Fast-tracking rare disease diagnosis and treatment

Patients with RARE GENETIC DISEASES often have to wait years for a diagnosis. By harnessing the power of DNA sequencing, the Genomics Thailand Initiative aims to reduce this to weeks.

Rare diseases affect more than five million people in Thailand, and roughly 80% are caused by changes to DNA. While standard pathways to rare disease diagnosis can take up to seven years, new sequencing technologies that read large portions of a person's DNA have the potential to offer diagnosis in weeks, if not days.

One of the reasons rare diseases take a long time to diagnose using standard tests is that there are roughly 7,000 rare diseases on record. "Because these diseases are so rare, it's impossible for doctors to have experience in diagnosing and treating all of them," explains geneticist, Vorasuk Shotelersuk, at Chulalongkorn University.

To help join up rare disease resources, between 2016 and 2020, Chulalongkorn University funded the creation of the Center of Excellence for Medical Genomics, which allied with the Excellence Center for Genomics and Precision Medicine at the King Chulalongkorn Memorial Hospital to begin forming a national network for rare and undiagnosed diseases.

The centre has already sequenced the genomes of 4,000 individuals with rare diseases, and, if fast tracked, it can produce reports for clinical interpretation within a fortnight. "Rapid whole-exome sequencing data has helped to diagnose 55% of the critically ill patients we've sequenced," Shotelersuk says. "In half of the cases, the diagnosis has led to changes in treatment management."

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Fast diagnosis focus

The country has been an early adopter of sequencing technology for rare diseases. "Thailand started sequencing patients' genomes in 2012, and since then Chulalongkorn University has been leading efforts to build knowledge and human resources to accelerate diagnosis of rare diseases," explains Shotelersuk.

To further drive the general use of genomic information in clinical care in Thailand, in 2019 the government allocated 4.5 billion baht (US$150 million) to the Genomics Thailand Initiative — a project driven by the Ministry of Public Health, the Ministry of Science and Technology and the Ministry of Education in Thailand — for the period between 2020–24.

In December 2019, Genomics Thailand established the Thai Society of Human Genetics, which will bring together clinical geneticists, healthcare personnel, bioinformaticians and scientists to explore how genomics can help medical practice and the best way to integrate new knowledge into the healthcare system.

"Clinical next-generation sequencing clearly benefits patients with rare diseases and their families," says Shotelersuk. Even if it doesn't lead to changes in treatment or outcome, accelerating the diagnosis of rare diseases can help patients and their families psychologically, socially and financially. It also saves the healthcare system the cost of further investigative procedures. Furthermore, it may allow parents to make informed reproductive decisions that reduce the risk of having children afflicted with serious impairments.

Single-gene knockout lessons

Genomics Thailand also aims to sequence the genomes of 50,000 people for further study, including those with rare and undiagnosed diseases in which the relevant genetic markers may still be unknown.

Identifying new genes associated with rare disease is the first step towards understanding the role of their products in disease progression, knowledge that is vital in order to develop effective treatments.

Furthermore, insight gained from rare diseases not only benefits the patients, but can also reveal information about normal biological processes, health, and the pathological mechanisms of other, more common diseases.

Genetic diversity means that each region of the world will be able to make unique and vital contributions to genetic research, says Shotelersuk. For example, thalassemia, which disrupts red blood cell development, has been reported to confer resistance against malaria, and shows greater incidence rates in malaria-prone regions of the world, including Thailand. A recent international gene-therapy trial involving Thai thalassemia patients has had promising results.

Vorasuk Shotelersuk and his team at Chulalongkorn University use genomics to speed up rare disease diagnosis.

In addition, patients with rare diseases are "naturally occurring single-gene knockout humans", says Shotelersuk, meaning they often have a mutation in just one gene. As such, they offer a unique opportunity to study the role of that gene. "Of 20,000-plus protein-coding genes in the human genome, we still know very little about their normal functions and how they are associated with disease."

To date, new human disease genes already identified through genome sequencing of Thai patients include the *MBTPS2* gene, which underlies a rare form of a bone-growth disorder, and *KIF6,* which is associated with intellectual disability. Shotelersuk has also identified that the addition of extra base pairs in the *YEATS2* gene is associated with a rare epileptic and movement disorder syndrome. These open new avenues to investigate the mechanisms underlying bone and neurological development.

Because there are so few study subjects, international collaborations are essential to accelerate discoveries and to share knowledge and treatment experiences of rare diseases, says Shotelersuk.

After winning the UK-based Newton Prize in 2017, he has been collaborating with Philip Beales at UCL Great Ormond Street Institute of Child Health in the UK on creating a workflow to facilitate the diagnosis of rare genetic diseases in children. Shotelersuk also exchanges rare disease genetic knowledge through the Undiagnosed Diseases Network International (UDNI), led by William A. Gahl of the National Institutes of Health in the US.

"Our next steps include strengthening international collaborations to ensure that the benefit of our research reaches patients and people all over the world." ■

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