlight useful information about a gene or gene variants that may affect gene ratings, or may be useful for future curation.

The tag is specific to a gene within a given disorder. The descriptions of key tags are:

PanelApp Tag	Tag description
anticipation	Where the age of manifestation reduces and the severity of symptoms of a genetic condition increases from one generation to the next.
nucleotide-repeat-expansion	For this phenotype, nucleotide-repeat-expansions can cause the disorder.
early-onset	This relevant phenotype shows early onset.
adult-onset	This relevant phenotype shows only adult onset.
CNV	There are pathogenic copy number variants reported for this gene.
deletions	There are pathogenic deletion variants reported for this gene
dominant-negative	Gene2Phenotype lists dominant negative as the mutation consequence.
founder-effect	There is only a single variant that has been reported to have a founder effect in a particular population, or a shared haplotype has been observed. Genes with a founder-effect tag are rated Red as there is not currently enough evidence that other variants in the gene are disease causing
gene-duplication	There are pathogenic gene duplication variants reported for this gene.
missense	Only missense variants have been reported for this gene for this phenotype/disorder.
monogenic-polygenic:	Both monogenic associations and polygenic associations have been reported for this gene.
polygenic	Only associations in combination with other variants in other genes have been reported. Genes with a 'polygenic' tag are rated Red as monogenic variants are reported for the 100,000 Genomes interpretation pipeline
multifactorial	The genetic association is in combination with environmental/other factors. Note that these genes are not Green genes.
new-gene-name	The HGNC gene symbol has been updated compared to the gene symbol on PanelApp. These symbols will be updated in-line with Ensembl.
non-coding-known-pathogenic	There are non-coding pathogenic variants reported for this gene

treatable	There is a treatment that targets variants in this gene, or there are treatment options for this disorder based on a diagnosis from variants in this gene, or supplementation may prevent or alleviate symptoms.
mosaicism	Mosaicism has been reported
x-linked over dominance	Gene2Phenotype records dominant negative as the mutation consequence
promoter	Pathogenic variants have been reported in the gene promoter, or variations to promoter length have been associated with the phenotype.
regulatory region	Pathogenic variants have been reported in the gene regulatory region known to influence expression of the corresponding gene.
structural-variant	Pathogenic structural rearrangements have been reported
sva	Pathogenic short interspersed nuclear element, variable number of tandem repeats, and Alu composite have been reported
pathogenic-synonymous	For genes with synonymous variants with proven pathogenicity
pharmacogenetics	Genes in which variants can affect drug response e.g. variants in CYP2C8 are associated with cerivastatin-induced rhabdomyolysis.
y-chromosome	Gene is encoded by the Y-chromosome.

Table 3. Description of tags attached to a gene within PanelApp.

Retired panel

A panel previously used for genome analysis but are no longer live in PanelApp, An example is the panel for Bilateral microtia, which is retired on PanelApp because it has now been merged into the 'Deafness and congenital structural abnormalities' panel. Refer to the PanelApp API for retrieval of these panels.

ClinVar variants

A link to the gene page on ClinVar is provided for quick access to information regarding variants within the gene that are associated with different conditions.

Current diagnostic

A checkbox for reviewers available in the Evaluate Gene tool to indicate whether or not they report variants in the gene as part of current diagnostic practice. If you are submitting an evaluation on behalf of a clinical laboratory and you report variants within the gene as part of your current diagnostic practice, please check the box.

Appendix F: Uses of PanelApp

I am a Clinician or other Healthcare Professional…

You could use PanelApp to:

- View and interpret a panel that has been applied to your patient (Section 3)
- Look at the evidence for inclusion of a gene(s) or genomic entity in your patient report during a MDT (Sections 3.4 and 3.5)
- Review gene(s), STRs or CNVson panel(s) for disease(s) matching your expertise (Section 4.3)
- Add diagnostic genes, STRs or CNVs missing from a panel (Section 4.7)
- Add your publications as evidence for gene-disease relationships (Section 4.4)
- Suggest additional panels to be added that would be useful for research or the clinical community
  (contact panelapp@genomicsengland.co.uk)
- Provide input on whether gene panels should be combined/merged
  (contact panelapp@genomicsengland.co.uk)

I am a Researcher…

You could use PanelApp to:

- Source data for hypothesis generation.
- Study gene-disease relationships for genome interpretation, pathway analysis and more.
- Use 'tagged' genes, STRs or CNVs to investigate genes and genomic entities with interesting disease-causing mechanisms (Appendix E).
- Use Red and Amber genes as a source of genes needing further evidence/investigation within your disease of interest for certain diseases (Section 2.5).
- Review genes and/or panels you have expertise in to help genome interpretation (Section 4.3).

- Add novel genes, STRs and CNVs to panels that you find within your research (Section 4.7)
- Add your publications as evidence for gene-disease relationships (Section 4.4)
- Suggest additional panels to be added that would be useful for research or the clinical community (contact panelapp@genomicsengland.co.uk)
- Provide input on whether gene panels should be combined/merged (contact panelapp@genomicsengland.co.uk)
- Query PanelApp data through WebServices (Section 3.15, and Appendix D).

I am a Bioinformatician…

You could use PanelApp to:

- Use panels for your exome/genome interpretation pipeline
- Query PanelApp data through WebServices (Section 3.15, and Appendix D).

9 Disclaimer

PanelApp Uses Exclusions of Liability

PanelApp gene lists are provided by Genomics England in good faith, and for the benefit of the research community. The original gene lists have been supplied through commercial and academic providers, but have not been separately verified by Genomics England. Equally, expert Reviewers and Curators adding content and comments through PanelApp do so under their own responsibility and without verification by Genomics England. Users must themselves verify the accuracy and content any information (including in respect of ownership of any intellectual property rights) obtained through PanelApp in advance of its use for any purpose. Genomics England, any expert Reviewers and Curators hereby exclude any and all liability, including without limitation under any laws of contract, tort (including negligence) or statutory duty or otherwise, and do not accept any liability or responsibility for uses made of the PanelApp gene lists or comments by individual reviewers.

PanelApp Connections Exclusions of Liability

Access to the PanelApp is not guaranteed. Genomics England accepts no liability and excludes all liability in respect of interruptions in accessing or inability to access the PanelApp gene lists at any time. Persons accessing PanelApp are responsible keep their anti-virus and security software up to date. Genomics England consequently accepts no liability for any loss or damage occurring as a result of any person using or connecting to or through PanelApp.

General Exclusion of Liability and Limitations on exclusions of Liability

Genomics England shall not be responsible for any of the following losses to persons using or accessing PanelApp, howsoever incurred, whether in contract, tort (including negligence), breach of statutory duty or otherwise: indirect losses, consequential losses, loss of income or revenue, loss of profit, third party claims, loss of business, loss of data, loss of anticipated savings, or any loss of opportunity.

No provision of this disclaimer shall operate to limit or exclude liabilities which cannot by the applicable laws of England be so limited or excluded.

10 Acknowledgements

PanelApp creator: Antonio Rueda-Martin

PanelApp Curators (past and present): Ellen McDonagh, Sarah Leigh, Rebecca Foulger, Louise Daugherty, Eleanor Williams, Olivia Niblock, Alice Gardham, Arianna Tucci, Helen Brittain, Anna de Burca, Rachel Jones, Eik Haraldsdóttir, Ellen Thomas, Richard Scott, Caroline Wright, Emma Baple, Damian Smedley, Chris Boustred, Kirsty McCaffrey, Chris Campbell, Maria Athanasopoulou.

Software Developers: Paul Hayes, Oleg Gerasimenko

Other contributors to PanelApp and PanelApp documentation: Augusto Rendon, Katherine Smith, Clare Turnbull, Jo Whittaker, Mina Ryten, Tom Fowler and members of the V&F GeCIP Domain, Kristina Ibanez-Garikano, Dalia Kasperaviciute, Corey Johnson, Lisa Carr, Lisa Dinh, Maria Asthanasopoulou and Alona Sosinsky.

Acknowledgment of reviewer names and affiliations can be viewed for each individual gene panel on PanelApp.

Thank you to all experts who have contributed gene lists during the development of rare disease eligibility statements and data models, or by submitting their own gene panels. These have been added to the gene panels on PanelApp where possible. Also thank you to all our reviewers and for all feedback that has aided the development of the PanelApp tool.

11 Document History

The controlled copy of this document is maintained in the Genomics England internal document management system. Any copies of this document held outside of that system, in whatever format (for example, paper, email attachment), are considered to have passed out of control and should be checked for currency and validity. This document is uncontrolled when printed.

This document has not yet received final approval from Genomics England internal governance processes or NHS England and is therefore potentially subject to change.

5.1 Version History

Version	Date	Description
3.0	21/08/2015	Incorporation of feedback from Eik Haraldsdóttir, Richard Scott, Katherine Smith.
3.1	24/08/2015	Formatting and grammatical changes.
3.2	02/09/2015	Formatting and grammatical changes.
3.3	03/09/2015	Formatting and grammatical changes.
3.4	08/09/2015	Formatting and grammatical changes.
3.5	08/09/2015	Formatting and grammatical changes.
4.0	19/01/2016	Update of the Handbook to reflect changes to the PanelApp website and tools, and addition of a disclaimer.
4.1	19/01/2016	Incorporation of feedback from Tom Fowler.
5.0	05/09/2017	Update of the Handbook by Rebecca Foulger, Ellen McDonagh, and Genomics England Curators to reflect current practices.
5.1	02.10.2017	Incorporation of feedback by Richard Scott and Helen Brittain
5.2	11.10.2017	Incorporation of PanelApp2 features and PanelApp2 URLs from Oleg Gerasimenko
5.3	31.10.2017	Formatting to finalise handbook
5.4	06.11.2017	Final check for release.
5.5	07.11.2017	Additional WebService queries added
5.6	10.11.2017	Additional updates with respect to PanelApp2 features, including new screen shot and connecting hyperlinks
5.7	14.11.2017	Correction of email address from panelapp@genomicsengland.ac.uk to panelapp@genomicsengland.co.uk

6.0	04.10.2018	Updates with PanelApp2.3.0 features including new screen shots for capturing STR and CNV information, Panel types, PanelApp activity, and new PanelApp API.
6.1	08.10.2018	Incorporation of general revisions from Sarah Leigh.
6.2	09.10.2018	Incorporation of revisions to Super panels and Panel Type sections from Ellen McDonagh
6.3	09.10.2018	Incorporation of PanelApp API revisions from Oleg Gerasimenko, and Cancer panel updates from Sarah Leigh.
6.4	10.10.2018	Incorporation of revisions from Ellen McDonagh, Arianna Tucci, Dalia Kasperaviciute and Alona Sosinsky.
6.5	10.10.2018	Formatting to finalise handbook.
6.6	11.10.2018	Correcting WebServices links in Appendix D

5.2 Reviewers

This document must be reviewed by the following:

Name	Title	Version
Sarah Leigh, PhD	Scientific Curator	6.3
Ellen McDonagh	Head of Curation	6.6

5.3 Approvers

This document must be approved by the following:

Name	Responsibility	Date	Version
Ellen McDonagh	Head of Curation	11.10.18	6.6

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