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Researchers identify first drug targets in childhood genetic tumor disorder

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Two mutations central to the development of infantile myofibromatosis (IM)—a disorder characterized by multiple tumors involving the skin, bone, and soft tissue—may provide new therapeutic targets, according to researchers from the Icahn School of Medicine at Mount Sinai. The findings, published in the *American Journal of Human Genetics*, may lead to new treatment options for this debilitating disease, for which the only current treatment option is repeated surgical removal of the tumors.

IM is an inheritied disorder that develops in infancy or even in utero and tumors continue to present throughout life. The tumors do not metastasize, but can grow large enough to invade the tissue surrounding them causing physical limitations, disfiguration, bone destruction, intestitinal obstruction, and even death. Currently, the standard of care is to excise the tumors when possible, which can be invasive, painful, and disfiguring, and most patients require multiple surgeries throughout their lives.

Led by John Martignetti, MD, PhD, Associate Professor of Genetics and Genomic Sciences, Oncological Sciences, and Pediatrics and other researchers at the Icahn School of Medicine at Mount Sinai and Hakon Hakonarson, MD, PhD at the Children's Hospital of Philadelphia, the global research team gathered blood samples from 32 people from nine different families affected by the disease and performed whole-exome sequencing, a type of genomic sequencing where all protein coding regions of the genome, called the exome, are analyzed. They identified mutations in two genes: PDGFRB and NOTCH3.

"We are very excited about the findings of this study, which started 10 years ago with the enrollment of the first family," said Dr. Martignetti. "The newest developments in sequencing technology have led to a new breakthrough in understanding this debilitating disease and we can therefore begin identifying drug-based treatments to save lives for some and avoiding the negative quality of life impact of extensive and repeated surgery in others."

PDGFRB and NOTCH3 are two genes that are targeted by existing drugs, including imatinib (GLEEVEC®) and sunitinib (Sutent®). Next, Dr. Martignetti and his team plans to test whether cells grown in the laboratory from myfibromatosis tumors are susceptible to these drugs. They also hope to learn why mutations in these two genes result in disease.

"If we can learn how these mutated genes get hijacked to cause cellular miscommunication, and also test existing and novel therapies to see if they shrink the tumors, we hope to improve the lives of the individuals battling this disease," said Dr. Martignetti.

Provided by The Mount Sinai Hospital