Just two kids worldwide are known to have this rare genetic disease. Their parents united for a cure

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When Yoni Silverman, now 13, was a toddler, his parents fretted as he missed milestone after milestone. The New York City couple took their son to a host of specialists, searching for answers about why he wasn't speaking and had difficulty with balance, among other developmental issues.

Fast forward a few years later, and a Boston couple was going through something similar with their now 8-year-old son, Ollie. At the time, unlike other toddlers, Ollie wasn't speaking, sitting up or looking at objects.

Neither family felt satisfied with the answers they were getting or the labels that specialists tried to place on their sons, so they pushed the envelope and ordered extensive genetic testing.

And that's where this story of hope and synergy really begins.

Yoni and Ollie may be the only two people in the world who have the exact same P312R genetic mutation on their PSMC5 gene.

The mutation is considered de novo, meaning it appears for the first time in these boys and has not appeared in previous generations.

The two families found each other through a geneticist in France who is studying how mutations in similar genes affect children's development.

"It was just amazing to have another person in the world who could understand what we were going through," said Ollie's mom, Michelle Myers.

They soon joined forces to form the PSMC5 Foundation, which aims to find more people affected with related genetic mutations while raising awareness and funds for research.

Ultimately, the families hope to learn more about this mutation and what it will mean for their sons as they age. Their work may also hold the key to neurodegenerative conditions like Alzheimer's and Parkinson's disease.

What are the odds?

The PSMC5 gene encodes one protein in the proteasome, a large protein machine inside all of your cells that uses energy to unfold and destroy proteins.

"The proteasome functions like an old-fashioned meat grinder, where you turn the crank and meat gets chopped up in the machine, and the pieces come out the other end," explained Alfred Goldberg, a retired professor of cell biology at Harvard Medical School in Boston.

He discovered the proteasome in 1987, and his career has been devoted to understanding how cells destroy proteins.

"The proteasome can eliminate misfolded proteins that could interfere with cell function," Goldberg said. When it doesn't function properly, misfolded proteins accumulate in the brain and interfere with cell function. This is a hallmark of diseases like Parkinson's or Alzheimer's.

That's why Goldberg was intrigued when he first heard about these two boys.

"The fact that Yoni and Ollie were alive and attractive physically was a surprise at the time, as we expected these mutations would cause much greater limitations," he said. "Ollie and Yoni have serious medical challenges, but these challenges are not as great as we had anticipated."

Yoni has speech and physical delays. "He is a smart guy, but his energy

level is low, so he needs to make a lot of effort to get things done," said his mom, Idit Silverman.

His dad, Joe, added: "He's come a long way. He didn't start talking until he was 4 and, slowly but surely, he is getting there."

Ollie can't speak, but communicates through touch and gestures. He isn't toilet-trained and has a developmental age of between 2 and 3.

Strength in numbers

There are likely more people who have the same genetic mutation as Ollie and Yoni, as well as other mutations in the genes that make up the proteasome.

"They wouldn't have been diagnosed unless they had their DNA sequenced," Goldberg explained. Such DNA analysis only became possible when the human genome was fully mapped out in 2003.

The cost of genetic testing varies and can be a deterrent for some families, and it's not necessarily covered by insurance.

"This specific mutation is pretty rare, but likely not confined to these two," said David Rubinsztein, a professor of molecular neurogenetics and deputy director of the Cambridge Institute for Medical Research. He is also the interim director at the UK Dementia Research Institute at Cambridge, in London.

Since starting the PSMC5 Foundation in 2020, the Silverman and Myers families have been in contact with a 25-year-old and 13-year-old twins who may have similar behavior to Yoni and Ollie and may share this mutation. They have identified 19 other kids with similar mutations.

"We want more children in our research studies, so we can form a bigger community and build this foundation," Idit explained.

Searching for a cure

Now, the challenge is to find ways to activate the proteasome so it eliminates misfolded proteins and keeps them from building up.

Advancing science takes time, and there are many steps involved in the research process. The foundation is helping fund the development of a mouse model of this genetic disease in Rubinsztein's lab. In addition, they are supporting the creation of a cell line to serve as a pure disease model to help better understand the effects of this mutation in Goldberg's lab.

Goldberg and his colleagues plan on publishing a paper in a peer-reviewed journal within the next six months that describes the two boys' genetic makeup.

"If this is an active disease process that continues to progress after the boys' early development, we hope to improve their quality of life by activating the proteasome or autophagy," Goldberg explained. Autophagy occurs when cells break down and destroy old, damaged or abnormal proteins.

There are still many unknowns. "We don't know the natural course of this disease because the boys are so young," Goldberg said.

There is already proof that drugs can impact the proteasome. Three proteasome inhibitors are approved by the U.S. Food and Drug Administration to treat a type of cancer known as multiple myeloma.

"In cancer, you want to block the proteasome so that proteins build up

and kill the cancer cells," he said. The goal is the opposite in genetic diseases like the one that Ollie and Yoni have, where the proteasome needs to be activated.

Trust your gut

At first, doctors thought Yoni had autism, but that never resonated with his parents. "We felt it was something else," Idit said.

Each specialist that Ollie saw spotted a new problem, including a heart murmur, a smaller optical nerve, and a poorly formed trachea (windpipe). No doctor could put all of these symptoms together and give the condition a name.

"Listen to your intuition as parents," Idit said. Consider genetic testing, cross-reference results with the GeneDx database, and find current research on the gene, she suggested.

Both families are taking things day by day and find joy in their sons' smiles and laughter.

Yoni loves comic books, Marvel superhero movies, playing with dogs (although the family doesn't have their own dog yet), and making people laugh. Ollie loves to snuggle and watch funny clips from his favorite movies.

Their parents hope the foundation will uncover new ways to help their boys and others with similar genetic diseases.

"I fear the unknown and what will be in 10 years with Yoni, and what effect this genetic disease will have on him," said Idit.

"We don't know the long-term prognosis as very few of these individuals

have been studied over time," said Rubinsztein. "The key thing is that these families are very involved and engaged in a remarkably constructive way."

More information: Learn more about the P312R mutation and other related genetic disorders at the PSMC5 Foundation.