# Major cause of rare genetic mitochondrial disease identified

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A cutting-edge study from the Murdoch Children's Research Institute (MCRI) has given hope to families of children born with a fatal heart muscle disease caused by faulty cell machinery.

The research, published in *Med*, a new journal from Cell Press, has found disruptions in the ATAD3 gene cluster caused fatal heart failure soon after birth. But because the gene cluster disruptions arose spontaneously, parents have a low risk of having further children with the same disease.

Mistakes in any one of around 350 genes can cause mitochondria, the powerplants inside our cells, to fail. This results in what are collectively called mitochondrial diseases, severely affecting at least one in 5000 people.

Often fatal, mitochondrial diseases can affect single organs or whole-body systems resulting in a spectrum of symptoms and syndromes. Because these diseases are caused by genetic errors, there is no cure. Existing treatments do not delay disease progression and most children with mitochondrial disease die before adulthood.

By carefully re-examining genomic data from 17 babies from families in Australia, Japan, New Zealand and the Netherlands, the new research, led by Professor David Thorburn and other senior MCRI genetics researchers, has confirmed ATAD3 as the most common cause of lethal mitochondrial disease soon after birth.

Professor Thorburn said, "The ATAD3 gene cluster lies within a genetic region where repeating DNA letters complicate even the latest genomic

diagnosis methods. This explains why standard genetic screens have missed ATAD3 mutations in the past."

"Using a combination of advanced gene and protein technologies, our team has shown that ATAD3 genes can be mistakenly copied and pasted next to themselves. These duplications create a faulty protein that disrupts normal ATAD3 function, sadly resulting in fatal heart failure around the time of birth."

"What's exciting for families involved in this study is that we have given them the confidence to plan for another baby, knowing that yes, they may have experienced some awful luck, but that it has an extremely low chance of happening again" said Professor Thorburn.

The team from MCRI and the Victorian Clinical Genetics Services (VCGS; which validated the diagnostic test) plans to re-analyse previously collected genetic data from families whose children died with similar unexplained symptoms. One of the "cold cases" described in the current study was of a family whose child died over 20 years ago.

MCRI Professor John Christodoulou who co-led the study, said, "Crucially, the study provides insight into the still unknown role of ATAD3 in the fatal disease, and highlights the importance of continual improvement in our screening capabilities."

"It also shows the importance of collecting and storing these samples. We might not have the technology or the insights to diagnose every genetic disease yet, but we are constantly making these incremental advances and providing answers to our families, even years or decades later. Their invaluable contribution means another family may be spared the same pain."

**More information:** Fatal perinatal mitochondrial cardiac failure

caused by recurrent de novo duplications in the ATAD3 locus. *Med*. DOI: doi.org/10.1016/j.medj.2020.06.004