phg foundation
making science work for health

Functional genomics
in clinical medicine

Functional genomics is a field of molecular biology where researchers attempt to answer questions about how genes are activated and operate in a dynamic, context-dependent, and synergistic fashion, using a range of genomics and associated 'omics datasets. The notable aspect of functional genomics is that it involves genome-wide investigation as opposed to a 'gene by gene' approach to understanding function. Although the field is relatively new, it is already proving important for understanding the role of genomic variation in disease. The principles of functional genomics approaches could be beneficial in genomic medicine for patient care. In this second of two policy briefings, we explore the potential impact of functional genomics on clinical medicine.

Summary

- Functional genomics investigates the complex relationship between genotype and phenotype.
- High-throughput technologies (e.g. sequencing and mass spectrometry) can be used to investigate the function of genes and gene products, and the impact of genetic variation on an organism's biology on a genome-wide scale.
- While tests exist in the clinical laboratory that can reveal specific functional consequences of predefined genetic variants, the use of multidimensional, genome-wide interrogation for untargeted investigations has not yet reached the clinic.
- Areas where functional genomics approaches could be useful in the clinic have been identified, particularly for rare disease and cancer to support interpretation of genomic information.
- Health systems will need to consider various challenges and practicalities if they wish to implement functional genomics investigations into genomic medicine services.

WYNG FOUNDATION

We thank the WYNG Foundation for supporting the research behind this briefing paper. Views expressed in this briefing do not necessarily reflect those of the WYNG Foundation.

Functional genomics

Understanding function through multiomics

Functional genomics is not defined as a set of technologies or analyses but rather as an approach that employs different tools to answer questions such as which genes are transcribed, how this process is regulated, how translation into proteins occurs, what functions the proteins have and their metabolic consequences. Any combination or number of 'omics datasets can be combined to understand genomic function. Due to recent technological advances including high throughput, next generation sequencing, improved protein and small molecule analysis techniques (e.g. mass spectrometry) and enhanced computing power, these investigations can be carried out on a large scale and in combination.

Different technologies can give us information about different processes in specific cells or tissues at a given time, including:

- The epigenome – modifications to DNA or RNA that control gene expression
- The transcriptome – all RNAs
- The proteome – all proteins
- The metabolome – all metabolites, which can include proteins and lipoproteins

Protein-DNA and protein-protein interactions can also be investigated.

Impact on personalised medicine

Understanding genome function is key to the application of medical genetics. However, despite recent progress, information from the genome alone is not always sufficient for clinical decision making. A major challenge is variant interpretation (i.e. the process of determining if a genetic change is pathogenic, benign or of unknown significance), which is hampered by incomplete understanding of the biological function of most areas of the genome. Complementing whole genome (WGS) or whole exome sequencing (WES) datasets with other 'omics datasets could have great clinical impacts for patients - in the medium term, those with rare disease and cancer and potentially, in the longer term, those with common complex disease.

Functional validation

WGS or WES uncovers tens to hundreds of thousands of variants in an individual patient[1]. A series of filtering and prioritisation steps can reduce this down to variants that may play a role in disease. Some of these variants will be of unknown significance. If a variant of unknown significance is found that is suspected to be causal but there is insufficient evidence, then specific tests can be carried out to confirm if the variant is indeed implicated in the disease (e.g. by investigating impacts on transcription). Results from these tests can form the basis for a diagnosis, provide insight into potential therapies and contribute to the knowledge base of the function of genomic variants.

However, this process requires some prior knowledge suggesting that the variant may be pathogenic. As the role of some genes and the vast majority of the non-coding regions of the human genome remains unknown, not all possible pathogenic variants will be selected for further functional validation, meaning the importance of the variant will remain unknown.

Functional genomics

This is where functional genomics approaches could be useful when integrated into genomic medicine services. The major benefits being that:

- Changes to biological processes might be revealed that are important for the disease in question but are not indicated or obvious by looking at the genome alone.
- The approaches can be untargeted so the investigating clinicians and clinical scientists do not need to have any prior assumptions about which genetic variant might be causal.

Rare disease

Integrating multiple 'omic datasets could further increase the diagnostic yield when genomics interrogation has not been conclusive (e.g. in patients with genetically undiagnosed rare muscle disorders[2] and mitochondrial disease[3]). This will allow for mechanistic interpretations, elucidating diagnostic and prognostic biomarkers, as well as the potential for drug repurposing opportunities and discovering novel drug targets.

Precision therapy in cancer

There are two ways that functional genomics could be useful for precision therapy in cancers. The first is that by using other 'omics datasets, mechanistic information can be derived to better understand tumour biology and may uncover biomarkers and drug targets. The second is the functional testing of tumour cells by assessing how they respond to different drugs (e.g. the Finnish Institute of Molecular Medicine Grand Challenge Programme into functional precision medicine). This method is routinely used in microbiology to tailor effective antimicrobials to a patient's infection.

Complex common disease

In the longer term, functional genomics could impact personalised medicine for many common complex diseases by enabling a greater understanding of the interactions between the genome and the environment relevant to the disease[4]. Polygenic risk scores – estimates of disease risk based on the cumulative effect of a large number of individually low-impact genetic changes – are currently not in widespread clinical use. More comprehensive understanding of the functional roles of variants linked to disease could support their future use, either alone or in combination with other biomarkers

Considerations for health systems

It is unlikely that functional genomics approaches will be needed for every patient. Aside from the additional costs this would incur, additional functional characterisation may not be necessary for clinical management. However, as the technologies required for functional analysis become more affordable, and the evidence linking variation at multiple levels of biology with disease increases, there are certain areas where multiple 'omics investigations may be useful.

Before adopting comprehensive, multidimensional investigations in genomic medicine for rare diseases and cancer, there are important considerations:

Functional genomics

Evidence of clinical validity and clinical utility

- Understanding of the functional processes beyond the genome is only just being uncovered. This is complicated by the dynamic and fluctuating nature of the transcriptome, epigenome, proteome and metabolome.
- Certain functional aspects will be tissue or cell dependent and it is not yet clear how well functional data derived from easily collectable samples (e.g. blood) will reflect functional genomic processes in other areas of the body that are not so easily sampled (e.g. brain).
- We are only just beginning to build comprehensive functionally annotated genomes compared to the vast amounts of genomic data that exists.

Technology, infrastructure and expertise

- Some of the technologies used for functional genomic investigations are already in use for diagnostics. For example, next generation sequencing technologies can investigate the transcriptome and epigenome with alterations to sample handling and processing.
- Additional 'omics investigations will require expertise in these specific areas as well as the integration and interpretation of currently unconnected datasets through bioinformatics analysis.

Practicalities for additional 'omics tests

- The turnaround time of additional testing whilst managing expectations of what may be found.
- The availability and quantity of patient samples required.
- Sample handling processes: for example, the preservation of RNA requires the tissue to be rapidly frozen or placed in bespoke fixatives.
- The numbers of tests reaching sufficient volumes to maintain high levels of quality and the implementation of diagnostic quality control checks.

References

1. Jamuar SS and Tan EC. Clinical application of next-generation sequencing for Mendelian diseases. Hum Genomics. 2015. 9: p. 10
2. Cummings BB et al. Improving genetic diagnosis in Mendelian disease with transcriptome sequencing. Sci Transl Med, 2017. 9(386)
3. Kremer LS et al. Genetic diagnosis of Mendelian disorders via RNA sequencing. Nat Commun, 2017. 8: p. 15824
4. Mattson DL and Liang M. Hypertension: From GWAS to functional genomics-based precision medicine. Nat Rev Nephrol, 2017. 13(4): p. 195-196

Authors: Dr Sarah Cook

Published: November 2020

UNIVERSITY OF CAMBRIDGE