CHIEF SCIENTIST OFFICE

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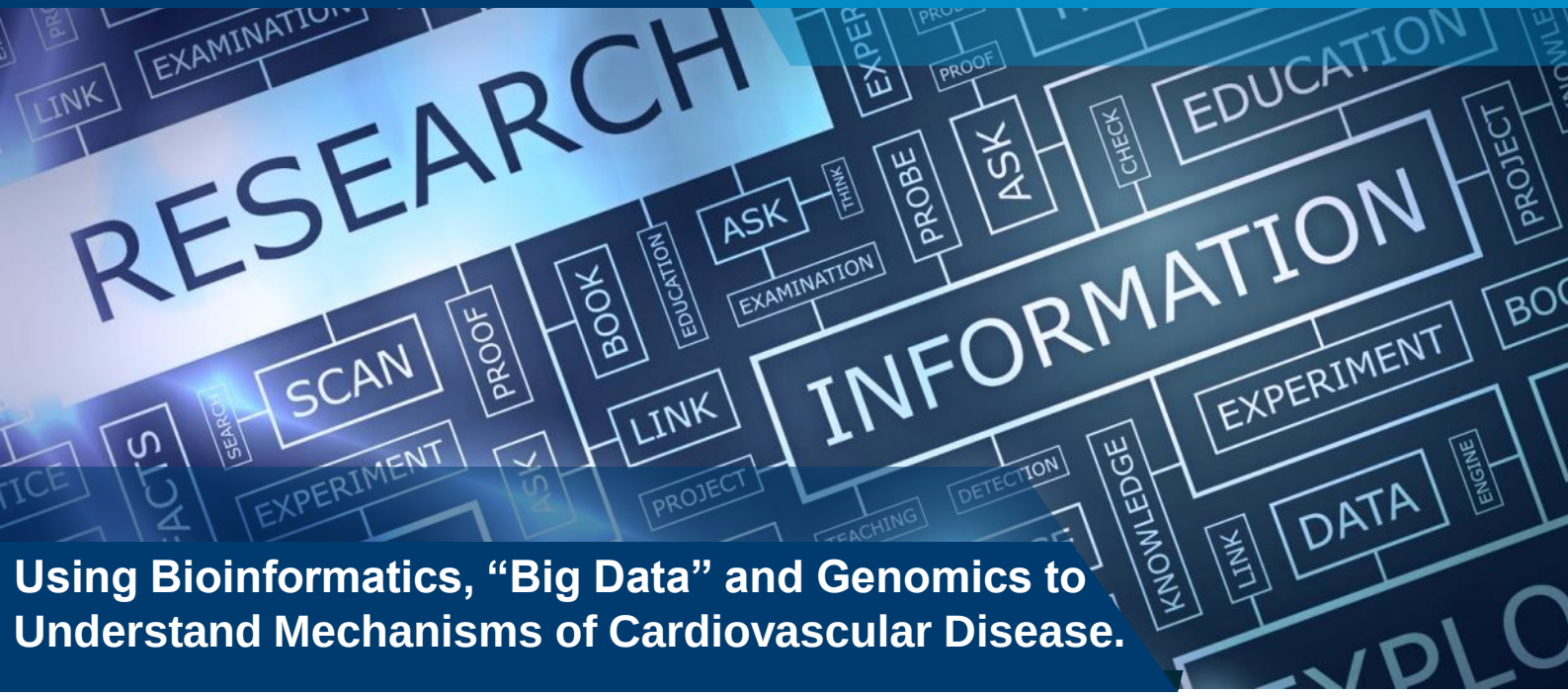
RESEARCH PROJECT BRIEFING



Using Bioinformatics, "Big Data" and Genomics to Understand Mechanisms of Cardiovascular Disease.

AIMS

The aim of this project was to use a mixed methods approach combining large clinical datasets, genomics and bioinformatics to identify novel markers of risk in cardiovascular disease and understand mechanisms of cardiovascular disease.

KEY FINDINGS

The use of genetic data and large observational datasets allowed:

- Mechanistic understanding of the role of diabetes, insulin resistance, obesity and coronary artery disease in risk of heart failure.
- Evidence supporting the bidirectional relationship between heart failure and diabetes.
- A potential explanation for the link between clarithromycin (a commonly used antibiotic) use and increased risk of heart attacks.

WHAT DID THE STUDY INVOLVE?

I undertook a period of training in genomic analysis techniques (Mendelian Randomization).

I utilised large clinical and genetic datasets available to me including the Tayside

echocardiography database (over 100,000 heart scans), the GoDARTS study (a study of 18,000 patients with and without type 2 diabetes who have genetic data available – www.godarts.org) and the HERMES study (an international genetic study including over 65,000 patients with heart failure - www.hermesconsortium.org/). I also linked data to the prescribing, admissions and clinical data provided by the Tayside Health Informatics Centre. I was able to use these datasets to answer my research questions using various statistical methods.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

- I used large genomic datasets to provide further insight into the role of various risk factors in heart failure. I found that genetic variants associated with type 2 diabetes and obesity were strongly associated with heart failure and also found evidence of a bidirectional relationship between diabetes and heart failure, finding that genetic variants associated with heart failure were associated with increased risk of development of diabetes.

- Linking this to electronic health record data, I found that patients with heart failure were significantly more likely to develop new-onset diabetes than similar patients with heart attacks (but no heart failure) and were likely to have poorer control of their diabetes despite the same treatments.

- I also found that genetic variants associated with coronary artery disease were significantly associated with risk of heart failure with reduced ejection fraction but not preserved. This might have important implications clinically as patients with heart failure with preserved ejection fraction often have coronary artery disease – intuitively one might think that treating this, e.g. with coronary stents might be beneficial, but this might not actually be true.

- I also conducted a study using a mixture of a traditional observational approach and a pharmacogenomic approach to try to understand the mechanism behind the increased cardiovascular risk seen with use of the antibiotic clarithromycin.

- In the observational study I found that people prescribed clarithromycin in Tayside between 2004 and 2014 had a significantly higher risk of having being hospitalized with a heart issue compared to those given amoxicillin (an alternative antibiotic often used for the same reasons). This risk was particularly increased in patients who were also prescribed medications which are metabolized via the P-glycoprotein pathway.

- Exploring this further, I conducted a genetic analysis which confirmed that individuals with genotypes that conferred low P-glycoprotein activity had a significantly higher risk of cardiovascular hospitalization after being given clarithromycin than individuals with higher genetically-predicted P-glycoprotein activity.

WHAT IMPACT COULD THE FINDINGS HAVE?

- **Implications for Patients**: The use of genomics could help us to identify novel mechanisms of risk and new treatments for cardiovascular disease. As genetic analysis becomes cheaper and more widespread there may be opportunities for personalised treatment.

- **Implications for Policy**: Scotland's unique record linkage data (supported by use of the unique Community Health index number) provides a rich seam of information that could help inform health policy.

- **Implications for Practice**: Genomics could be used in routine practice, for example, my data might support avoidance of clarithromycin use in patients also taking medications metabolised via the P-glycoprotein pathway.

HOW WILL THE OUTCOMES BE DISSEMINATED?

I have already published 2 journal articles based on this data and further will be disseminated at conferences and with manuscripts submitted for publication.

Mordi IR, et al. PLoS Med. 2020 Nov 23;17(11):e1003372.
Mordi IR et al. Circulation. 2019 Feb 12;139(7):986-988.

Future research will be based on identification of further mechanisms of disease using genomics in heart failure subtypes, and exploring novel treatment strategies based on this – for example treating insulin resistance in patients with heart failure.

CONCLUSION

I have shown the utility of bioinformatics, large datasets and genomics, demonstrating its translational potential in identification of novel markers of risk in cardiovascular disease and understanding mechanisms of cardiovascular disease.

RESEARCH TEAM & CONTACT

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Additional Information

Project completed August 2020.