CHIEF SCIENTIST OFFICE

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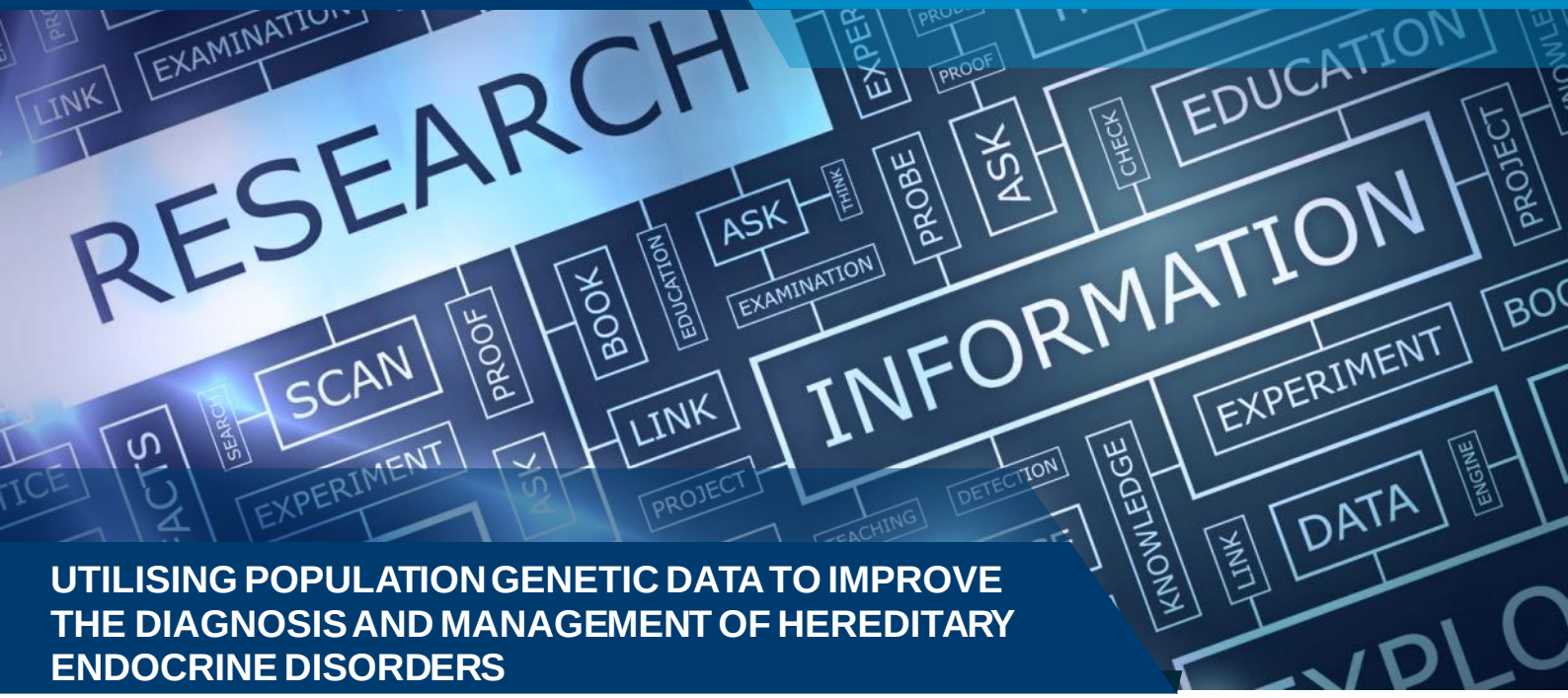
RESEARCH PROJECT BRIEFING



UTILISING POPULATION GENETIC DATA TO IMPROVE THE DIAGNOSIS AND MANAGEMENT OF HEREDITARY ENDOCRINE DISORDERS

AIMS

Advances in DNA sequence technology have revolutionised the opportunities for genetic testing in the clinical setting. Identifying individuals at risk of hereditary disease offers opportunities to improve health outcomes (e.g. through tumour surveillance programmes, provision of disease-specific treatments).

Although individually rare, hereditary disorders affecting the endocrine system (i.e. hormone producing glands) cumulatively present a major health burden resulting in substantial morbidity and premature mortality. Genetic testing is used to identify individuals at risk of such hereditary disorders, which frequently result from a DNA change or 'mutation' within a single gene, and is increasingly employed in both diagnostic as well as predictive settings (i.e. in those with relevant clinical features, and asymptomatic individuals, respectively). However, the use of such testing relies on the accurate interpretation of the genetic information obtained and reliable estimates of the associated health risks.

In these studies, we aimed to analyse genetic data from large scale population-level DNA databases together with disease-specific mutation (or 'variant') repositories to develop an improved approach to genetic test interpretation and to generate new metrics to facilitate improved clinical application.

KEY FINDINGS

- High cumulative rates of rare DNA sequence changes are observed in many of the genes associated with hereditary endocrine disorders in the background 'healthy' population, and may confound genetic test interpretation, leading to uncertain or inaccurate test results.
- In some instances genetic changes reported to be associated with hereditary endocrine disorders are likely to have been misclassified, and instead represent harmless changes or are associated with a much lower risk of disease then previously thought (i.e. low disease penetrance). Such findings have important implications for patients and their families.
- The application of new high-throughput computational/bioinformatic methods may improve the risk stratification of genetic changes identified during genetic testing, leading to improved test interpretation as well as more accurate estimates of any associated disease risks, thereby guiding patient care.

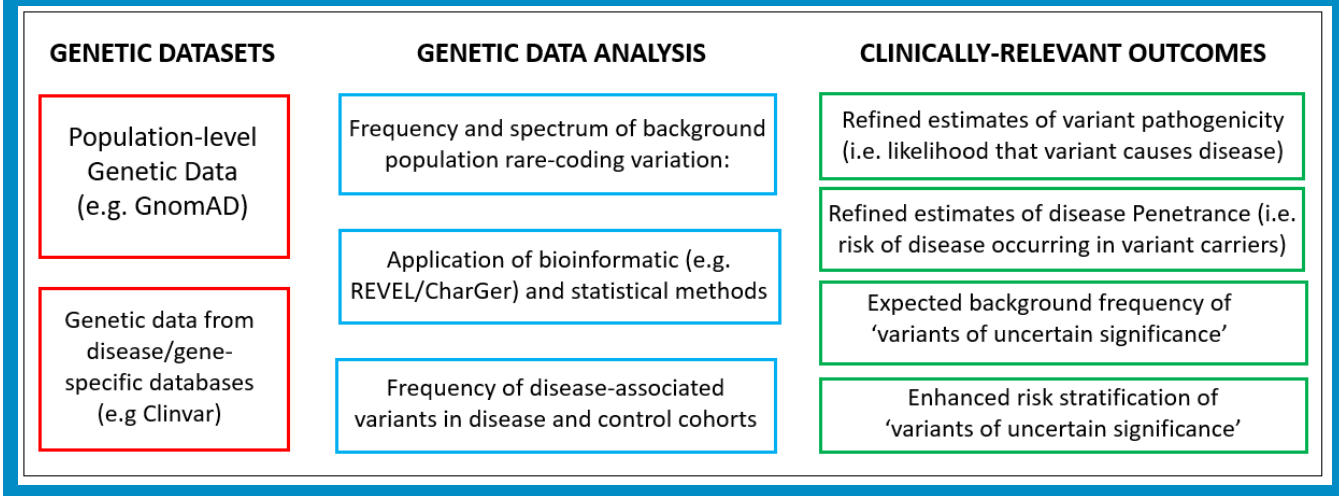
WHAT DID THE STUDIES INVOLVE?

Large population-based genetic databases were employed (e.g. GnomAD (gnomad.broadinstitute.org), ExAC (exac.broadinstitute.org)), to evaluate the frequency and type of rare DNA sequence changes observed in genes associated with hereditary endocrine disorders. Depending on the specific project, variants from disease-specific mutation databases (e.g. ClinVar; ncbi.nlm.nih.gov/clinvar) were also identified and analysed. Both control population and disease-specific DNA variants were evaluated using a number of methods which included computer-based bioinformatic tools as well statistical approaches. These methods allowed new gene-specific information to be established (e.g. cumulative rare variant frequencies; refined estimates of variant pathogenicity and penetrance; and risk stratification of 'variants of uncertain significance'). The results of these studies were applied to 'real-world' clinical scenarios to demonstrate potential clinical utility.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

The frequency and spectrum of rare genetic variants predicted to impact on protein function was established for a large number of genes associated with a range of different hereditary endocrine conditions. Marked differences in rare variant frequencies were noted between the different genes and this correlated with their degree of evolutionary conservation. Comparisons of the rare genetic changes observed in control and disease-specific DNA databases and the application of bioinformatic tools identified information that could aid the clinical interpretation of DNA changes found during genetic testing. Furthermore, this analysis identified that several DNA changes reported to be disease-causing (i.e. pathogenic) were likely to have been misclassified and were in fact harmless 'benign' DNA changes, or alternatively were associated with a much lower disease risk than previously thought (i.e. low 'penetrance'). This included 'mutations' in a number of genes associated with hereditary endocrine cancer syndromes where the implications of variant misclassification may be profound (e.g. influencing treatment decisions and need for tumour surveillance programs). Furthermore, these studies have provided insight into the significant burden of potential 'variants of uncertain significance' which may be uncovered during genetic testing, and has developed new approaches to stratify the risk of these variants. Taken together, these studies highlight the challenge of interpreting the clinical significance of rare DNA sequence changes identified during genetic testing and has established new information that may help in this process..

Overview of Study Design and Outcomes



WHAT IMPACT COULD THE FINDINGS HAVE?

These studies have a number of potential impacts:

- For Academia: The detailed analysis undertaken in these studies further illuminates the diversity of naturally-occurring DNA sequence changes that occur in the population, which in turn may confound the application of genetic testing in the clinical setting. The studies provide a resource for scientists and clinicians working in this field, and highlight methods that can be applied to other disease areas.
- For Patients: Accurate genetic test interpretation remains a major clinical challenge, with the potential for uncertain test results forming a barrier to clinical application. These studies provide an enhanced framework for variant interpretation across a breadth of endocrine disorders with direct clinical implications (e.g. refined estimates of penetrance influencing tumour screening programs)
- For Policy: The increased application of genetic testing in the clinical setting requires clinicians to have the appropriate education and knowledge for this to be applied safely. These studies contribute important information that could be incorporated into relevant training resources.

HOW WILL THE OUTCOMES BE DISSEMINATED?

The work arising from these projects has been presented at national and international scientific meetings, with some of the studies published in peer-reviewed journals (see below), with additional publications expected. The lead author is involved in a number of ongoing projects relating to the 'best-practice' for clinical genetic testing, which involves multiple stakeholders, with the current work having utility in educational and clinical practice settings. Ongoing and future studies aim to understand how changes in DNA sequence in endocrine genes may influence response to treatment.

Peer-Reviewed Publications ***1.*** *Newey PJ. Genetic testing in Endocrinology: current concepts and contemporary challenges. Clin Endocrinol. 2019;91:587-607* ***2.*** *Maniam P, et al. Pathogenicity and Penetrance of Germline SDHA Variants in Pheochromocytoma and Paraganglioma (PPGL). J Endocr Soc. 2018; 2:806-816.* ***3.*** *Newey PJ et al. Utility of Population-Level DNA Sequence Data in the Diagnosis of Hereditary Endocrine Disease. J Endocr Soc 2017; 1: 12: 1507–1526* ***Peer-Reviewed Research Abstracts: 1.*** *Vennard, H et al. Frequency of pathogenic germline variants in hereditary endocrine tumour genes in patients with discordant cancer phenotypes. Endocrine Abstracts (2019)* ***65*** *P146* ***2.*** *H Vennard, et al. Risk stratification of variants of unknown significance (VUS) in monogenic endocrine tumour genes using population-level genetic data and computational analysis. Endocrine Abstracts (2019)* ***65*** *P132*

CONCLUSION

The successful implementation of clinical genetic testing relies upon the accurate interpretation of test results which may be confounded by naturally-occurring changes in DNA sequence that occur in the background population. Utilising data from large-scale DNA sequence databases provides a powerful resource to better understand this diversity of genetic variation, and allows the application of computer-based bioinformatic and statistical methods, which can help determine the clinical significance of genetic changes identified during testing, and ultimately improve patient care.

RESEARCH TEAM & CONTACT

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Additional Information

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