Australian Functional Genomics Network Stream 1 Submission

Record ID

Contact Information

First Name: _____
Last Name: _____
Email: _____
Submission Category: **Stream 1: Assessing the impact of variants in known or novel disease genes**
This will support the investigation of variants that change the coding sequence of a gene or variations that encompass genomic alternations likely to alter gene expression or splicing.

Cases may include:

- Investigating genetic changes in individuals with clinically diagnosed disease who lack mutations in known disease genes.
- Genetic variants in known disease genes which do not reach the necessary threshold to provide diagnostic certainty but for which a compelling case for causation can be made. This might include a pattern of familial inheritance, de novo appearance and/or bioinformatic or other analyses that establish the potential impact on protein function or gene expression.
- Investigation of novel oligogenic mechanisms of disease in which pathology arises through cumulative effects of mutations in more than one disease gene in an affected individual.

Submission subcategory

1. Novel gene

- A gene not previously associated with disease
- A potential pathogenic variant identified in a single patient/family/isolated population
- Additional functional data is necessary to support disease-causation.

2. Novel variant in a known disease gene

- Gene not previously associated with disease, but supported by genetic evidence (potential pathogenic variants identified in more than one case of unrelated patients with a similar clinical phenotype)
- Functional data is being rapidly sought prior to publication.

3. Phenotype expansion of a known disease gene

- A variant in a known disease gene causing a clinical phenotype that appears to be different to previously reported genotype-phenotype reports
- Functional data required to determine how the gene contributes to the phenotype.

4. Variant of unknown significance

- The variant has characteristics of being an independent disease-causing mutation, but insufficient or conflicting evidence exists
- Functional data needed to confirm variant is causative.

* must provide value

- ◯ Novel gene
- ◯ Novel variant in a known disease gene
- ◯ Phenotype expansion of a known disease gene
- ◯ Variant of unknown significance

Patient details

Note: This information is collected to facilitate the return of results to your patient if you are no longer involved in their care at the time that research findings become available.

These fields will be hidden such that only the Project Management Team will be able to access this information.

Patient age
* must provide value

Patient sex
* must provide value

- ◯ Male (46, XY)
- ◯ Female (46, XX)
- ◯ Other variation

Consent

Participant information sheet
Download our participant information sheet to facilitate discussion of submission to the AFGN with your patient.

Attachment: PRN78873_AFGN_Participant_Information_Sheet(V2.0,_11_February_2022)_Clean.docx (0.29 MB)

What method of consent will be used to support this application?

* must provide value

- ○ Verbal consent - sign on-screen
- ○ Existing consent - upload consent form

Consent form available to upload?

- ○ Yes
- ○ No

Case summary

Gene Name

* must provide value

test

Provide a brief summary of the case

* must provide value

50 words remaining

Summarise the rationale for pursuing pathogenicity of the variant(s):

* must provide value

- ☐ Strong clinical and genetic evidence that the gene/variant is disease-causing
- ☐ Severe disease with high medical need
- ☐ Functional studies may help to create potential therapies
- ☐ There is a therapeutic need due to lack of existing therapies
- ☐ Significant change to clinical management (e.g., start/stop a therapy/intervention/screening)
- ☐ Significant impact on counselling (e.g., reproductive options, implications for family members)
- ☐ Other

(Select all that apply)

Patient Phenotype Description

Type key clinical features in the boxes and HPO terms will be suggested. You may add up to 10 clinical features.

Major organ system(s) affected

* must provide value

- ☐ Limb/appendage
- ☐ Cardiovascular
- ☐ Eye and ear
- ☐ Head and neck
- ☐ Musculature
- ☐ Nervous system
- ☐ Respiratory system
- ☐ Skeletal and connective tissue
- ☐ Blood and immune
- ☐ Endocrine system
- ☐ Integument
- ☐ Digestive system
- ☐ Genitourinary

Principal phenotype features

* must provide value

(HPO term)

Principal phenotype feature summary:

- _____
- _____
- _____
- _____
- _____
- _____
- _____
- _____
- _____
- _____

Are there any other phenotypic features that are not listed above?

* must provide value

- ○ Yes
- ○ No

Non-genetic clinical investigations and evidence

Do you have clinical documentation describing the phenotype and/or clinical investigations?

* must provide value

- ○ Yes
- ○ No

Do you have clinical images that are important for this application?
(i.e. dysmorphic features as evidence for gene-disease association)

* must provide value

◯ Yes ◯ No

Family History

Alternatively, upload a de-identified pedigree

Attention: Documents must be de-identified by removal of name, DOB and hospital # prior to upload

Are the parents of this individual consanguineous?

* must provide value

◯ Yes ◯ No

Ethnicity

How many known affected family members are there?

* must provide value

◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 ◯ >10

Has segregation testing of the variant in the family been performed?

Or

Has the variant been segregated through genetic testing?
e.g., trio WGS/WES?

* must provide value

◯ Yes ◯ No

Is the variant *de novo* or inherited?

* must provide value

◯ Confirmed de novo
◯ Assumed de novo
◯ Inherited

Are there family members of reproductive age for whom variant resolution will be informative?

* must provide value

◯ Yes
◯ No

Is there a reproductive urgency to confirm the pathogenicity of the variant?

* must provide value

◯ Yes ◯ No

Is there a therapeutic urgency to confirm the pathogenicity of the variant?

* must provide value

◯ Yes ◯ No

Previous genetic/genomic testing

Genetic tests completed

* must provide value

☐ Whole Genome Sequencing
☐ Whole Exome Sequencing
☐ Targeted Gene Panel
☐ Single Gene Test
☐ Chromosomal Microarray Analysis

(select all that apply)

Was DNA sequenced in an accredited facility?

e.g., NATA, CLIA

* must provide value

◯ Yes ◯ No

Were data analysed in an accredited facility?

e.g., NATA, CLIA

* must provide value

◯ Yes ◯ No

Are samples available for functional studies?

* must provide value

◯ Yes ◯ No ◯ Unknown

Information concerning the gene and phenotype-associated variant

Gene:

test

OMIM number

Not found? please specify:

Human disease association:

Describe what is currently known about the gene-disease association, include reference to relevant sources.

e.g., ClinVar, Decipher, denovo-db, OMIM, PubMed

* must provide value

What is the status of the Gene in PanelApp Australia?
https://panelapp.agha.umccr.org/panels/entities/

- ○ Green
- ○ Amber
- ○ Red
- ○ Not present

Variant Zygosity

* must provide value

- ○ Compound heterozygous
- ○ Heterozygous
- ○ Homozygous
- ○ X-linked

Inheritance Pattern

* must provide value

- ○ Autosomal Dominant
- ○ Autosomal Recessive
- ○ X-Linked
- ○ Mitochondrial
- ○ Mosaic

Please specify the details of the variant in the table below:

Genomic location and variant description				
Gene test	**Chromosome**	**Exon** **e.g., 2/13**	**Variant description (DNA Change)** **e.g., c.274G>T**	**Variant description (Protein Change)** **e.g., p.Asp92Tyr**
Transcripts				
Genome build	**Refseq genomic position** **e.g., NC_000011.10:g.112088971G>T**	**Ensembl transcript** **e.g., ENST00000375549.3**	**Refseq mRNA transcript** **e.g., NM_003002.3**	**Refseq protein transcript** **e.g., NP_002993.1**
Variant consequence and classification				
Variant type ☐ Sequence variant ☐ Structural variant **Please specify further below:** ***- Sequence variant type*** ***- Structural variant type***	**Predicted variant consequence** ☐ Missense ☐ Synonymous ☐ Splice site ☐ Splice region ☐ Frameshift ☐ Stop gained ☐ Inframe insertion ☐ Inframe deletion ☐ Stop lost ☐ Start lost ☐ Protein altering ☐ Coding sequence ☐ 5 prime UTR ☐ 3 prime UTR ☐ Intron variant ☐ NMD transcript ☐ Non coding transcript ☐ Transcription factor binding site ☐ Regulatory region ☐ Intergenic ☐ Other (please specify below)	**Variant classification** ○ 5 Pathogenic ○ 4 Likely Pathogenic ○ 3A VUS with high clinical significance ○ 3B VUS (default for labs not using 3A/B/C) ○ 3C VUS trending towards benign ○ Cannot be classified	**ACMG criteria applied**	**Has the variant been confirmed by sanger sequencing?** ○ Yes ○ No

Were there other rare variants identified that could match inheritance?

* must provide value

○ Yes ○ No ○ Insufficient information

Were there any low coverage regions of potential clinical significance?

* must provide value

○ Yes ○ No ○ Unsure

Evidence of variant pathogenicity

To assist the prioritisation of your case, please ensure that detailed descriptions of the curation evidence used to reach ACMG classification and computational (in silico) predictions are provided either by:

- uploading a test report, curation report or presentation document

  OR

- using the free-text boxes provided

Do you have a PowerPoint presentation or other document that outlines the evidence for pathogenicity?

Upload the document and select 'contained within uploaded report' in relevant fields to minimise data entry.

* must provide value

- ○ Yes
- ○ No

Human disease association data:

_____

Population data:

State the allele frequency in healthy population including dataset used (i.e., Topmed, gnomAD, in-house datasets), prevalence of variant in affected individuals compared to controls, gnomAD constraint

○ Contained within uploaded report ○ Provide free-text description

Computational and predictive data:

e.g., predicted molecular consequence and impact on gene product, previous reports at same amino acid residue

○ Contained within uploaded report ○ Provide free-text description

***In-silico* pathogenicity predictions:**

e.g., CADD, FATHMM, Grantham score, MutationAssessors, MutationTaster, PolyPhen2, SIFT, REVEL

○ Contained within uploaded report ○ Provide free-text description

Sequence conservation:

e.g., Nucleotide level (GERP) & Amino acid level (PhastCons & PhyloP)

○ Contained within uploaded report ○ Provide free-text description

Functional domain:

Is the variant located in a functional domain?

- ○ yes
- ○ no
- ○ unknown

* must provide value

Protein structure and function:

Describe what is known about the structure and function of the protein and its relevance to the patient's phenotype.

Include reference to data sources (e.g., NCBI gene, OMIM, KEGG, UniProtKB, GenAtlas, PubMed)

○ Contained within uploaded report ○ Provide free-text description

Gene expression:

Where is the gene expressed?

e.g., Human databases (DbMae, GTex & Protein Atlas)

○ Contained within uploaded report ○ Provide free-text description

Functional studies:

Describe any established functional studies and their relevance to the patient's phenotype.

Provide PMID or doi link to publications.

○ Contained within uploaded report ○ Provide free-text description

***De novo* data:** _____

Additional evidence:

e.g., highly specific phenotype, additional cohort data, previous reports of variant, additional comments, any evidence not contained in uploaded report

Efforts taken to resolve the variant

Has the variant been uploaded to Shariant?

* must provide value

◯ Yes ◯ No ◯ Unknown

Has the variant been submitted to Matchmaker Exchange?

* must provide value

◯ Yes ◯ No

Have any other efforts been made to resolve the variant?

e.g., research activities, expression studies, attempts to connect to other patients/researchers, direct contact with local/overseas labs, direct contact with corresponding authors

If a match is not found with an Australian researcher, are you happy for us to search our partner international registries for a match?

* must provide value

◯ Yes ◯ No

Describe any ideas/specific requests for functional studies, if any.

If a research partner has already been identified to undertake functional studies, please provide:

- Reasons for selecting partner
- Preferred model organism and justification for its use
- Details of work completed to date

Survey Completed Time 29-03-2022 D-M-Y

Form Status

Complete? Complete