Genetics researchers find new neurodevelopmental syndrome

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Kosuke Izumi, MD, PhD, is a clinical geneticist and genetics researcher at Children's Hospital of Philadelphia Credit: Children's Hospital of Philadelphia

Researchers have identified a gene mutation that causes developmental delay, intellectual disability, behavioral abnormalities and musculoskeletal problems in children. The newly diagnosed condition, called *NKAP*-related syndrome, arises from mutations in the *NKAP*

gene, which plays a key role in human development.

"This gene mutation disrupts transcription, the process in which DNA information is converted into RNA," said study leader Kosuke Izumi, MD, Ph.D., a clinical geneticist and genetics researcher at Children's Hospital of Philadelphia. "As my lab continues to explore the function of *NKAP* in our bodies, we aim to discover clues for future treatments."

Izumi and co-authors from eight nations published their report of *NKAP*-related syndrome today in the *American Journal of Human Genetics*.

The scientists performed exome sequencing on 10 individuals, all children and young adults, with developmental delay, intellectual disability, behavioral problems such as ADHD and aggressive behavior, and tall stature, scoliosis and joint conditions. The subjects' tall stature and musculoskeletal problems are "Marfanoid": similar to traits found in the long-known genetic disorder Marfan syndrome.

The exome sequencing pinpointed mutations in the *NKAP* gene on the X chromosome. Consistent with an X-linked recessive condition, *NKAP* mutations caused symptoms only in males. Further analysis showed that transcription disruption patterns were similar in the patients—a higher proportion of genes were downregulated than upregulated, that is, the mutation "dialed down" the gene's effects on RNA and proteins. Experiments with zebrafish models revealed similar effects from an analogous mutated gene.

"The function of *NKAP* in our bodies has been poorly understood," said Izumi. "We discovered novel functions in brain and musculoskeletal development. Furthermore, we have started a patient registry to collect clinical information on patients with this rare diagnosis. Identifying more patients may help to reveal the full spectrum of medical issues seen

in *NKAP*-related syndrome."

In addition to providing a definitive diagnosis to a subset of patients with developmental delay and intellectual disability found to harbor this mutation, biological insights may eventually translate into clinical benefits. "As we further investigate biological mechanisms in this syndrome, our goal is to identify molecular pathways to target for future treatments for patients," added Izumi.

More information: Sarah K. Fiordaliso et al, "Missense Mutations in NKAP Cause a Disorder of Transcriptional Regulation Characterized by Marfanoid Habitus and Cognitive Impairment," *American Journal of Human Genetics* (2019). DOI: 10.1016/j.ajhg.2019.09.009 , www.cell.com/ajhg/fulltext/S0002-9297(19)30348-9

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