Researchers identify a new cause of childhood mitochondrial disease

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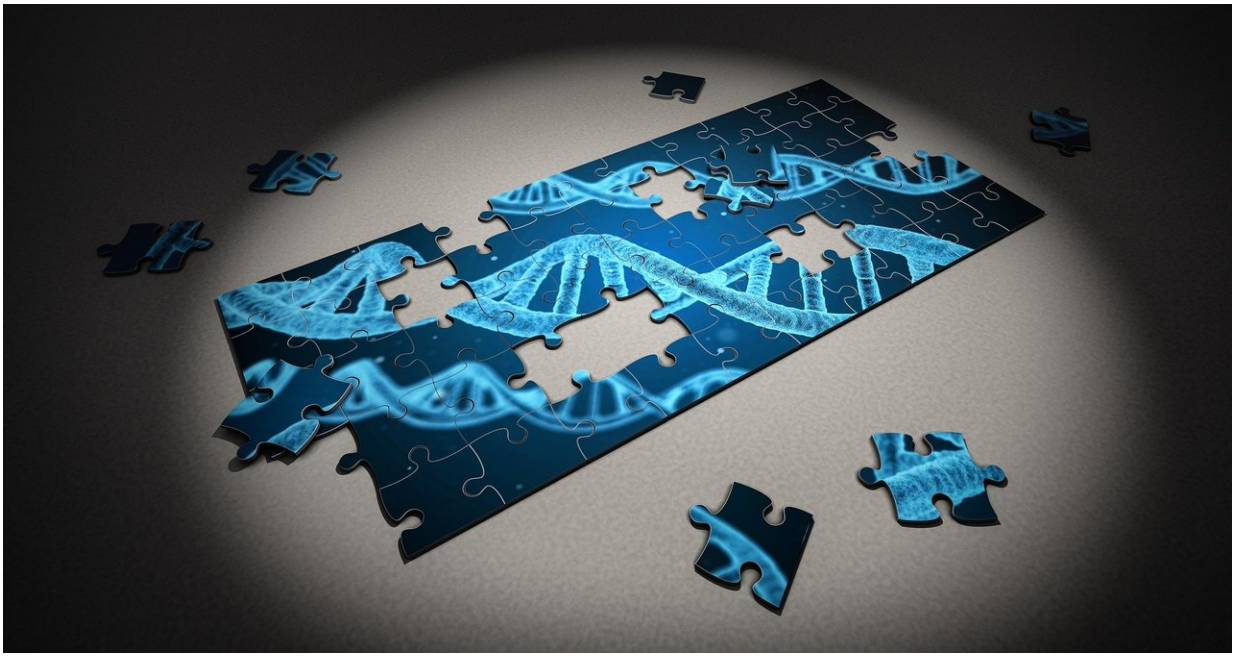

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A rapid genetic test developed by Newcastle researchers has identified the first patients with inherited mutations in a new disease gene.

The team of medics and scientists, led by the Wellcome Centre for Mitochondrial Research at Newcastle University, found four children with defects in a building block of complex I called NDUFA6.

Mitochondrial diseases are genetic conditions affecting the batteries of the cell, with around one in 4,300 affected children born every year. Symptoms include muscle weakness, blindness, deafness, seizures, learning disabilities, diabetes, heart and liver failure. There is no cure and affected children often sadly die in early infancy.

Publishing today in the *American Journal of Human Genetics*, the researchers identify the four cases—three of whom are children in the UK. The first child was identified in Newcastle using a rapid gene test, another child was identified as part of the "Next Generation Children" project in Cambridge, the third child was a identified by the Highly Specialised mitochondrial laboratory in Oxford whilst the fourth patient was a young boy born in Germany.

Each of these children was found to have new genetic variants that affect a protein that's essential for normal mitochondria, the "batteries of the cell". Knowing that these new variants cause a defective NDUFA6 building block means that scientists worldwide can easily recognise them as a cause of human disease.

Lead author, Dr. Charlotte Alston at Newcastle University, whose research was funded by the National Institute for Health Research (NIHR), said: "You can think of the genetic variants or defects in the building block as spelling mistakes. Genetic tests, such as the 100,000 genomes project, are very good at finding out what variants are in each patient, the problem is that we all have thousands of them—they are what makes each of us unique. In fact, only a very small number of variants cause something sinister, like mitochondrial disease. The challenge is working out which of the spelling mistakes are important. It is often very difficult and can take years of painstaking research to prove that the variants we find in our patients are the cause of their disease."

"For our patients, it is important to pursue this because it gives parents

an answer to why their child was poorly. It also offers them some choices for the future—if we know what disease-causing spelling mistakes run in the family, we can test their next children at an early stage of pregnancy to see if they will be healthy. Hopefully we can prevent them having to suffer the loss of any more children to this devastating and incurable disease."

Finding the correct genetic diagnosis is important to families as it means that they can find out what is wrong with their child and enable doctors and scientists to help them understand the risks to their future children and help prevent them losing another child. For a family with one child affected with this type of mitochondrial disease, there is a 25% chance of each further child being affected with the devastating condition.

Professor Rob Taylor from the Wellcome Centre for Mitochondrial Research, who also leads the NHS Highly Specialised Mitochondrial Diagnostic Laboratory at the Newcastle Hospitals NHS Foundation Trust says: "We are able to offer this test on the NHS which ensures we are world-leading in this field and providing the best diagnostic service for our patients, which is free at the point of need."

Highly-specialised mitochondrial services are NHS funded and streamlined across the country so this genetic test is now available within routine practice to patients nationally.

More information: Alston et al., Biallelic Mutations in NDUFA6 Establish Its Role in Early-Onset Isolated Mitochondrial Complex I Deficiency, *American Journal of Human Genetics* (2018), doi.org/10.1016/j.ajhg.2018.08.013

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