Medical Mysteries

This is a series that spotlights rare diseases or unusual conditions.

Cracking the code

Diagnosing rare medical conditions can take up to 15 years

There are about 3,000 people in Singapore who live with a rare disease

Judith Tan
Correspondent

For men and women suffering from medical conditions and diseases so rare they are practically unheard of, finding a cure – or at least relief from symptoms – often feels impossible.

In fact, having a rare disease – defined as one that affects fewer than one out of 2,000 people – feels like drawing the short straw at birth.

Since they are so few and their symptoms are often non-specific, many conditions can slip through the cracks or go unnoticed, said Adjunct Associate Professor Chin Hui-Lin, a geneticist with the National University Hospital (NUH).

There are about 3,000 people in Singapore living with such conditions, and while some were diagnosed in infancy, others were diagnosed only in childhood or adulthood.

Thus far, 7,600 genetic diseases have been identified, and more are being discovered every year. Genetic disorders are usually caused by differences or changes in a person's genes. While many genetic conditions are inherited from parents who are affected or are carriers, some can arise in children even when neither parent has the condition, Prof Chin said.

New mutations can occur in a sperm or an egg cell, or during early embryonic development. At that stage, every time a cell splits, the DNA needs to be replicated in both parts.

Geneticists said it is less like photocopying, and more like manually typing, which means errors can occur.

Often, genetic testing may not be done early for a patient with a rare condition, as most doctors test for common treatable conditions first, among other considerations.

"Medical teams may defer genetic evaluations due to prevailing beliefs that most genetic conditions lack curative treatments, but rapid advances in the field (of medicine) are changing this," said Adjunct Associate Professor Chan Yee Cheun, a senior consultant with the division of neurology in the department of medicine at NUH.

He cited home baker Poonam Choudhary, 43, as an example.

Ms Poonam began experiencing sudden weakness in her legs in 2018, causing her to fall.

With doctors suspecting that her condition was due to a spinal dysfunction, she was put through scans and blood tests to ascertain its cause.

"Among them was vitamin B12 deficiency. (Ms Poonam) was found to have very low vitamin B12, and that was thought to be the main reason, and so the treatment was focused on that, and she responded well," Prof Chan said.

But her condition deteriorated, and by 2025, an MRI scan showed more abnormalities in her brain.

"We were also very puzzled that while the vitamin B12 levels were improving, her homocysteine levels continued to rise," Prof Chan said.

Homocysteine is an amino acid in the blood that can lead to cardiovascular disease, stroke, blood clots and cognitive decline, including memory loss, confusion and fuzzy thinking or brain fog.

(From left) Genetic counsellor Shreya S Shetty, senior consultant Chan Yee Cheun, senior resident Lau Kin Mun and geneticist Chin Hui-Lin. The hope of many geneticists is for physicians and patients to consider the possibility of a genetic cause for the disease earlier to avoid a diagnostic odyssey for the patient, said Adjunct Associate Professor Chin. ST PHOTO: GIN TAY

TURNING TO GENES

Usually, when a patient's condition does not improve, specialists from different disciplines tend to float the issue to colleagues in the genetic field, often as a last resort.

This is where Prof Chin and her team take over.

The specialists at the division of genetics and metabolism at NUH work hand in hand with numerous disciplines across the institution to unlock clues presented by seemingly puzzling symptoms, aiming to give answers to patients who may otherwise spend years without answers about their ailments.

According to statistics from the National Center for Advancing Translational Sciences in the US, it can take between three and 15 years before a rare disease is accurately diagnosed, giving patients answers "as early as possible so that they have the best chance at a better outcome", Prof Chin said.

A timely diagnosis translates to earlier discussions with patients about treatment options, prognosis and anticipatory care, providing some level of certainty and assurance in difficult circumstances.

"Having worked with the different disciplines, especially the neurology team, I would do due diligence by going through the list of investigations previously carried out, and knowing the teams are thorough, I would be able to just focus on the potential genetic causes of the conditions," Prof Chin told The Sunday Times.

In Ms Poonam's case, Prof Chin said that when she reviewed the results of the patient's biochemical tests, she noticed that her vitamin B12 and folate levels were low, accounting for some of her symptoms.

But when B12 was administered and there was incomplete resolution of symptoms, Prof Chin turned to defects in either Ms Poonam's metabolism or genes for the answer.

"This is extremely rare. We have perhaps seen a couple of cases in the last 10 years, but having that experience led us to suspect that it could be methylenetetrahydrofolate reductase-related autosomal recessive hyperhomocysteinemia," Prof Chin said.

The condition affects approximately one in 100,000 to one in 200,000 people and leads to elevated levels of the amino acid homocysteine.

For patients like Ms Poonam, who are grappling with the uncertainties of a possible rare disease diagnosis, genetic counselling offers tailored information, guidance and support to help them understand their condition, navigate testing options and make informed decisions about their care.

An important member of Prof Chin's team is Ms Shreya S Shetty, a genetic counsellor.

Though not medically trained, Ms Shreya is pivotal in working with the doctors to explain the benefits, risks and usefulness of genetic testing to patients, while also coordinating the testing process for them.

"I help patients make informed decisions regarding diagnosis and even reproductive choices, should they want to have children. The goal here is to empower patients with knowledge and support in navigating genetic health decisions and management," she said.

Once the genetic cause was ascertained, Ms Poonam was prescribed betaine in November 2025 to help clear the hyperhomocysteinemia.

"We have seen significant improvements in her cognitive function, memory, movement and coordination," Prof Chin said.

"The hope of many geneticists is for physicians and patients to consider the possibility of a genetic cause earlier in the healthcare journey to avoid a diagnostic odyssey for the patient," she added. "This way, patients who achieved a diagnosis (early) could have different treatment options made available."

juditht@sph.com.sg