CHIEF SCIENTIST OFFICE

CODE: PCL/20/02

RESEARCH PROJECT BRIEFING

AIMS

DNA (Deoxyribonucleic acid) is the blueprint for how our cells function and respond to the environment. Our DNA contributes to our individuality - our height, our eye colour, and our risk of disease. The aims of our work was to:

- Understand how differences in DNA can impact how severely people are affected by the same disease, including rare and common diseases.
- Use differences in DNA that put people at risk of severe inflammatory lung disease to discover new molecules that may be targets for therapies.
- Develop laboratory and computer-based methods to understand and detect changes in DNA that are thought to contribute to increased disease risk. The primary focus was on responses to inflammation.

KEY FINDINGS

- Differences in DNA that are thought to contribute to the differences between people and their risks of disease are marked by specific molecular signatures.
- Differences in DNA that are important for disease processes, such as diseases that cause lung inflammation. Differences between people can be found in regions of DNA the code for protein molecules, such as enzymes and receptors, that govern cell function. Other regions outside DNA that codes for proteins can also contribute to disease. These regions are likely to control how much protein is in a cell through an intermediate molecule called RNA (Ribonucleic acid).
- Some differences in DNA can change the code of proteins enough to disrupt their ability to function normally. When these proteins, found in the lung for example, are disrupted, they can cause more severe disease such as lung inflammation.

WHAT DID THE STUDY INVOLVE?

To understand how differences in DNA can alter risk of disease, we used a combined approach consisting of experimental and computer-based analyses. For the experimental approach, we used human cells grown in the lab, which is a conventional method for understanding the effects of DNA changes. We looked at how changes in DNA can contribute to the altered control of RNA, the signaling molecule that makes proteins, or how the proteins themselves can be affected. We used computer approaches that mine large data from multiple human cells to look for signatures to understand how DNA changes work.

As part of the project, public involvement has been sought through various stages. We had engagement from survivors of critical illness, patients with pulmonary fibrosis which is a disease of lung inflammation we have worked on, and charitable entities, who have had input towards the funding priority and public facing outputs of the work.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

- To study how changes in DNA can alter disease, we have used cells grown in a dish, and introduce DNA with differences that are linked to disease. We study the effect this has on genes. We have found that changes in proteins caused by differences in DNA can increase risk of disease.
- We have used computer-based approaches and taken data published from other studies, more than 50,000 experiments, from human cells and tissue, to understand in which types of cells and tissues changes in DNA can contribute to disease. Our findings will allow other researchers to identify which changes in DNA are more likely to contribute to disease.
- Our results are being used by the scientific field to identify changes in DNA that are more likely to alter risk of disease. The findings have applications to all diseases that have a genetic component, not just those related to diseases of inflammation.

WHAT IMPACT COULD THE FINDINGS HAVE?

Our work will help us, and other researchers, uncover DNA changes that are important for disease processes. There is already demonstratable impact from publication of the results. Other researchers have used our approach to identify important disease mechanisms. We focused on a protein linked to lung inflammation and found a change in DNA that increases risk of severe lung inflammation. This could be a target for drug therapies.

In the future, using our approaches, we aim to identify targets that can be used for therapy, which would help patients and potentially contribute to personalised medicine, by using DNA signatures to predict the people who will have the greatest benefit from specific therapies.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Part of the work undertaken during this project has been disseminated through peer-reviewed publication. In addition, the work has been presented at regional, and international meetings and conferences through poster or oral presentations, including in genetics conferences in Edinburgh, Leicester, Portugal, and the USA, and a clinical conference in Glasgow.

Some of the work has been published in 2024 in the journal Genome Biology. Another part of the project is currently being written for dissemination in a peer-reviewed publication. This part of the work will be presented at international conferences in the UK and Denmark in 2025.

Further work is required to understand how genetic differences produce the effect on disease risk. Further funding will be sought to address this.

CONCLUSION

The differences in DNA between people are part of what define us as individuals. These differences are inherited, and contribute to different risks of disease, including if people get severe forms of common diseases. We have uncovered numerous ways differences in DNA can contribute to disease, and how these can be uncovered by many diseases. This includes changes in DNA that code for proteins, and regions of DNA the control how much protein in present in the cells of a body. Both of these have important contributions to disease. While our work has focused on inflammatory lung disease, we have demonstrated that the principles are applicable to many disease processes.

RESEARCH TEAM & CONTACT

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Additional Information
This funded project was completed on 4th February 2025