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New genetic cause of epilepsy found

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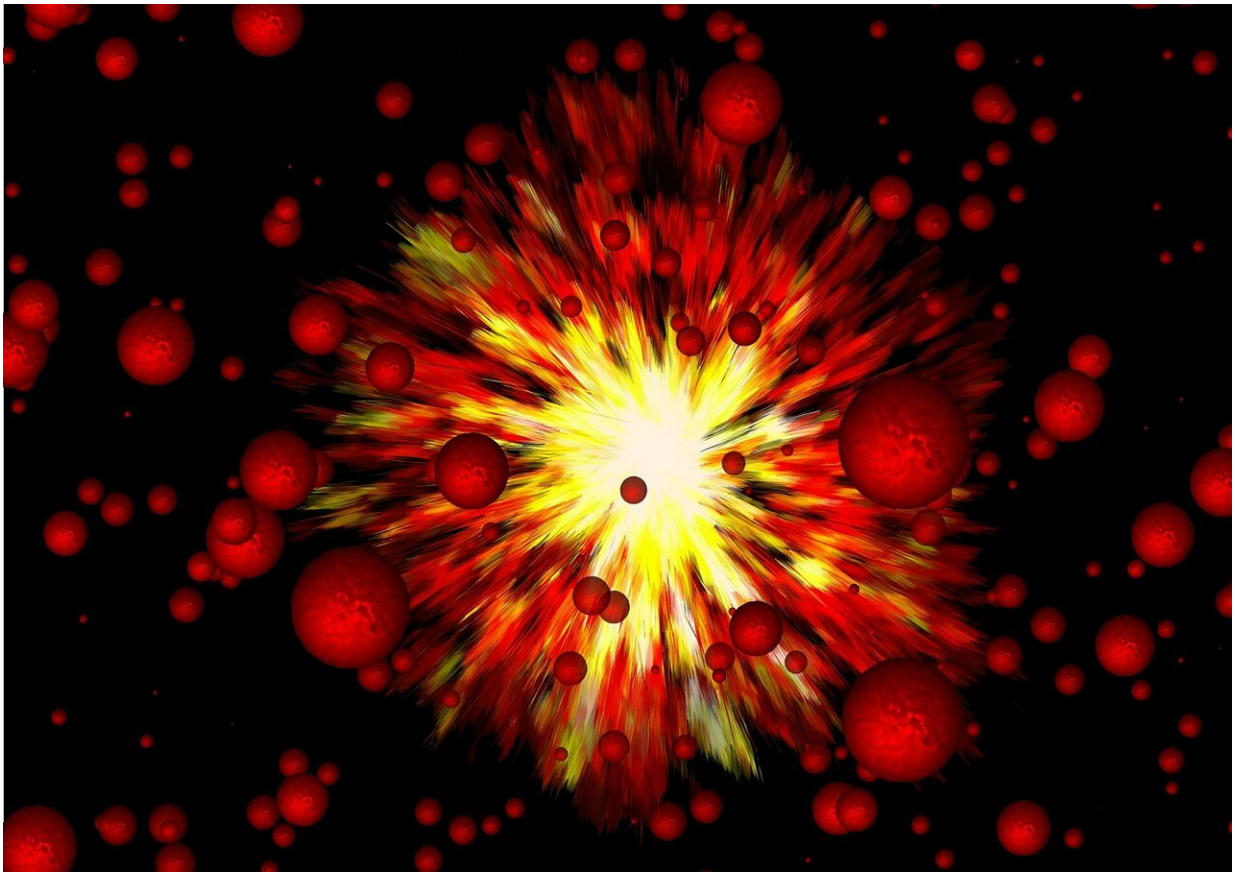

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Researchers from the Walter and Eliza Hall Institute have contributed to a decades-long global effort that has revealed two new gene mutations that cause a rare type of epilepsy.

The Institute research team also traced one genetic mutation back to its origin; an individual with the spontaneous mutation who lived more than 5000 years ago. The team developed technologies that can detect the specific mutations—called repeat expansions—even in small sample groups, and the tools to trace the ancestry of a mutation to its origin.

The discoveries were published in back-to-back papers in *Nature Communications*. Dr. Mark Bennett, Dr. Haloom Rafehi and Professor Melanie Bahlo from the Institute were part of the international consortium, which included clinicians, bioinformaticians and biologists from Australia, Germany, France and the Netherlands.

Repeat problems

Familial adult myoclonic epilepsy (FAME) is a rare form of epilepsy that runs in families and typically begins in a person's 20s or 30s. It is caused by a "dominant" genetic mutation meaning that, even though it is rare in the general population, children of affected parents have a 50/50 chance of inheriting the disease. There are several subtypes of FAME, dubbed FAME1, FAME2, FAME3 and FAME4.

Institute researchers have been part of a dedicated international effort, spanning two decades, to hunt the genetic cause of these epilepsies. Now, researchers have discovered the mutations—in the genes STARD7 and MARCH6—that cause FAME2 and FAME3, respectively.

The genetic mutations are an unusual type called repeat expansions. Repeat expansions are typically associated with neurological diseases, including Huntington's disease, ataxia, autism and FAME.

Dr. Rafehi said discovering the genetic cause of this disorder could help to diagnose patients with FAME and other neurological diseases caused by repeat expansions.

"We know that a genetic diagnosis is very important for patients—it provides answers, and allows them to progress with family planning options and potential treatments," Dr. Rafehi said.

"And now, for the first time, families with suspected FAME can be referred for testing, with a high chance of obtaining a life-changing, definitive genetic diagnosis."

A decades-long mystery

The Bahlo lab has developed highly specialized bioinformatics tools to identify repeat expansions, putting them at the forefront of the search for these rare disorders.

Dr. Bennett said researchers worldwide had spent more than two decades searching for the genetic mutations that caused FAME in families from Australia and around the world.

"In the past year, there has been a breakthrough in determining the genetic cause of familial adult myoclonic epilepsy, with the discovery that this disease is caused by a repeat expansion," Dr. Bennett said.

"Detecting repeat expansions in DNA can be very difficult. Our laboratory has developed a tool called exSTRa (expanded short tandem repeat algorithm) that can search the entire genome for repeat expansions, even with small data sets. This is important because typical analysis methods cannot detect repeat expansions, so they are often ignored as a cause of disease."

He said the Institute research team used exSTRa to independently verify the genes that were mutated in these families with FAME.

"Many of these patients have been waiting for years—even

generations—to know the cause of their disease. Thanks to this discovery, they finally have an answer," Dr. Bennett said.

"Identifying the genes linked to FAME is an important step in understanding this disease, which we hope will ultimately lead to better diagnostic and treatment options for patients."

An age-old question

Dr. Rafehi developed software that enabled the researchers to trace the genetic family tree of one of the mutations, MARCH6.

"By comparing the DNA sequence located around the mutation, we were able to show that all patients with subtype FAME3 have the same mutation of MARCH6, which tells us they are all distant relatives," Dr. Rafehi said. "We were also able to estimate the age of the mutation, and showed that FAME3 began as a single, spontaneous mutation in a European individual 253 generations—more than 5000 years—ago."

Dr. Rafehi said estimating the age of a genetic mutation was not just a curiosity, it also provided valuable information about the disease and its pattern of spread.

"This discovery tells us that mutations in the MARCH6 gene are uncommon, and unlikely to arise again independently. It also confirms that FAME3 is likely restricted to European populations, whereas other forms, such as FAME1, are unique to Asia. We have now published a website that enables researchers around the world to use our algorithm to study other genes of interest, helping to discover the cause and spread of more genetic diseases."

More information: Unstable TTTTA/TTTCA expansions in MARCH6 are associated with Familial Adult Myoclonic Epilepsy type

3, *Nature Communications* (2019). DOI: 10.1038/s41467-019-12763-9

Mark A. Corbett et al. Intronic ATTTC repeat expansions in STARD7 in familial adult myoclonic epilepsy linked to chromosome 2, *Nature Communications* (2019). DOI: 10.1038/s41467-019-12671-y

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