Australian Genomics

Research Snapshot
June 2021

Australian Functional Genomics Network

The Australian Functional Genomics Network fosters collaboration between model organism researchers, human geneticists, and clinicians to facilitate collaborations for the interpretation for VUSs and translation of that knowledge into clinical practice.

Background

One of the main goals of medicine is to diagnose disease, to discover its origin or nature in a patient.

But rare and yet-to-be-described conditions are particularly problematic for patients, their families and their physicians. The lack of an accurate diagnosis makes managing the condition much more difficult, making the need for targeted treatment more pressing.

Due to its impressive results, clinical genomic analysis is being used to diagnose rare, unexplained or complex cases of human disease. For example, rapid singleton, whole-exome sequencing performed on acutely unwell paediatric patients with suspected monogenic disorders yielded a diagnosis in more than 50 per cent of those patients (White et al 2018).

An increasing body of evidence is supporting the uptake of genomic medicine in the Australian healthcare system.

This increase in demand is likely to lead to a surge in reports of novel genetic variants associated with human disease (Boycott et al 2014).

But if the pace of discovery of novel variants outstrips our ability to understand their impact on biological function and relevance to pathological processes, clinical interpretation is compromised.

An unacceptably large proportion of newly-identified variants will be categorised as variants of uncertain significance (VUS).

Resolution of VUSs can be achieved with well-designed biological modelling in animals or cell systems that have been applied successfully to human research, including research into Mendelian diseases and cancer (Bellen et al 2017, Berger et al 2017).

There is a pressing need – and opportunity - to identify and implement strategies to facilitate the exchange of ideas and information between clinical medicine and biomedical research.

With the technological advances in genomic medicine and the functional characterisation of genetic variants, the current environment is presenting us with an opportunity for basic scientists and clinical researchers to build upon each other's expertise.

A potential outcome is the integration of functional validation into the patient diagnostic pipeline.

The **Australian Functional Genomics Network** is a national consortium with the principal aim of fostering collaboration between model organism researchers, human geneticists, and clinicians to facilitate collaborations for the interpretation for VUSs and translation of that knowledge into clinical practice.

"Australian Model System teams are encouraged to register and indicate their gene/pathway/cellular system areas of interest and expertise."

Project overview

The key to success and to maximum benefit to patients will be to establish efficient mechanisms for catalysing connections, collaboration and cross-talk between scientists and clinicians.

The Australian Functional Genomics Network will expedite the "match-making" of clinicians, diagnostic labs and researchers through the use of the Australian Functional Genomics Registry, a database of model system teams in Australia.

Australian Model System teams are encouraged to register and indicate their gene/pathway/cellular system areas of interest and expertise.

The intention is to identify a model system team(s) that has a track record of research in the functional evaluation of the newly identified disease gene (or orthologue) and, ideally, has the capacity to embark upon functional analyses rapidly.

The result will be an establishment of collaboration between clinicians and model system investigators to conduct immediate functional experiments relevant to the gene of interest.

Network aims

Gather and facilitate the sharing of phenotype data to guide experimental studies.

A key to the success of such collaboration is access to detailed clinical phenotyping information in patients and their families, data that are often inaccessible to basic investigators.

1) **Identify clinically relevant genes as priorities for functional studies.**

   Through a clinical review panel, a selection of high-priority genes for functional studies will be established on the basis of potential clinical importance and experimental feasibility. High-priority genes will be matched with scientific teams for further investigation while unmatched genes will be recorded and regularly updated to provide a key resource for future opportunities in clinical and experimental research. High-priority genes will include known disease genes with newly identified variants expanding the previously reported genotype-phenotype reports, as well as genes of unknown function, particular genes under strong evolutionary constraints.

2) **Generation of a database of model system teams in Australia.**

   The Australian Functional Genomics Registry is a database of model system teams in Australia. The Registry captures profiles of scientific investigators who have nominated their area of interest and expertise by gene/pathway/cellular system. The registry can be queried when a VUS is identified and the best-matched model system team(s) can be invited to undertake research on the candidate disease gene/variant of interest. Researchers are able to access the registry at any time to edit and update their information. Currently the registry houses 232 research lab profiles, with over 2280 genes listed.

3) **Improve scientific-clinical interactions in functionalizing genomic variants.**

   We aim to help bridge the gap between basic scientists and clinical geneticists by fostering opportunities for formal and informal interaction. By building Australian diagnostic capacity to apply functional genomic and model organism evidence to genomic interpretation and diagnosis, rare genomic variant information can be increasingly incorporated into clinical care.

functionalgenomics.org.au

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Potential impact

- Provide functional validation of human genetic variants that cause disease
- Develop insights into an evidence-based rationale for treatment (e.g. identification of candidate drug targets) via knowledge of disease gene function and molecular pathway
- Complement clinical disease discoveries with functional genomics investigation that lead to significant research output, such as publications, changes in health policy and clinical management
- Establish sustainable collaborations between clinical teams and model system research teams to conduct outstanding research that will attract further competitive funding support.

Conclusion

Australian Genomics responded to a need to improve the consent process for genomic research studies, coordinating a multi-disciplinary effort to deliver a product inspired by the principles of dynamic consent.

The consent and engagement platform is being used by research participants enrolled in Australian Genomics Flagships clinical projects.

Future work will focus on improvements to make the website better, primarily with participant experience in mind, but also so that dynamic consent approaches can be readily adopted by research organisations.

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