Cold cases gone hot: Researchers solve decades-old medical mysteries using genetics

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The mystery began in 1976. Adolfo Pampena was diagnosed with a rare form of cancer that caused a strange combination of symptoms and was associated with the occurrence of multiple tumours in his stomach and colon. His medical team was stumped and was unable to answer the most important questions for him and his family: the cause of his disease and the risk for future generations.

Now, 35 years later, the answers are at hand thanks to a genetic study led by investigators at the Research Institute of the McGill University Health Centre (RI MUHC), the McGill Program in Cancer Genetics at the Gerald Bronfman Centre for Clinical Research in Oncology and the Lady Davis Institute for Medical Research at the Jewish General Hospital. The study was recently published in *The* New England Journal of Medicine.

The researchers were able to pinpoint the gene responsible for the disease (BUB1B), which is involved in the regulation of chromosomal separation. Instability during cell division can result in chromosomes ending up in the wrong place, which can lead to the development of tumours. "The general significance of this discovery is that individuals can be seen at our genetic clinic with an unknown condition and end up with a diagnosis that is relevant to patients and their families," said Dr. William Foulkes, senior author of the study and a researcher in genetics at the RI MUHC, the Lady Davis Institute.

"My father and family were relieved that the cancer risk for other family

members is much less than we thought," said Mary Pampena, Adolfo's daughter. "Now we know more about my father's genetic history and the cancers he had. We know what screening test to do in the future. This is important information for us, our children and future generations."

In another study published in the January, 2011 Journal of the American Medical Association (JAMA). Dr. Foulkes details a second solved mystery involving five families with a long history of nontoxic multinodular goiter (MNG). Goiter is a thyroid disease which can lead to extreme swelling of the neck or larynx. The most common form of the disease is not genetic and is due to iodine insufficiency. However, this form of MNG was known to be genetic, but to date, no one had ever localized the specific gene or mutation responsible. Dr. Foulkes, Dr. Marc Tischkowitz (from the Program in Cancer Genetics and the Lady Davis Institute) and their team finally succeeded, and found the mutation in a surprising place.

As it turns out, the mutation, in a gene called DICER1, was extremely unusual, Foulkes said, who is also James McGill Professor of Medicine, Human Genetics and Oncology and Director of the Program in Cancer Genetics at McGill University. "It changes the protein in only one place, and that single change is enough to trigger multinodular goiter. Generally speaking, when you have a mutation in a disease gene, it causes a multitude of problems, not just one illness. But in this case, we have no evidence that it causes anything except goiter.

Intriguingly, women in three of the families had been diagnosed with an unusual type of ovarian tumor called Sertoli-Leydig Cell Tumor and thus Foulkes and his colleagues were able confirm that there is a genetic link between multi-nodular goiter and these rare tumors. This link had first been postulated in 1974.

"In the future, our challenge as researchers is to be able to help people

with an unknown condition by finding out rather quickly what the genetic cause of their problem is" explained Foulkes. "We can hope in the long-term to have an impact on treatment, diagnosis and other aspect of management."

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