Genetic Portal to our Past and Future

By Will Goodbody

A team of Trinity geneticists have unlocked some fascinating discoveries about the ancestral past of Irish people.

Who do you think you are? What makes me who I am? Where did we come from?

Questions more and more of us are asking these days, as we seek to understand our ancestral past.

Increasingly the answers lie in once futuristic, but now very much present technology.

From DNA testing to online family trees, and digital archives to genealogy apps, there is a wealth of tools available to help us burrow back into our personal history.

But a team of geneticists at Trinity College Dublin is applying a similar approach to something much more important – the development of treatments for neurodegenerative illnesses like Motor Neurone Disease (MND).

In the process they've also made some fascinating discoveries about the genetics of the Irish people, which challenge the axiom that our population is genetically quite homogenous.

"If you are going to be researching the genomics of diseases, you need to have a good handle on what we call population genetics, meaning what differences in our DNA make us uniquely Irish and what differences in our DNA make us susceptible to disease," says Dr Russell McLaughlin, Ussher Assistant Professor in Genome Analysis.

"Those two things can interfere with one another. So if we want to figure out what causes a disease we need to figure out what makes us uniquely Irish, for example, in order to tease those two things out."

Consequently, Dr McLaughlin and Ph.D. student Ross Byrne set out to explore the DNA of regional populations using existing detailed genetic data sets for 1,000 people in Ireland, with and without MND.

A dataset containing the genetic information of about 6,000 people from Britain and mainland Europe was also probed.

The researchers plotted the genetic similarities and differences between all the individuals and then turned it into a data visualisation.

When they did, they were astonished to see

that they were, in effect, looking at a map of Ireland.

"We found that those similarities and differences track very closely to where people are from in Ireland," Dr McLaughlin explains.

"So using only genetic data we can project people onto two axes like latitude and longitude and we can more or less redraw a map just based on genetic data."

People from south Munster are similar to each other and slightly different to people from Leinster, for example, who in turn are similar to each other, they found.

And that continues all the way up the island to Northern Ireland and across to Britain as well, with only a few exceptions.

One, for example, was South Wales where the population appears to have retained a lot of ancient Brittonic variation which differs from the modern Anglo-Saxon distinction that appears to dominate the island.

Another important variation was found in a cluster of individuals whose DNA appears to link them to Northern Ireland but who instead are heavily influenced by Scottish genes.

"Which we reckon is a very direct signature of the Ulster plantations a few hundred years ago," Dr McLaughlin claims.

But the reverse was also true, with some Scottish people also showing signs of Northern Irish genetic variation as well.

"There are several superimposed contacts between Northern Irish and Scottish people which could be driving this affinity between the two populations," the Ballygowan native says.

"Obviously the Ulster plantations is a very prominent driving force in that whole thing. There was also an ancient maritime kingdom called Dalriada which spanned southwest Scotland and northeast Ireland."

"And that probably would have led to quite a lot of exchange of people in very old times. And then actually a constant flux of people between the two islands with economic migrations."

But not only did the genetics reveal clusters of common-descent with remarkable geographic precision. It also provided an insight into historical events.

"What we found is that we can recapitulate, using only genetic data again, historical migratory events such as the Viking invasions in the 10th century and to some extent the Norman invasions and then later the British plantations as well," Dr McLaughlin reveals.

"We found that not only can we find signatures in our DNA of those events, but we can also figure out when they were likely to have happened."

"And we found that it reconstructs the historical record quite accurately."

In all, the research team identified 50 distinct genetic clusters within Ireland and Britain.

Dr Russell McLaughlin, Ussher Assistant Professor in Genome Analysis

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"History shapes our genomes, but you can leave it for hundreds of years and those signatures are still there," he says.

"Everybody's genome carries a story of their ancestry and just using that genetic data alone you can reconstruct that ancestry in really, really exquisitely fine detail."

Their findings, published in the journal *PLOS ONE* might one day prove incredibly important for future studies of disease because the subtle genetic similarities and differences of people on the island could potentially obscure the causes of rare diseases.

"So we need to have a really good handle on exactly how people are similar simply on a population level and that will allow us to further tease apart the contributors towards disease."

It would of course make things easier if the entire genomes of large population samples here could be sequenced, Dr McLaughlin says, as it would allow even more subtle effects to be identified.

As a result, the scientist argues Ireland could benefit significantly from a publicly funded genome-sequencing project, like those underway in some European countries including the UK. The idea is that if you understand the baseline genetic variation that exists in a population, it makes it much easier to build studies that investigate rare causes of certain inherited diseases.

It is estimated that such a programme could cost around €2 million to get up and running it is estimated.

But the payback would be multiples of this, Dr McLaughlin reckons, as the knowledge would lead to better treatment strategies and ultimately more efficient patient management.

"The country, the economy and science development would benefit hugely from that," Dr McLaughlin claims.

In the absence of such a national programme though, the Trinity team is involved in an international effort called Project MinE, which aims to sequence the genomes of 22,500 people with and without Motor Neurone Disease all across Europe, including 1,100 here.

"We will only be generating 350 healthy Irish genomes, but it would be so much better to have thousands of them," he says with a hint of frustration in his voice. That's because to do more will require further hard-to-come-by philanthropic donations.

In the meantime, Russell McLaughlin and his team are hedging their efforts across a range of other possibly promising avenues of MND research.

"When you don't know what causes a disease like Motor Neurone Disease, the best thing in my opinion is to spread your bets across lots of different ideas."

And is he hopeful that one-day genetics will lead to a breakthrough in the research area? Absolutely, he answers confidently.

In 2011, for example, a gene called C9orf72 was discovered to have a strange mutation in it that can cause around 10% of MND cases.

There are now therapies in human clinical trials to directly target that disease, Dr McLaughlin says.

"That's a really nice example to show that a fundamental understanding of this disease inevitably leads to better therapies and treatment strategies and cures and that kind of thing."

"That speaks to the importance of fundamental research in general."

Fundamental research of the present, grounded in our genetic past, may one day unlock the door to a healthier future for millions.

ABOUT THE AUTHOR

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