

Tracing a rare smooth muscle disorder to a single mutation in a non-coding gene

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A team of investigators from Massachusetts General Hospital (MGH), a founding member of Mass General Brigham (MGB) and Mass General for Children (MGfC) has identified—for the first time—the mutation in a single non-coding gene of a young patient responsible for the extremely rare disease known as multisystemic smooth muscle dysfunction syndrome (MSMDS), which causes profound

cerebrovascular, gastrointestinal and urologic impairment.

For the child's family, the discovery helped unravel the mystery of a condition that had afflicted their son since birth and will now enable physicians to initiate treatment to lessen the risk of future strokes.

The team's findings were reported in *The Journal of Clinical Investigation*.

"Thousands of other families live with the burden of children with undiagnosed diseases whose lives could be significantly changed with the help of the latest research and technologies to shed light on what are often hereditary disorders," says senior author Patricia Musolino, MD, Ph.D., a [critical care](#) and vascular neurologist at MGH and a globally recognized authority in MSMDs.

"The child we evaluated had been to five other hospitals before Mass General, which is part of the Harvard Clinical Site of the Undiagnosed Diseases Network(UDN) study. Without that specialized team of experts under one roof, it would have been impossible to arrive at the diagnosis we did for this child."

Past research has shown a mutation in the coding gene ACTA2 to be commonly associated with multisystemic smooth muscle dysfunction syndrome, which prevents smooth muscle throughout the body from contracting and working properly.

In the case of the young MGH patient, the disease was characterized by multiple strokes beginning at age three, along with severe bowel, bladder and feeding issues. Standard genetic testing did not detect a mutation in the ACTA2 gene as the source of the problem.

MGH's Undiagnosed Diseases Network team was the first to put all the

clinical pieces together.

Co-authors David Sweetser, MD, Ph.D., and Lauren Briere, MS, CGC, narrowed the search to a single nucleotide variant in the gene MIR145, a microRNA gene.

The team followed up with a detailed molecular analysis which confirmed that the variant affects the expression of several cytoskeletal proteins and smooth muscle cell function. The genetic breakthrough represents only the sixth recorded monogenetic disorder (resulting from the dysfunction of a single gene) attributed to the microRNA (miRNA) class of [genes](#).

"Despite major advances in genetic testing that now allow us to routinely sequence the [entire genome](#), large numbers of patients with suspected genetic disorders still remain undiagnosed," notes Sweetser. "One reason for this might be that practically all [genetic testing](#) performed today focuses on protein coding genes. The UDN has allowed us to delve much deeper, beyond standard clinical testing.

"The finding of disease-causing mutations in regulatory non-protein encoding genes, such as this microRNA, opens up a new frontier in our search for answers that can impact [patient care](#)."

"As it turns out, the patient's MIR145 variant actually causes the same [cellular changes](#) that result from the well-described MSMD5-causing ACTA2 variants," says Briere.

"That finding meant we were able to identify for the first time a second gene that interacts with ACTA2 to influence smooth muscle behavior," adds co-author Mark Lindsay, MD, Ph.D., an MGfC cardiologist.

"More important, though, is the impact it may have on the MGH patient,

whose condition had baffled clinicians for so long," adds Lindsay.

"The hopeful message from this case is that advanced genetic research can change the course of a disease not just for one family, but potentially for others faced with the same debilitating condition," says Musolino.

"But that will only happen if the Undiagnosed Diseases Network, which Mass General is fortunate enough to be part of, is able to significantly expand its research."

More information: Christian Lacks Lino Cardenas et al, A seed sequence variant in miR-145-5p causes multisystem smooth muscle dysfunction syndrome, *Journal of Clinical Investigation* (2023). [DOI: 10.1172/JCI166497](https://doi.org/10.1172/JCI166497)

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