UNLOCKING RARE DISEASE TREATMENTS FOR SICK CHILDREN

Close collaboration between clinicians and researchers can lead to IMPROVED DIAGNOSES AND BETTER OUTCOMES FOR YOUNG PEOPLE WITH RARE AND UNDIAGNOSED CONDITIONS.

A programme focused on securing timely diagnoses and offering precision treatment in patients with new diseases is improving health outcomes for children in South Korea.

Seoul National University Children's Hospital (SNUCH) launched the Korean Undiagnosed Disease Program (UDP) in 2017. The programme has played a pivotal role in establishing a nationwide network for the precision diagnosis and treatment of rare paediatric diseases.

As the main children's hospital in South Korea, SNUCH sees many young patients with undiagnosed health conditions, says Eun Hwa Choi, the hospital's director. A key strength of SNUCH in tackling these cases is the close link between research and clinical work, she says. It enables researchers and clinicians to develop, test and then rapidly implement new diagnostic and treatment technologies that are feasible and valuable in a clinical setting.

SNUCH innovations under the UDP include a rapid genomic diagnosis platform that uses next generation sequencing technology to diagnose 254 treatable, but ultra-rare, genetic diseases in young children and newborns. "This platform enables swift diagnosis — within a week — and the chance for early treatment to alter the course of patients' conditions," explains Jong-Hee Chae, leader of the paediatric neurology team at SNUCH.

Prior to launching the UDP, SNUCH already had a strong track record of rare and undiagnosed disease research and treatment, says Chae. She has represented South Korea in the Undiagnosed Disease Network International (UDNI) initiative since 2016, and it was Chae who secured a grant to launch the UDP in 2017.

DATA DRIVEN PRACTICE

Chae heads SNUCH's neuromuscular clinic. As one of the largest in Korea, at any given time it manages about 2,000 patients with various neuromuscular disorders. Most neuromuscular disorders are considered rare diseases.

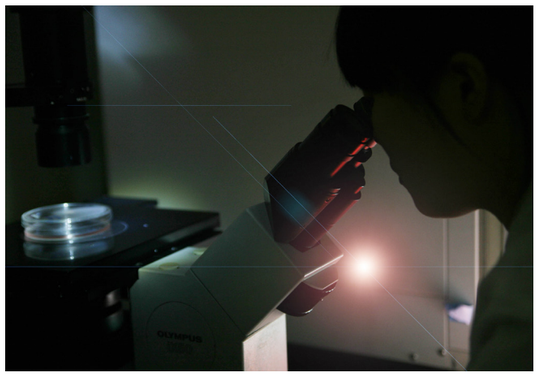
"My research is particularly focused on developing new diagnostic technologies in a clinical setting, discovering new diseases and unravelling their underlying mechanisms," Chae says. She also develops novel treatments and conducts clinical trials for promising therapeutics in this field.

"When it comes to diagnosis, we have consistently pushed the boundaries to integrate emerging genomic technologies into clinical settings," Chae says. The clinic is implementing advanced technologies such as long-read sequencing and RNA sequencing, along with single-cell genomes. It will play a key role in South Korea's whole genome project in rare diseases, which will launch in 2024.

The clinic now diagnoses 50 to 100 new patients every year with neuromuscular diseases such as muscular dystrophy, congenital myopathies and mitochondrial disorders. "We are continuing to accumulate genome data to further enhance our understanding and treatment of neuromuscular disorders," says Chae.

SMART NEUROSURGERY

SNUCH researchers work across multiple areas of rare disease research, including personalized, gene-targeted therapeutic approaches for congenital and acquired diseases. At the Paediatric Clinical Neuroscience Center, Seung-Ki Kim is working alongside other researchers and clinicians to develop new targeted therapies and surgical techniques to treat various brain tumours and rare diseases.



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▲ **Seung-Ki Kim at Seoul National University Children's Hospital (SNUCH) studies brain tumour cells to develop targeted therapies to treat the condition (left). Researchers at SNUCH are leveraging genetic analyses to rapidly diagnose and treat rare diseases (right).**

▲ **Seoul National University Children's Hospital sees many children with rare or undiagnosed health conditions, referred from healthcare centres from all over South Korea as well as from outside the country.**

One such disease is moyamoya disease.

This uncommon disorder, which affects children and adults, is characterized by the progressive narrowing of large arteries within the brain and the subsequent development of small collateral blood vessels around the blockage, which can lead to ischemic stroke or intracranial hemorrhage.

"My research into the pathophysiology of moyamoya disease has identified the gene responsible for the condition, established novel cell models and suggested potential new therapeutics," Kim says. Through clinical investigation, he also demonstrated the remarkable long-term effectiveness of indirect bypass surgery in preventing strokes in people with moyamoya disease. This surgical intervention achieved a 10-year stroke-free survival rate of 99.2%, and a 10-year hemorrhage-free survival rate of 99.8%.

GENETIC UNDERPINNINGS

Recent work at SNUCH to improve rare disease diagnosis and treatment builds upon strong foundations. Skeletal disease is one area where SNUCH has a long track record of pioneering rare condition diagnosis. Professor of paediatric orthopaedics, Tae-Joon Cho, has combined his clinical and research experience to establish genetic diagnosis and improved treatment of several genetic skeletal diseases.

"OUR EFFORTS SIGNIFICANTLY IMPROVED THE DIAGNOSTIC JOURNEY FOR RARE DISEASE PATIENTS."

Because of the large number of patients he saw as a surgeon, Cho and his team were able to then identify the causative genes for a number of rare conditions. "Finding the causative gene provides the tools — like being given a map and a compass in the middle of the desert — to develop better treatments," he says.

One disease for which Cho identified the causative gene is osteogenesis imperfecta type V, a rare skeletal disorder characterized by weak bones that fracture very easily. He also devised a novel surgical implant and surgical technique to treat osteogenesis imperfecta. The technique has become popular with surgeons globally, he says.

Cho and his team have also identified the mechanism of another rare condition, congenital pseudarthrosis of the tibia, a deformity in the lower leg leading to fractures that don't heal. The treatment for this disease is a difficult surgical intervention, which Cho describes as one of the most challenging in paediatric orthopaedic medicine.

Cho uncovered the disease mechanism using patient tissue obtained during surgery, which has led to better patient outcomes by providing surgeons with the theoretical background to the condition. "The basic research on patient tissue has explained why some procedures work in certain cases and others do not," he says.

BUILDING A GENOME BANK

"Before the national UDP, patients often endured long diagnostic journeys and received incorrect treatments," says Chae. "Our efforts have significantly improved the diagnostic journey for rare disease patients."

Further gains should come from increased collaboration and data sharing with local and international researchers to help uncover even more new genes and patho-mechanisms underlying rare conditions in children, Chae adds. The goal is to build a genome bank for rare diseases to assist in the discovery of new genetic diseases, she says. Importantly, it will be freely accessible to all researchers globally.

"The abundance of genomic data gathered from the Korean population is valuable for diagnosing rare diseases in other Asian populations, and we are actively working to expand our network regionally to include other regions within the Asia-Pacific," Chae says. ■

SNUCH will host the tenth anniversary meeting of UDNI in Seoul in September 2024.

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