Functional Genomics Platform to Assess Multiple VUS in a Single Gene

Funding brief

Many known and novel disease genes have significant numbers of potentially disease-causing variants that do not meet the current threshold for a definitive genetic diagnosis. Parallel assessments of these genetic variants’ functional consequences can enhance our understanding of the underlying genetic basis of disease.

**The** [**Australian Functional Genomics Network (AFGN)**](https://www.functionalgenomics.org.au/about-afgn/) **is inviting expressions of interest from Australian researchers, to establish platforms that will resolve multiple variants of uncertain significance (VUS) in priority genes identified by Australian diagnostic laboratories and clinicians.**

**Application Procedure:**

Step 1: A list of high priority genes has been compiled. Interested applicants will identify the gene(s) they wish to apply for via the website: [www.functionalgenomics.org.au/eoi-s2-2024/](https://www.functionalgenomics.org.au/eoi-s2-2024/). Expressions of interest will close on Friday October 4th.

Step 2: Within 2-6 weeks of submission, applicants will be notified, allowing time for the finalisation of the variant list. VUS from diagnostic laboratories will be collected for inclusion in the platform proposal.

Step 3: Once the variant list is released, applicants will have 4 weeks to submit a full platform proposal using the provided [form below](#_Expression_of_Interest). Proposals should be submitted via [email](mailto:functional.genomics@mcri.edu.au?subject=AFGN%20Stream%202%20EOI).

Step 4: The AFGN Scientific Review Committee will review the applications. Short-listed applicants may be interviewed by the Network chairs.

**Assessment criteria –** Priority will be given to proposals for platforms that are:

* Already established and scalable (new and boutique platforms will also be considered);
* Achieve clinically relevant turnaround (6-12 months);
* Leveraged by appropriate expertise as well as cash and/or in-kind contributions;
* Have the potential to be cost efficient and scaled to resolve multiple VUS through diagnostic testing beyond the study.

**Project design:**

In proposing a platform, applicants should consider the stringency of evidence required to elevate a variant from VUS (3) to likely pathogenic/pathogenic (4/5). All platforms should include known benign and pathogenic variants as controls. See: [Brnich et al. Genome Medicine (2020)](https://doi.org/10.1186/s13073-019-0690-2).

We encourage the use of existing resources. **Phenomics Australia,** an NCRIS-funded initiative, offers expertise in developing disease models. For more information, contact John Parisot at [j.parisot@therapeuticinnovation.com.au](mailto:j.parisot@therapeuticinnovation.com.au) or visit <https://phenomicsaustralia.org.au/>

**Budget:**

No minimum amount is set for a single grant. The maximum funding for a single grant is $200,000. Budgets will be evaluated based on the complexity of the platform and number of variants being analysed.

**Enquiries can be directed to:** [functional.genomics@mcri.edu.au](mailto:functional.genomics@mcri.edu.au).

**Gene-List:** [S2EOIR2\_gene list.docx](https://www.functionalgenomics.org.au/wp-content/uploads/2024/09/S2EOIR2_gene-list-v1.1-dated-26-09-2024.docx)

# Expression of Interest Form:

Functional Genomics Platform to Assess Multiple VUS in a Single Gene

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| COORDINATING PRINCIPAL INVESTIGATOR | | |
| First name: |  | |
| Last name: |  | |
| Institute: |  | |
| Position: |  | |
| Department: |  | |
| Email: |  | |
| Phone: |  | |
| Project title: |  | |
| Model system(s): | *Type an ‘X’ to indicate the most relevant model system(s) used in your proposed platform:* | |
|  |  | Cell models |
|  | Mouse |
|  | Zebrafish |
|  | Fruit Fly |
|  | Roundworm |
|  | Budding Yeast |
|  | E. coli |
|  | Other, please specify: |
|  |  |  |

***Add additional rows as required:***

|  |  |  |  |
| --- | --- | --- | --- |
| ADDITIONAL INVESTIGATOR(S) | | |  |
| # | Name | Email | Position, Department, Institute |
| 1 |  |  |  |

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| GENE NAME: | DATE: |
| BACKGROUND (1/4-page)  *Provide information on the background of the gene/variant and experimental strategy* | |
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| PROJECT PROPOSAL SUMMARY (1 – 2-page) |
| *Provide information on the proposed platform and details of the experiments to be conducted to resolve multiple variants in a single gene, including methodologies applied, generation of model organism(s)/system, phenotypic analyses, and anticipated results together with interpretation in the context of stringency of evidence for a clinical outcome.* |
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| VARIANT LIST |
| *Provide a list of variants that will be analysed using the excel spreadsheet provided. Please submit this with your platform proposal. The variant list should include information about selected VUS and all relevant controls.*  🡪 Download here: [*Supplementary table - variant list.xlsx*](https://www.functionalgenomics.org.au/wp-content/uploads/2024/09/AFGN_S2EOIR2_variant_supp_GENE_Surname_DD-MM-YYYY.xlsx) |

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| --- | --- | --- | --- |
| SAMPLE REQUIREMENTS |  | |  |
| Are patient-specific sample(s) required? |  | *Type ‘X’ in the box to indicate ‘Yes’ or ‘No’* |  |
|  | Yes |
|  | No |
|  |  |  |
| If yes – what type: |  | | |

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| --- | --- | --- |
| PROPOSAL TIMELINES & CAPABILITIES | | |
| How long is platform development and validation expected to take? |  | |
| What is the expected turnaround-time for functional validation of a single variant with this platform? |  | |
| Once the platform is validated, what is the estimated cost per variant to be tested to produce a report? |  | |
| Is the platform gene-specific? |  |  |
|  | Yes |
|  | No |
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| PROPOSAL SCALABILITY & SUSTAINABILITY |
| Comment on the scalability of the design (including capacity limits), opportunities for technology transfer to other facilities, and team-based approach. |
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| Do you plan to use the data generated by this project in future research grant applications to support the sustainability of the platform for testing future variants? Comment on your strategy for maintaining the platform's capability to test new variants once this funding opportunity has concluded. |
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| DELIVERABLES and MILESTONES (1/3 page) |
| Outline the expected outcomes of your experimental strategy and milestones for the platform development including resourcing and staffing, experiments, validation proposals, and contingencies. |
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| DELIVERABLE | MILESTONE | DURATION | COMPLETION  DATE |
| *Project outputs* | *Key indicators signifying successful completion of deliverables/key stages* | *(Months)* | *(MM/YY)* |
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*Add table rows as required.*

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| BUDGET and BUDGET JUSTIFICATION (1 page) |
| *Please distinguish between REQUESTED funding and estimated TOTAL COST. Recognise existing infrastructure and co-funding to inform service modelling estimates in the future. Budget should include staffing, reagents, services etc. Equipment over $10,000 requires detailed justification and quotations.\** |
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\* Please note that overheads are not eligible for acquittal under the funding rule.

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| BIOGRAPHY (1/2 page per CI) |
| For each CI proposed, provide a brief summary of evidence of your capability to deliver this project.  You may include up to 5 relevant publications. Note your current funding, national collaborations, and how these may contribute to delivery of the project. |
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| REFERENCES (maximum five (5) relevant references) |
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