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Otago family reveals genetic secrets

A chance discovery of recurring mildly low blood platelets in a local family has led University of Otago researchers on a fascinating international collaborative journey to unlock genetic secrets that could prove vital in the battle against major diseases.

Dr Ian Morison from Otago's Department of Biochemistry says the research - just published in prestigious journal Nature Genetics - started more than 10 years ago, with one family member whose surgery was cancelled due to mildly low platelets.

"Some blood tests later, we knew we had found a condition that had never before been described."

The low level of platelets - the cells in the blood that help stop bleeding - was not causing any great problem for affected family members, aside from slightly more bruising than usual.

But it was enough to trigger the curiosity of Dr Morison and his team and they began their search for the gene responsible.

"It was one of those amazing needle in a haystack stories, to find a single letter among three billion letters of DNA within the genome that was shared by this family but not by others," Dr Morison says.

Fortunately for the researchers, a family genealogist had already tracked the family tree back to 1831 and beyond - at a time when their ancestors were mining tin in Cornwall.

They were able to trace each branch of the family and eventually gathered blood samples from 80 family members, finding about 30 with low platelets. Those samples helped them begin their search for the elusive letter and, after three years, they had narrowed it down to a small section of the genome with only one million letters.

When they eventually found the change unique to the family, it provided quite a surprise. The gene in question affected a protein called cytochrome c - a well-known protein that is an essential part of a cell's energy production.

What was even more surprising was that the mutation affected part of the protein that has remained exactly the same for two billion years across a broad range of living organisms, from yeast to the grey whale.

The mutation does not affect energy production. Instead, it affects a second, recently-discovered role of cytochrome c - the control of programmed cell death, or "cell suicide", a natural process necessary for maintaining the correct number of cells in the body.

Work by Paris-based platelet expert Professor Elisabeth Cramer-Bordé from the Institut Cochin found that platelet production was remarkably abnormal.

Megakaryocytes, which are the bone marrow cells that produce platelets, were dying early and releasing their platelets into the bone marrow space, instead of into the circulation.

This was backed up by studies in the laboratory of another Otago biochemist Dr Liz Ledgerwood, showing that the mutation makes cytochrome c better at triggering cell death.

Dr Ledgerwood says conventional wisdom suggests affected family members would be ill or die young from brain disease. However the family members are generally healthy and long-lived.

"Answering this paradox will be immensely important in understanding a critically important normal cellular process," says Dr Ledgerwood.

"Correctly-controlled cell death is very important. In cancer, cells don't die when they should, while in Alzheimer's they die prematurely.

"Using the information gained from studying this unique New Zealand family, we hope to be able to develop new ways to modify the death process. This may help treat some of the diseases that involve abnormal cell death in the future."

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