# Understanding unexplained low blood sugar in children: More than normal variation

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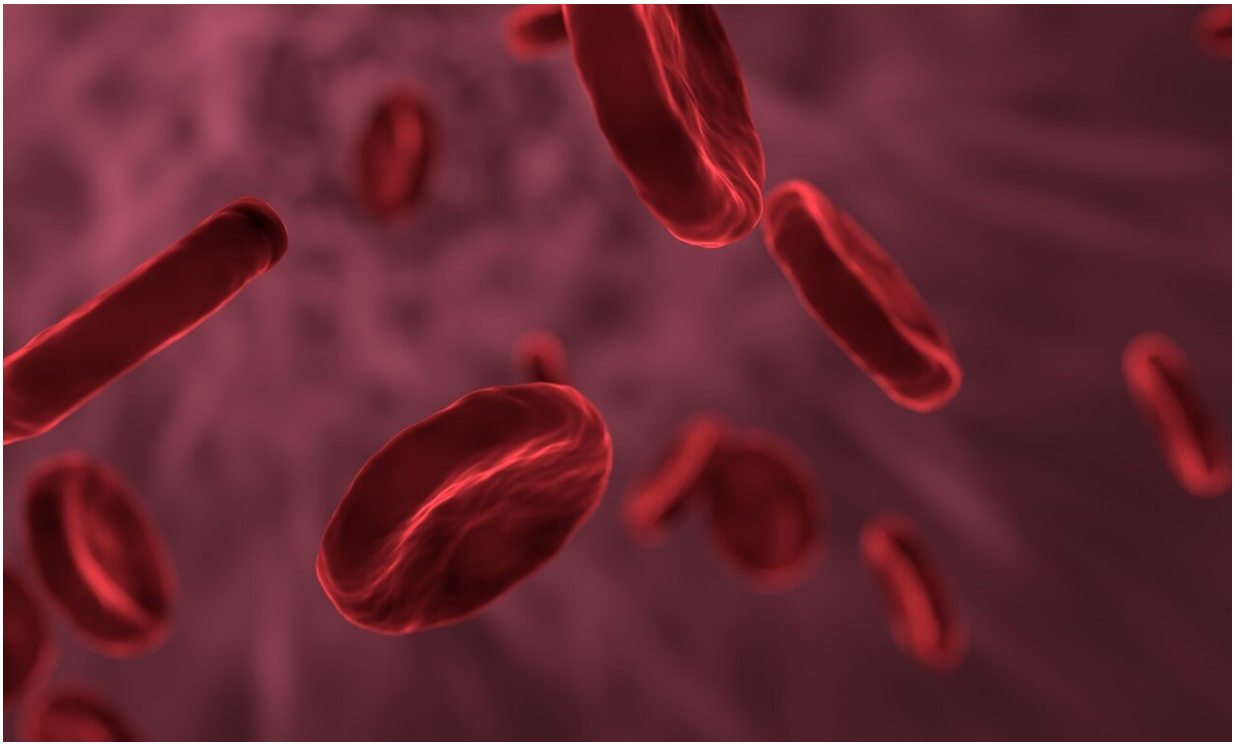

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Low blood sugar in children is often unexplained despite intense investigation into hormone Imbalances and inborn errors of cell metabolism. Despite its frequency, very little progress has been made in understanding this disease entity since 1964, where it was first named idiopathic ketotic hypoglycemia (IKH). Researchers from University of

Southern Denmark and Odense University Hospital, Denmark, have now identified mutations in four novel genes that appear to explain IKH.

Lisa is two years old. She often gets uneasy—shaking and sweating—especially in the morning. She vomits and refuses to eat. Her mother, Karoline, knows she has to act before Lisa starts to deteriorate.

To avoid convulsions and loss of consciousness, Karoline desperately tries to give Lisa sugar-rich drinks but has to proceed with energy gel applications on Lisa's chin and today, also an intramuscular glucagon injection. Lisa improves, but it takes hours before she wants to eat and drink normally again.

"It's because of the accelerated fat burn," explains Yazeid Alhaidan, Ph.D. Alhaidan has spent three years trying to understand the genetic background of IKH in children like Lisa.

## Looking for genetic explanations

"Lisa's sugar deposits are somehow ineffective, so a normal night's fasting after high physical activity the day before can be enough to provoke low blood glucose (sugar) and toxic substances like acetone because of accelerated fat burn," Yazeid Alhaidan explains. "And then she gets nausea and vomits. This will not stop until she burns sugar again and her fat-burn ketones have been eliminated, and this can take several hours."

Idiopathic ketotic hypoglycemia (IKH) is often relatively mild and may remain undiagnosed. Luckily it often disappears with age. But severe variants, sometimes affecting several family members, have prompted the research team at the Complex Hypoglycemia Center, Odense University Hospital, Denmark, to dive more deeply into potential new genetic explanations for this disease.

## Previously unknown causes of low blood sugar

"We have identified four novel genes that appear to explain the IKH in at least four families," Alhaidan continues. "I searched in all 22,000 genes in the human genome and was lucky to be able to pinpoint mutations in NCOR1, IGF2BP1, SGLT2, and NEK11 in four families with IKH."

These genes are related in different ways to glucose metabolism and may well be previously unknown causes of low blood sugar. Known genetic causes were identified in four other families while no mutations were found in nine families.

## First step towards new drugs

"Every gene involved in glucose metabolism and low blood sugar is of high interest for diabetes research," says Henrik Thybo Christesen, professor in pediatric endocrinology and leader of the Complex Hypoglycemia Center.

To understand the genetics in children like Lisa may be the first step in designing a novel drug against diabetes.

"In type 2 diabetes, you want to lower the blood sugar. If you can design a drug that acts like the mutation in patients like Lisa, you may have a successful treatment, provided the blood sugar doesn't get too low and the side effects are acceptable," explains Professor Christesen.

## More studies needed

Molecular biologist and associate professor Klaus Brusgaard, who has led the study, calls for caution.

Although the mutations in the four novel genes seem to be severe and potentially disease-causing, more studies are needed to show their exact functional significance.

"If other researchers can find mutations in the same genes in other patients, this will also be helpful. Until then, we can only call them candidate genes. Our study may be the first of many to identify novel genetic explanations for IKH—which may also end up being split into many specific diseases. And each novel disease may have its own treatment. That's what we call precision medicine," Dr. Brusgaard explains.

**More information:** Yazeid Alhaidan et al, Exome sequencing revealed DNA variants in NCOR1, IGF2BP1, SGLT2 and NEK11 as potential novel causes of ketotic hypoglycemia in children, *Scientific Reports* (2020). DOI: 10.1038/s41598-020-58845-3

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