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Genome sequencing provides diagnosis for some types of intellectual disability

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A study published today in the *New England Journal of Medicine* is one of the first to show the life-changing benefits of genome-wide sequencing for children with certain kinds of intellectual disability. The work was led by researchers at BC Children's Hospital, an agency of the Provincial Health Services Authority, and the University of British Columbia.

The researchers diagnosed 68 per cent of the 41 families in the study with the precise underlying genetic condition and, based on this, were able to offer targeted treatments to more than 40 per cent of cases. They also discovered 11 new disease genes and described new physical traits and symptoms associated with a number of known diseases.

"This research is very encouraging because for a subset of patients we can identify the genetic underpinning of their intellectual disability and then determine the right intervention," says Dr. Clara van Karnebeek, the study's lead author, a paediatrician and biochemical geneticist at BC Children's Hospital, and principal investigator in the Centre for Molecular Medicine and Therapeutics at the University of British Columbia. "There's a bright future ahead for personalized medicine informed by genetic diagnosis."

Some people's intellectual disability is due to rare genetic conditions that interfere with the processes the body uses to break down food. Because of these metabolic dysfunctions, there is an energy deficit and build-up of toxic substances in the brain and body leading to symptoms such as

developmental and cognitive delays, epilepsy, and organ dysfunction. Some of these rare diseases respond to treatments targeting the metabolic dysfunction at the cellular level and range from simple interventions like dietary modifications, vitamin supplements and medications to more invasive procedures like bone marrow transplants. Because the right treatment can improve cognitive functioning or slow or stop irreversible brain damage, early intervention can improve lifelong outcomes for affected children and their families.

Dr. van Karnebeek's work is changing the paradigm for diagnosing and treating these conditions. In previous research, her team developed a mobile app that helps clinicians review the intellectual disability patient's symptoms and arrive at diagnosis as early as possible, based on the best available evidence.

The goal of the current study was to diagnose patients with genetic conditions and discover and describe new diseases with potential for treatment. The study included patients with neurodevelopmental conditions that doctors suspected were genetic or metabolic in origin but had not been diagnosed using conventional methods. All the children in the study were referred by clinicians at BC Children's Hospital with the exception of three international patients.

Dr. van Karnebeek and her team tested the children and their parents using a combination of metabolomic (large scale chemical) analysis and a type of genomic sequencing called whole exome sequencing. With this state-of-the-art technique, experts analyze and interpret the portion of DNA that codes for proteins.

During the study, researchers discovered a new genetic disease called carbonic anhydrase VA deficiency that presents during early childhood with life-threatening sleepiness and coma due to hyperammonemia (the build-up of a toxin if the body's cells cannot properly break down

proteins into energy). Researchers found that a drug called carglumic acid can prevent brain damage in children with this condition.

The researchers also discovered a new metabolic disease called glutamic oxalo-acetic transaminase 2 deficiency that affects the brain and is characterized by small head size, seizures, and developmental delays. Treatment with an amino-acid called serine and vitamin B6 improved the symptoms.

The study also provides insights into brain development and functioning. For example, the importance sialic acid production for normal brain and bone development was demonstrated by the discovery of NANS deficiency in one of the TIDEX study patients. Detailed description of this disorder in nine individuals from B.C. and Europe with bone abnormalities and intellectual disability, along with a potential treatment target, will be published on May 23rd in Nature Genetics, by Dr Superti-Furga (Lausanne, Switzerland) and an international group including Dr. van Karnebeek.

"Our findings open the door to life-changing treatments for a small yet meaningful percentage of patients," says Dr. van Karnebeek. "We're learning more about brain function and the mechanisms underlying intellectual disability. These results are meaningful to individuals around the world who suffer these rare conditions."

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