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Researchers find gene that causes progeroid and lipodystrophy syndrome

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Researchers at the Translational Genomics Research Institute (TGen) have identified a genetic mutation associated with the appearance of premature aging and severe loss of body fat in children.

TGen's Center for Rare Childhood Disorders found that the appearance of premature aging, a neonatal form of Progeroid syndrome, in a 3-year-old girl was caused by a mutation in the gene CAV1, according to a study published today in the scientific journal *PLOS ONE*.

The Center for Rare Childhood Disorders was established in 2010 to examine the genetic basis of disease in children with medical conditions that have no definitive diagnosis. Since its inception, the Center has enrolled more than 900 participants and analyzed the genomes of more than 200 families, with a diagnostic success rate of nearly 40 percent.

Progeroid syndromes are a group of rare genetic disorders that mimic physiological aging, making affected individuals appear to be older than they are. In this instance, the patient has a triangular appearance to her face, and a large area at the top front of the head where a growing young child's cranial bones eventually fuse together known as the anterior fontanelle.

The CAV1 mutation was discovered following genomic sequencing of the girl and her parents, in which the billions of pieces of information in their DNA were spelled out, using TGen's state-of-the-art technologies and capabilities for whole-genome sequencing.

"Having a diagnosis is a major step in the continuing care of our patients," said Dr. Matt Huentelman, Co-Director of TGen's Center for Rare Childhood Disorders and the study's senior author. "This is a unique discovery and a prime example of how children born with rare, undiagnosed conditions may benefit from a diagnosis obtained through genetic sequencing."

The young patient in this study also has a form of high blood pressure (pulmonary hypertension) that specifically affects the heart and lungs. She also has had a feeding disorder, and a failure to thrive. In addition, she has symptoms of lipodystrophy, a medical condition characterized by a severe loss of body fat. Patients with lipodystrophy have a tendency to develop insulin resistance, diabetes, high triglyceride levels, and fatty liver.

"We characterize further association of CAV1 dysfunction with a syndrome of severe premature aging and lipodystrophy, showing clearly how these specific genetic changes expand the spectrum of CAV1-associated disorders" said Dr. David Craig, Co-Director for TGen's Center for Rare Childhood Disorders, and another author of the PLOS ONE scientific paper.

The CAV1 gene codes for Caveolin 1, a key protein in the plasma membrane of individual cells. The plasma membrane surrounds the cell and contains a multitude of molecules that enable the cell to send and receive information to and from the environment. Caveolin 1 helps regulate many cellular functions, including tumor suppression; but also vesicle trafficking, the movement of important biochemical signal molecules through vesicles in the cell, or the traffic of molecules between different membrane-enclosed compartments in the cell; and cellular senescence, the phenomenon in which cells stop growing and dividing.

"This study may contribute to a better understanding of the pathogenic mechanisms that contribute to the severe reduction of body fat, the appearance of premature aging, as well as the serious medical problems that affect our patient," said Dr. Vinodh Narayanan, Medical Director of TGen's Center for Rare Childhood Disorders, and also an author of the *PLOS ONE* paper. "Such understanding may lead to better approaches to her treatment, and allow us to anticipate, detect and treat complications before they become severe."

The patient's lack of body fat could be due to the cumulative combination of the defective functions not only of the CAV1 gene, but also of the LPIN1 and ADPAT2 genes, the study said.

Despite her premature aging appearance, the patient shows no neurological problems, said Dr. Isabelle Schrauwen, a Research Assistant Professor in Dr. Huentelman's lab and the lead author of the scientific paper.

"She has been active, playful, interactive and well spoken. In fact it has always been such a treat to see her smiling face at our Center outreach events," Dr. Schrauwen said. "We really owe a debt of gratitude to her, her family, and all of the families who work with us at the Center. Without their commitment to research we wouldn't be where we are today."

The Center for Rare Childhood Disorders is co-directed by Drs. Huentelman, Narayanan and Craig. The Center has established collaborations that stretch across the globe.

The authors of the paper thank the patient and her family for participating in this groundbreaking research as well as the donors who support the ongoing work in TGen's Center for Rare Childhood Disorders.

The study published today in *PLOS ONE* is titled: A Frame-Shift Mutation in CAV1 Is Associated with a Severe Neonatal Progeroid and Lipodystrophy Syndrome.

More information: "A Frame-Shift Mutation in CAV1 Is Associated with a Severe Neonatal Progeroid and Lipodystrophy Syndrome." *PLoS ONE* 10(7): e0131797. DOI: 10.1371/journal.pone.0131797

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