Plain language summary of the study looking at genetic differences in the NCIG collection 2023

MOTIVATION - *Why was this study worthwhile; what did we set out to understand?*

The genomes of all people around the world are very similar due to our shared ancestry. However, the small genetic differences that do exist between people can make a big difference to someone's chance of getting a particular disease. Understanding how these differences vary across countries and around the world can explain why people in some communities are more likely to get a particular disease than people in other communities.

This information has been well understood for people from Africa, Europe, Asia, and the Americas for many years and has been used to benefit these people by improving health care.

Our question is, **what are the genetic differences between people from within the same Aboriginal community?**

To increase the value of this information, we compared these differences to those between people from different Aboriginal communities, and from elsewhere around the world.

It is our hope that these results will empower Aboriginal individuals and communities, and the medical field, to know when it is okay to use the same medical treatment for everyone, and when each community will need a different response.

NEW APPROACHES - *Have any new technologies or approaches been used?*

This is the first time enough people have been included from multiple communities to properly compare the geographic distance between people (where people come from) with their "genetic distance" (a measure of shared ancestry).

STUDY – *How was this work carried out?*

We measured ('sequenced') the genomes of 159 people from four communities: 59 from the **Tiwi Islands**, 48 from the Far North Queensland community of **Yarrabah**, 14 people from the Central Desert community of **Titjikala**, and 38 from the North-East Arnhem Land community of **Galiwin'ku** on Elcho Island.

All these people provided informed consent to be involved in this study and we sequenced their DNA from saliva samples collected in the last 10 years.

The DNA sequences (genomes) were compared to each other and to those of people elsewhere in the world using computer programs. The results of this work are being prepared for publication in a scientific journal this year (2023), with the title "Indigenous Australian Genomes Show Deep Population Structure and Abundant Novel Variation".

KEY FINDINGS OF THIS STUDY

The "genetic distance" between Aboriginal ***communities*** is large, compared with how far apart they are on the map, compared to what is seen outside Australia.

The "genetic distance" between ***people*** in each community is generally quite small, and this has been the case for thousands of years.

There appears to have been very little movement of people (migration) between communities over tens of thousands of years. There is some evidence of a very ancient connection between the ancestors of the Tiwi and Galiwin'ku peoples with people from Papua New Guinea, and of a more recent connection between Papua New Guinea and people in Yarrabah.

All these observations mean there are very many genetic differences (or 'variation') in each community that are unique to them, and seen nowhere else.

KNOWLEDGE IMPACT

Aboriginal people know their distinctiveness lies deep in time: our work demonstrates how this has shaped genetic variation over tens of thousands of years.

We highlight two practical consequences. First, there would be an increasing benefit to all if more communities join in the next phase of this work. In fact, the participation of many more communities will be required to build a full picture of Aboriginal genetic variation.

Second, our work shows that only a small number of people, maybe 30 or so, would be need to participate from each community in order to for this to be done, and complete the picture.

POTENTIAL IMPLICATIONS FOR HEALTH CARE

Aboriginal people understand that their communities can be quite distinct from one another, and that this extends to some health difficulties that are faced in some communities but not others.

Our work highlights that diseases that occur more often in one community may be partly caused by genetic variation that is not present in other communities or anywhere else in the world.

It also explains why healthy genes can look very different in different communities. Just because they are different, does not mean they are causing health problems.

Our work suggests that medical programs that seek to understand or treat diseases may need to consider each community on their own, and even in some cases, the close relationships between people within a community. Research and health programs in the broader population will almost certainly need to adjust their methods to properly account for the patterns we have observed.

KEY WORDS

Shared ancestry – close kinship or relatedness recently or many generations ago.

Genomes – A long piece of DNA inside our cells that records ***some but not all*** aspects of shared ancestry.

Genetic differences or **genetic variation** – Small or large differences between people's genomes. Most variation has no effect, but some cause differences between people, including changes that benefit people or cause disease.

Genetic distance – The number of genetic differences between two people that captures ***some but not all*** aspects of shared ancestry.

Genetic size – The amount of genetic variation within one community. Related to, but ***not the same*** as the number of people in a community over many generations.

Migration – The movement of people in the past that resulted in more shared ancestry between communities.