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Researchers discover treatment option for rare genetic disorder

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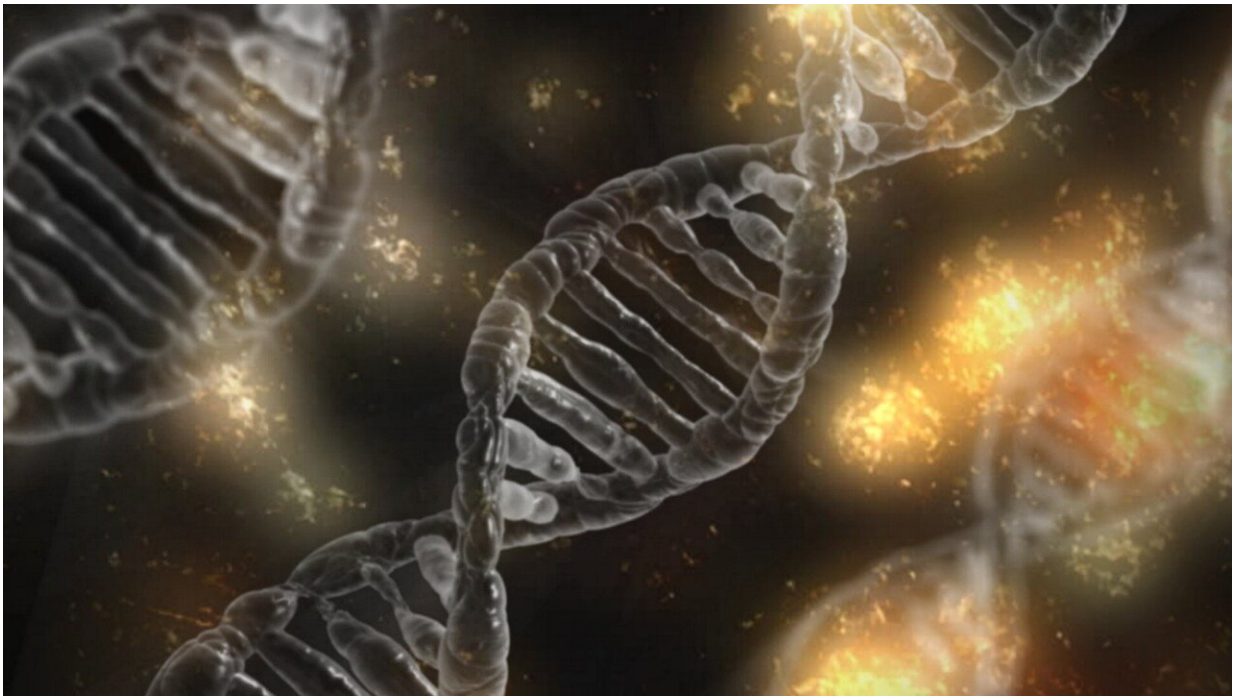

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Researchers from the Icahn School of Medicine used a novel genetic sequencing technology to identify the genetic cause of—and a treatment for—a previously unknown severe auto inflammatory syndrome affecting an 18-year-old girl since infancy.

The technology, tailored to the patient's own genetic code at a single cell

level, helped the researchers characterize an unknown mutation in a gene called JAK1 that caused the patient's immune system to be permanently turned on, resulting in rashes over much of her skin, growth abnormalities, kidney failure, allergic hypersensitivities, and an unusual inflammatory condition throughout the digestive tract.

The study, led by Dusan Bogunovic, Ph.D., Associate Professor of Microbiology, and Pediatrics, at the Icahn School of Medicine at Mount Sinai, faculty member of The Mindich Child Health and Development Institute and the Precision Immunology Institute at Mount Sinai, and Director of the Center for Inborn Errors of Immunity, was published in the August 3 issue of the journal *Immunity*. The discovery points toward new ways to study how genetic diseases manifest and presents a model of personalized diagnosis and treatment for patients with genetic diseases.

Autoinflammatory diseases are caused by abnormal activation of the immune system, leading to recurrent episodes of inflammation that may result in damaged or failed organs. The researchers determined that not all of the patient's cells carried this mutation and had different genetic makeups or genotypes, what the researcher describe as a mosaic.

"Most genes use both their maternal and paternal copies, called alleles," said Dr. Bogunovic. "Our findings show the JAK1 mutation in this patient used only one copy per cell, known as monoallelic expression. This challenges the textbook principles of genetics and may help explain irregularities that are frequently encountered across genetic diseases."

In the paper, the researchers describe the use of next-generation genomic, molecular, and multi-parametric immunological tools to probe the effects of the patient's JAK1 mutation. By mapping the genotype of JAK1 across the patient's body, researchers were able to pinpoint precisely when the mutation arose in early development in the embryo. It

later gave way to a host of symptoms from early childhood to early adulthood. The hunt began for a specific therapy that would curb the excessive activity of her mutant JAK1 and potentially cure her inflammatory symptoms.

"We identified one drug, tofacitinib, a JAK inhibitor, that curbed the excessive activity of her hyperactive inflammation. When administered the therapy, she rapidly improved within weeks. Her skin lesions cleared, her daily gastrointestinal symptoms resolved, and the clinical signs of inflammation went away, putting the patient in remission for two years until her unfortunate demise from coronavirus-related illness," said Dr. Bogunovic.

"This research helps better understand the basic function of JAK1, which has broad implications for diseases of the immune system and how to treat them. In addition, the genetic discoveries uncovered in this case open up new research avenues into the complexities of how genetic diseases manifest and present a model of the future of personalized medicine. By coupling advanced clinical care with next-generation sequencing and detailed laboratory studies, we successfully diagnosed and treated a life-threatening disease."

More information: Conor N. Gruber et al, Complex Autoinflammatory Syndrome Unveils Fundamental Principles of JAK1 Kinase Transcriptional and Biochemical Function, *Immunity* (2020). DOI: 10.1016/j.immuni.2020.07.006

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