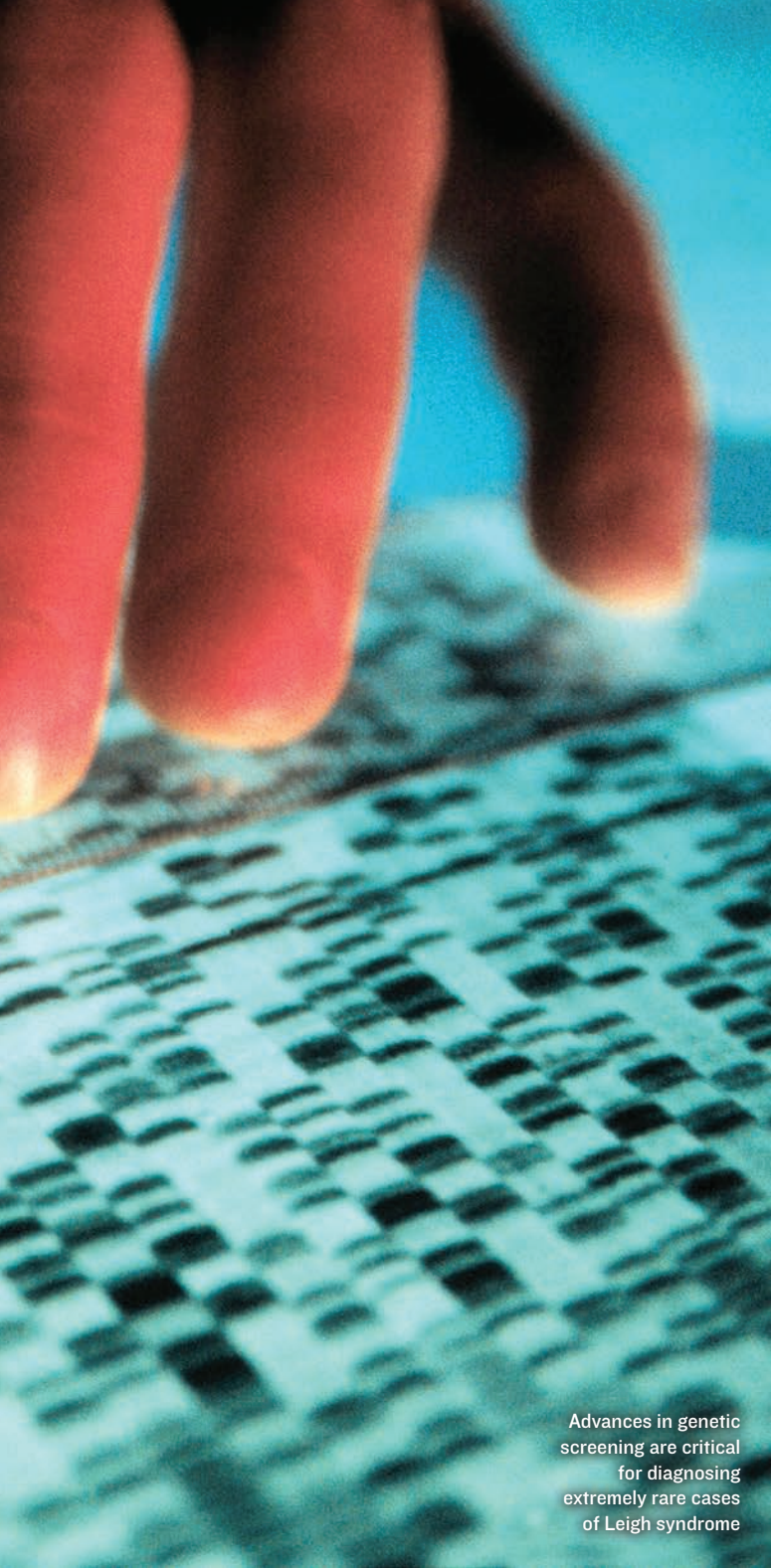




# New mutation linked to Leigh syndrome

A new mutation causing Leigh syndrome has been detected in two newborns in Saudi Arabia.





Advances in genetic screening are critical for diagnosing extremely rare cases of Leigh syndrome

**L**eigh syndrome is a severe genetic disorder that leads to potentially fatal respiratory failure, brain abnormalities and loss of muscle strength. In most cases, enzyme defects are thought to cause the disease by interfering with the body's ability

to produce energy in the mitochondria. Around one in 36,000 people are born with the condition.

Now, a case study of two siblings, both who died within two days of birth, has led to the first report of a rare mutation that shuts down a key enzyme called short-chain enoyl-CoA hydratase (SCEH).

Encoded by the *ECHS1* gene, SCEH plays an essential role in converting fat into energy for healthy development, and has only recently been investigated in the context of Leigh syndrome.

### "A disruption in just one step of a common pathway of metabolism can lead to big changes in our bodies."

Previous studies had revealed different Leigh syndrome-causing mutations in the *ECHS1* gene, carried by either the father or the mother. However, for the first time, researchers at KAIMRC, in collaboration with King Faisal Specialist Hospital and Research Centre in Riyadh, identified a novel homozygous variant (carried by both parents) that causes a lethal phenotype of this condition.

"Given the consanguineous nature of the parents and apparent recurrence of the same condition, we assumed it is caused by a shared homozygous ancestral mutation," says Fuad Al Mutairi, a clinical geneticist at KAIMRC.

At first, despite extensive analyses using "all commercially available next-generation sequencing genetic

tests", Al Mutairi says that the mutation remained undetected. By repeatedly 'zooming in' on the shared genomic region between the two children using exome sequencing, a technique that targets protein-coding portions of the genome, the researchers were able to pinpoint a single homozygous variant of the *ECHS1* gene.

A disruption in "just one step of a common pathway of metabolism can lead to big changes in our bodies," says Al Mutairi. "In this rare case, there was severe damage to protein synthesis, which affected the whole gene function and stopped enzyme activity."

The study highlights the limitations of conventional genetic screening techniques, and the need for advances in bioinformatics and wider availability of population-based genomic data. To this end, the Saudi Human Genome Project, a growing resource for population-based genomic data, will play a central role in enhancing the discovery of gene-disease associations.

"Knowing the cause and understanding the pathophysiology of the disease gives hope in other cases where therapeutic options may be available," says Al Mutairi. "Identifying the genetic defect as a first step can be enormously helpful for families in order to prevent recurrence of the disease."

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Al Mutairi, F., Shamseldin, H.E., Alfadhel, M., Rodenburg, R.J. & Alkuraya, F.S. A lethal neonatal phenotype of mitochondrial short-chain enoyl-CoA hydratase-1 deficiency. *Clinical Genetics* 91, 629-633 (2016).