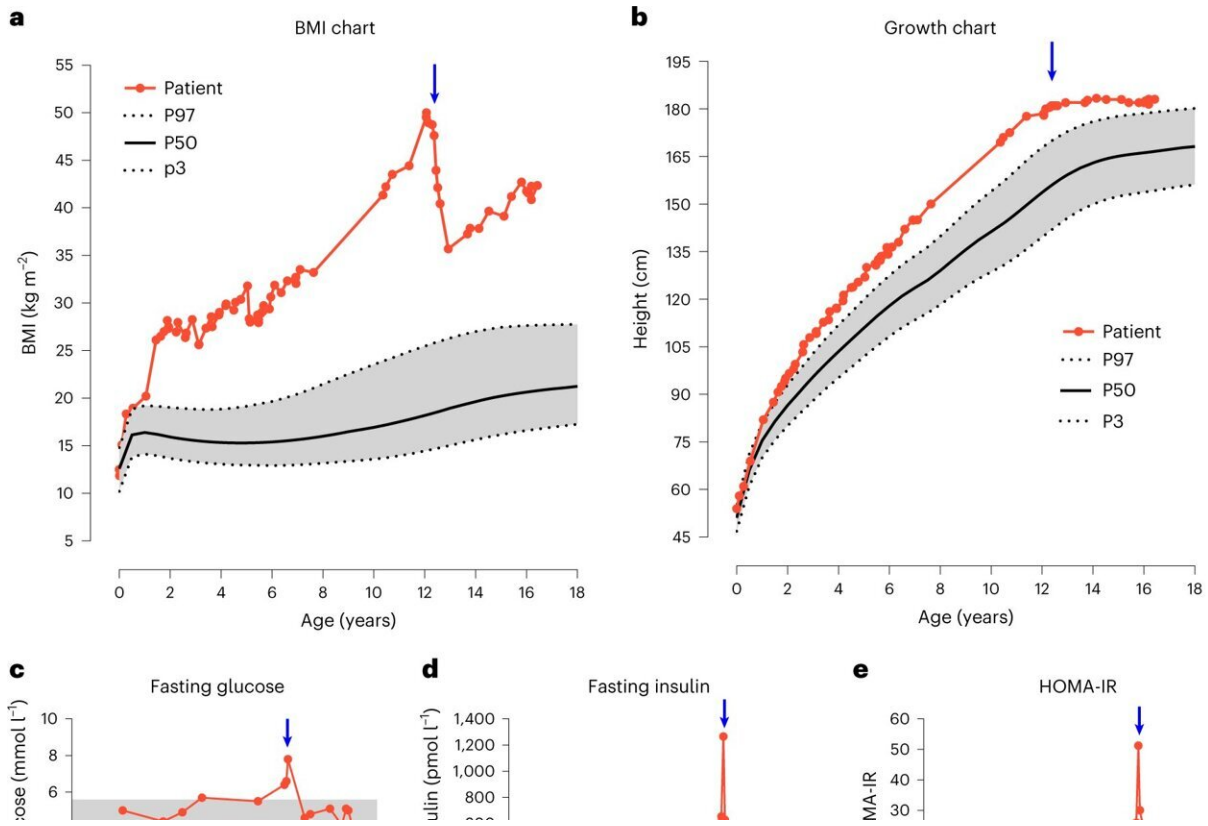
Obesity researchers discover new gene mutation in children

December 21 2022, by Kerstin Gackle



Clinical characteristics of the index patient and her family. **a**,**b**, Course of BMI (**a**) and height (**b**) of the patient (red dots) from birth to adolescence in relation to 3rd (P3), 50th (P50) and 97th (P97) sex-specific reference percentiles according to Kromeyer-Hauschild et al. Data from the patient were corrected for gestational age until the age of 2 years. **c–g**, Parameters of glucose metabolism with the respective reference ranges of either the local hospital laboratory depicted as gray areas or with prediabetes cut-offs according to the American Diabetes Association indicated by a dotted line. **h**, Serum levels of liver enzyme

alanine aminotransferase (ALAT) in comparison to the reference values according to Bussler et al. (shaded in gray). Blue arrows mark the time point of bariatric surgery at the age of 12.4 years. **i**, Pedigree of the family; females are indicated by circles, the father by a square. Individuals carrying the *ASIP* tandem duplication are indicated by black symbols, the open symbol indicates the mother not carrying the mutation. The index patient is indicated by a red arrow. Photographs present patient at age of 3.5 years and father at age 52 years. HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; 2 h glucose, glucose levels after 2 h of oral glucose tolerance testing. Credit: *Nature Metabolism* (2022). DOI: 10.1038/s42255-022-00703-9

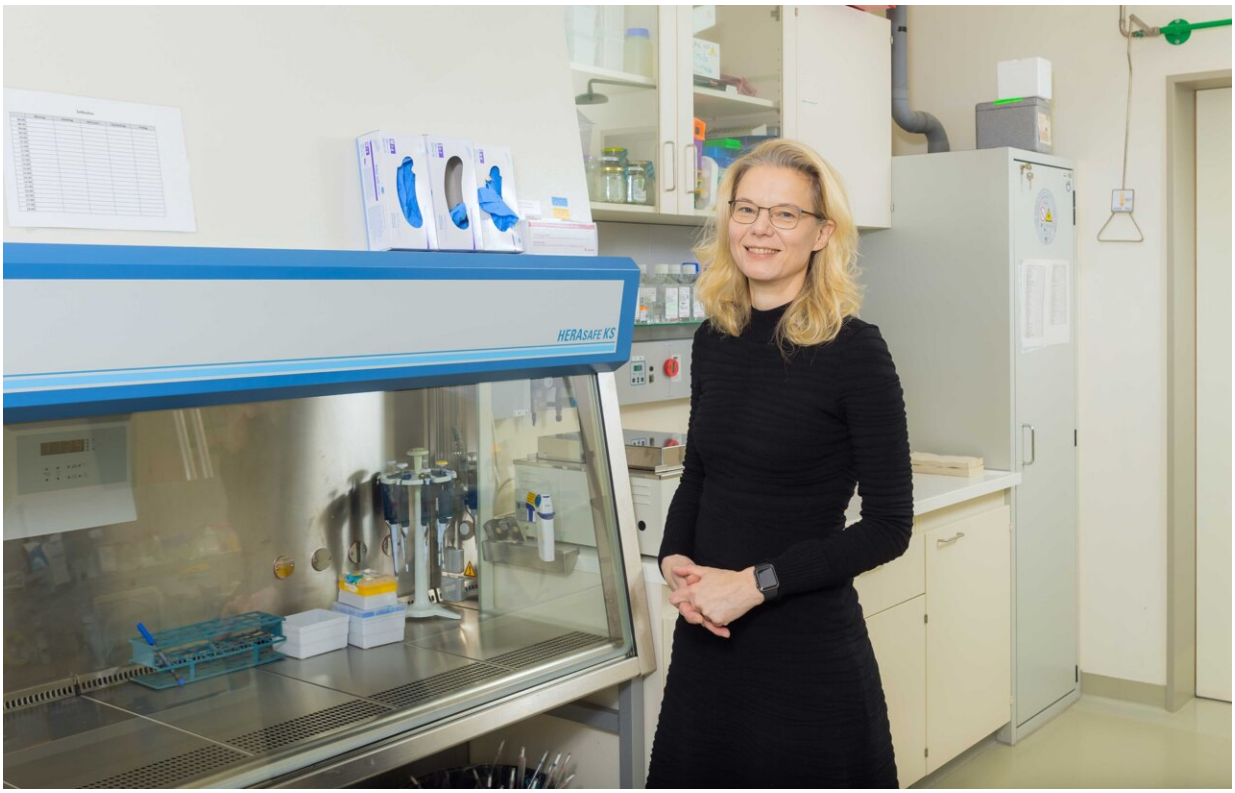
A research team at Leipzig University's Faculty of Medicine has discovered a new mechanism that is associated with severe obesity in children. This genetic rearrangement leads to an unusual expression of a gene involved in hunger control and is not detected by most routine genetic tests for obesity. The findings were published in the journal *Nature Metabolism*.

Obesity and diseases associated with obesity are among the leading causes of death worldwide, but its causes are not yet fully understood. However, it is known that several factors are responsible for the development and progression of the disease and that genetic factors also play a role. In most of the individuals affected, the combination of an unhealthy lifestyle and a genetic predisposition called a polygenic disorder leads to severe obesity. A polygenic disorder is one in which several genes are affected.

Researchers at Leipzig University Hospital and the Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) at Helmholtz Munich also want to identify the rare cases of monogenic obesity. In these patients, defects in a single gene are the cause of the disease. Those affected often show a decreased sensation of satiety in early childhood

and suffer from a constant feeling of hunger.

While studying tissue samples from a girl with severe obesity, the Leipzig researchers found that a specific gene, the agouti-signaling protein (ASIP) gene, was produced at high levels in cells where it is not normally present (e.g., in fat cells, white blood cells and neuronal cells).



Professor Antje Körner in the research lab. Credit: Swen Reichhold, Universität Leipzig

Project head Antje Körner, professor of pediatric research and pediatrician said, "This discovery is a kind of missing piece of the puzzle in research on monogenic human obesity. It is also evidence for the

importance of key molecular regulatory mechanisms of energy balance and body weight via melanocortin 4 receptor neurons in humans and provides us with a unique opportunity to study these mechanisms."

The type of mutation found in the current study escapes standard genetic screening algorithms, which means that it remains undetected in many affected patients. Thanks to targeted screening of the Leipzig Childhood Obesity cohort, Professors Körner's team has identified four additional patients with the same mutation.

"Given this discovery, I believe we need to rethink the strategies we use to identify patients with monogenic obesity. The ultimate goal of our research is to transfer the findings from genetic studies to future personalized treatment options for obesity," said Professor Matthias Blüher, director of HI-MAG and spokesperson of the CRC 1052 "Obesity Mechanisms" in the Faculty of Medicine.

More information: Elena Kempf et al, Aberrant expression of agouti signaling protein (ASIP) as a cause of monogenic severe childhood obesity, *Nature Metabolism* (2022). DOI: 10.1038/s42255-022-00703-9

Provided by Leipzig University

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