





A Reviewers' Guide To PanelApp Australia



PanelApp Release 3.0.2

Reviewers' Guide V1.

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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 diagnosticgrade 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.





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Creating a PanelApp Reviewer Account, and Logging in



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Health Alliance

Genomi

Log in

PanelApp Panels Genes and Entities Activity

PanelApp Australia

A crowdsourcing tool to allow gene panels to be shared, downloaded, viewed and evaluated by the Scientific Community



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.







https://panelapp.agha.umccr.org

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PanelApp (Panels) Genes and Entities	Activity		rebecca_revi	ewer Log out
293 panels Clicking of the Filter	on Panels in the top Toolbar wil • panels box to find your panel o	l list all panels. Typ of interest.	ein	
Panel V		Evaluated genes	Reviewers	Actions
Filter the list by typin	g in key words			3 panel
VACTERL-like phenotypes Level 3: Limb disorders Level 2: Dysmorphic and congenital abnormality Relevant disorders: Version 1.22	 Click on a panel name to: 1) View the panel descriptio 2) View the panel type. 3) View Genes on the panel, ratings. 4) Select a gene on the panel 	n. , and their current	viewers	≵ Download
Limb girdle muscular dystrophy	4) Select a gene on the part		Jieviewers	🛓 Download
Level 3: Neuromuscular disorders Level 2: Neurology and neurodevelopmental dis Version 1.12 Limb disorders	Each panel is versioned. Each change to a panel increas Version 1.11 to Version 1.12. N recent than Version 1.2.	ses the minor versi lote that Version 1	on incremen .12 of a gene	tally (e.g. e panel is mo
Version 1.2				





An overview of information captured on a PanelApp panel



217 Entities

215 reviewed, 114 green

	List 🛧	Entity	Reviews	Mode of inheritance	Details	
	Filter Ent	ities				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	
symbol to see	Green	<u>ARSE</u>	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, 3029 • X-linket recessive chondrodysplasia punctata • CHONDRODYSPLASIA PUNCTATA 1, X-LINKED Tags	50
etails, and provide	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 • Syndactly, mesoaxial synostotic, with phalangeal re • 609432 • Polydactyly Taos	duction,

Click on a gene further gene de a review.







Understanding Gene Ratings in PanelApp







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.

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.

- 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.

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 <u>not</u> used for diagnostic testing.



A. There are plausible disease-causing variants¹ within, affecting or encompassing an interpretable functional region of this gene² identified in multiple (3 or more) unrelated cases/families with the phenotype³.

OR

B. There are plausible disease-causing variants¹ 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 phenotype³.

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 setting⁴.

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.*

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

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

⁴Intermediate penetrance genes should not be included.



Adapted from references: PMID:28552198 and PMID: 25529582



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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





Genes in panel					
↑ Prev	Next	≁			
ARHG	AP31	3			
ARSE		2			
BHLH/	49	3			
BMPR	1B	2			
BRCA	2	0			
BRIP1		0			
DLX5		3			
	6	2			
OVL1		3			
EBP		1			
EOGT		2			
ERCC	4	0			
ESCO	2	0			
FAM58	BA	4			
FANC/	4	0			
FANCE	В	0			
• FANC	C	0			
FANCI	D2	0			
FANCE	E	0			
FANCI	F	0			



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Genes in	panel			
↑ Prev	Next	•	• Gene: ARSE	Genomics
ARHG	AP31	3	3 Green List (high evidence)	england
ARSE		2	2 Health Alliance	
BHLH/	A9	3	³ EnsemblGenelds (GRCh38): ENSG00000157399	
BMPR	R1B	2	² EnsemblGenelds (GRCh37): ENSG00000157399	
BRCA	2	0	0 OMIM: 300180, Gene2Phenotype	
BRIP1	1	0	ARSE is in 6 panels	ise the disease
DLX5		3	³ Reviews (2) Details History phenotype, please select an option i	n the mode of
DOCK	K 6	2	² Review gene pathogenicity dropdown menu.	
DVL1		3	³	
EBP		1	Rating: 0	ction place loove a
EOGT	г	2	² If provide rating exceptions to loss-of-run	ction, please leave a
• ERCC	24	0	Mode of Inheritance: Tree-text comment to explain your set	lection (e.g. detailing
ESCO	02	0	o Provide a mode of inheritance literature or clinical evidence).	
FAM5	8A	4	Mode of pathogenicity:	
FANC	A	0	0	
FANC	в	0	• Mode of pathogenicity: 😯	
FANC	С	0		
FANC	D2	0	Provide exceptions to loss-of-function	¥
FANC	E	0	⁰ Provide exceptions to loss-of-function	
FANC	F	0	⁰ Loss-of-function variants (as defined in pop up message) DO NOT cause this phenotype - please provide details in the	e comments
			Other - please provide details in the comments	

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





Limb disorders Gene: ARSE Green List (high evidence) ARSE (arylsulfatase E (chondrodysplasia punctata 1)) EnsemblGenelds (GRCh38): ENSG00000157399 EnsemblGenelds (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

Publications (PMID: 1234;4321): Publications (PMID: 1234;4321)

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

Phenotypes (separate using a semi-colon - ;)

Current diagnostic:
Current diagnostic



Add any relevant publications.

- Please provide PubMed IDs separated by a semicolon: 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







Adding Genes to a PanelApp Panel

Adding a **gene** to a Panel:



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Red Ready	ZFYVE26	2 reviews Add review 1 red	BIALLELIC, autosomal or pseudoautosomal	 Sources Expert Review Red Phenotypes Autosomal recessive spastic paraplegia 15 (#270700) complex form of the disease including ataxia. Pyle et al. (2015), Brain, 138, pp.276-283. Implicated in undiagnosed ataxia.
Red Ready	<u>ZNF592</u>	2 reviews Add review	BIALLELIC, autosomal or pseudoautosomal	Sources Radboud University Medical Center, Nijmegen UKGTN Expert Review Red Phenotypes Spinocerebellar ataxia, autosomal recessive 5
+ Add a	Gene to this panel + Add	a STR to this panel	 Add a Region to this particular to the particular to	anel
,		lf ca Er	any genes are In add them us Itities list:	missing from a panel, you sing the tool bar below the
+ Add a	a Gene to this pa	anel +	Add a STR to	this panel + Add a Region to this panel





Add gene to panel

Gene symbol:	
Source:	
Mode of pathogenicity: 🕖	
Provide exceptions to loss-of-function	
Mode of inheritance: 😧	
Provide a mode of inheritance	
Penetrance:	
Publications (PMID: 1234;4321):	
Publications (PMID: 1234;4321)	

Tags:

Rating: 🔞

Provide rating

Current diagnostic: 🔞

Current diagnostic

Comments:



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. 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.



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03/04/2025







View Changes to Panels and new reviews



PanelApp	Panels	Genes and Entities	Activit	y Add pa	nel Impo	ort panel	F	Resource	es 🗸) A G	ustro enon	alian nics
				From th	e PanelA	pp hom	nep	bage, c	click	on tł	ne 'Ac	tivity'	page		* He	ealth Al	lliance
Activi	ty ⊤			This will filtered f name of	display a or date, Reviewe	ctivity panel n r or Cu	for nam rate	all pa ne, ver or	nels rsion	in Pa , ger	anelA ie act	pp and ivity ty	l can l pe,	be		-	
Date	Panel				Item	Activit	ty										
Filter activiti	es												30	00 action	S		
24 Nov 2019	Early ons disease_l	set Parkinson MelbourneGenomics_V	CGS v0.2		PDE8B	Zornitz	za S	itark Mar	ked ge	ene: PI	DE8B as	ready					
24 Nov 2019	Early ons disease_l	set Parkinson MelbourneGenomics_V	CGS v0.2		PDE8B	Zornitz Evider	za S [.] nce).	tark Gen	ne: pde	8b has	s been o	classified	as Greer	n List (Hig	h		
24 Nov 2019	Early ons disease_l	et Parkinson MelbourneGenomics_V	CGS v0.2		PDE8B	Zornitz	za S	tark Clas	ssified	gene:	PDE8B	as Green	List (hig	h evidenc	e)		
24 Nov 2019	Early ons disease_l	et Parkinson MelbourneGenomics_V	CGS v0.2		PDE8B	Zornitz Evider	za S [.] nce).	tark Gen	ne: pde	8b has	s been o	lassified	as Greer	n List (Hig	h		
24 Nov 2019	Early ons disease_l	set Parkinson MelbourneGenomics_V	CGS v0.1		PDE8B	Zornitz gene: diseas Mode autoso	za S PDE se_M of in omal	tark gen 88 was 1elbourne heritanc I or pseu	e: PDE added eGenor ce for g idoauto	8B wa to Ear mics_\ ene: P osoma	is addeo Iy onse /CGS. 9 DE8B v I, NOT i	d t Parkinso Sources: I vas set to mprinted	on Expert R MONOA	eview ALLELIC,			

How to view updates on individual Panel or Gene pages:



nelApp Panels Genes and Entities Activity	Log in	r aneixpp Paneis	Contestant Entations Activity	Australia		
anels / Limb disorders		Panels / Limb disord	ders / ARSE	Health Alliance		
imb disorders (Version 1.3)		Genes in panel				
		♠ Prev Next ↓	Gene: ARSE			
nel types: Rare Disease 100K, GMS Rare Disease Virtual		ARHGAP31 3	Green List (high evidence)			
lescription	12 reviewers	ARSE 2	ABSE (andoulfatano E (abandraduanlania nunotata	1))		
Sonpron		BHLHA9 3	EnsemblGenelds (GRCh38): ENSG00000157399	1))		
This panel is a virtual panel that can form part of the analysis of a broader phenotype,	Ellen McDonagh (Genomics Curator)	BMPR1B 2	EnsemblGenelds (GRCh37): ENSG00000157399			
This is not a primary panel for any GMS clinical indications.	Group: other Workplace: other	BRCA2 2	OMIM: 300180, Gene2Phenotype			
The content of this panel is overseen by NHS Genomic Medicine Service governance.	Tompidoor outor	BRIP1 2	ARSE is in 7 panels			
This panel was originally developed for the 100,000 Genomes Project and is still being	Richard Scott (Genomics En	• DLX5 3	Reviews (2) Details History			
used for participants in the project. For the rare disease eligibility criteria refer to: https://www.genomicsengland.co.uk/rarediseasecriteria100K	Workplace: Genomics England	• DOCK6 2				
This gene panel is designed to cover the following limb disorders, where limb disorder is	Ana Beleza (Guy's and St The Foundation Trust) Group: Other NHS organisation	• DVL1 3	Filter Activity Filter Activity From a Gene	ne page, click on the		
the primary or secondary feature : - Brachydactyly (HP:0001156)		• EBP 1	11 Dec 2018, Gel status: 4 'History' t	ab and then 'Filter		
- Oligodactyly (HP:0012165)	Workplace: NHS clinical servic	EOGT 2	Eleanor Williams (Genomics England Cura Δ Ctivity'			
Syndactyly (HP:0001159) Belvdosti (HP:0001159)	Olivia Niblock (Genomics En	• ERCC4 4	Ana Beleza: Tier 1			
- Amelia (HP:0009827)	Group: Other Workplace: Other	ESCO2 3				
- Phocomelia (HP:0009829) - Ulnar ray abnormalities		FAM58A 4	5 Apr 2018, Gel status: 4 Added New Source, Added New Source, Added New So	wrce. Set mode of inheritance		
- Radial ray abnormalities (HP:0410049)	Sarah Leigh (Genomics Engla Group: Other	FANCA 2	Ellen McDonagh (Genomics England Curator)	dice, set mode of infernance		
Rare multisystem ciliopathy genes are not included on this panel. If a patient is suspected of having a ciliopathy, or the possibility of a ciliopathy cannot be excluded,	Workplace: Other	FANCB 5	Expert Review Green was added to ARSE. Panel: Limb disorders Radboud University Medical Center, Nijmegen ARSE. Panel: Limb disorders UKGTN was added to ARSE. Panel: Limb disorders Model of inheritance for gene A			
the 'Rare multisystem ciliopathy disorders' panel (https://panelapp.genomicsengland.co.uk/panels/150/) should be applied in addition for	Rebecca Foulger (Genomics	FANCC 2	to X-LINKED: hemizygous mutation in males, biallelic mutations in female	3		
genome analysis. Ciliopathy genes were therefore made grey (removed) on this panel.	Group: Other Workplace: Other					
Panel Activity	Louise Doughorty (Ocassian F	ingland		na an ta tu an an ta an		
	Louise Daugnerty (Genomics E	nyidhu	This will display the relevan	t activity can be		
			filtered for date, version, ac	tivity type, name		
		_				
From a Danol nago click on (Danol Act	-iv/itv/		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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