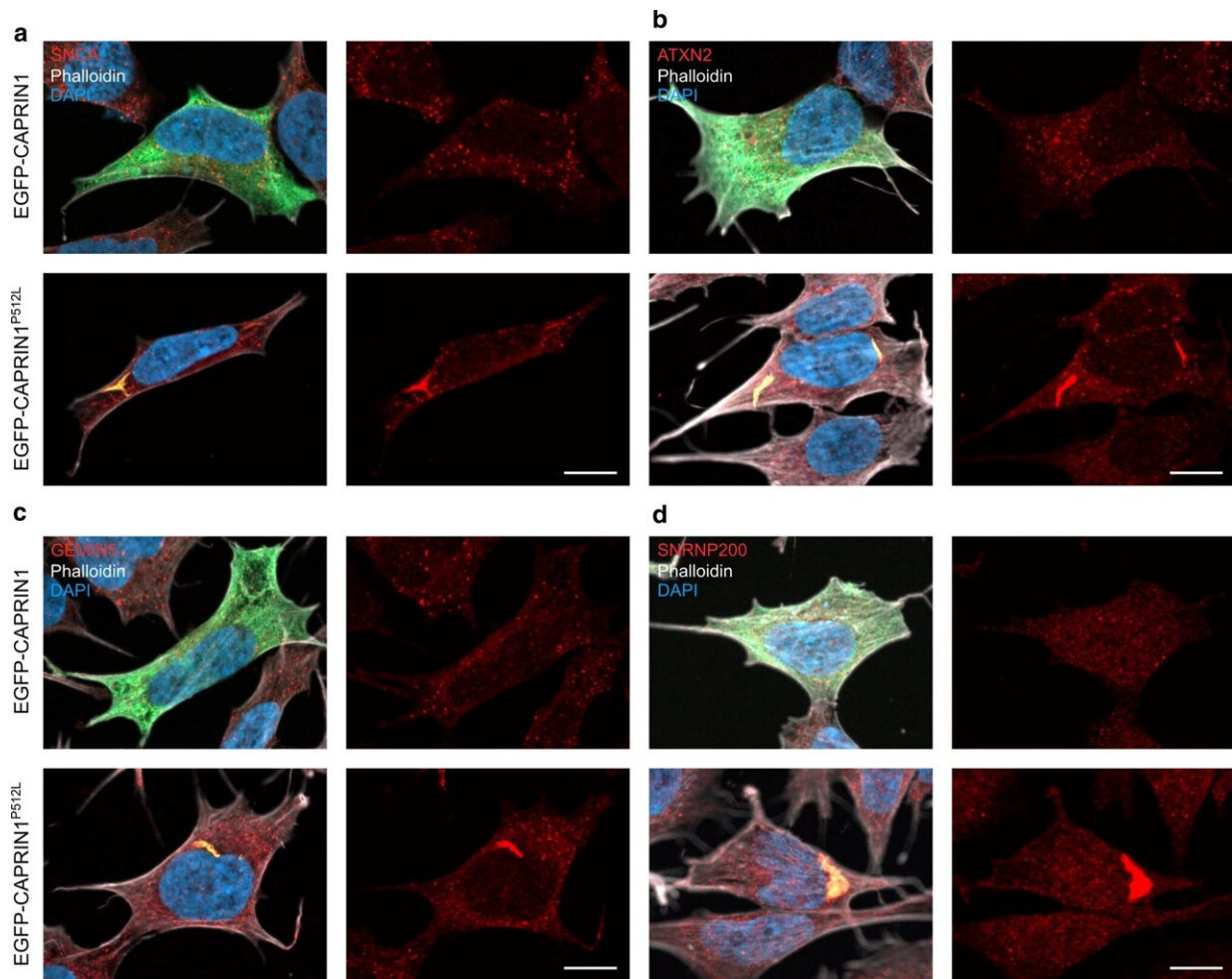


Studies link gene mutation to language impairment, ADHD and myasthenia

September 22 2022, by Mathias Martin



CAPRIN1^{P512L} aggregates are positive for NDs-related proteins. a EGFP-CAPRIN1^{P512L} aggregates are positive for SCNA. b EGFP-CAPRIN1^{P512L} aggregates are positive for ATXN2. c EGFP-CAPRIN1^{P512L} aggregates are positive for GEMIN5. d EGFP-CAPRIN1^{P512L} aggregates are positive for SNRNP200. (Scale bar: 10 μ m). Credit: *Cellular and Molecular Life Sciences*

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Two studies have revealed that certain disorders of the CAPRIN1 gene have significant consequences for people. First, the research team showed that insufficient production of the protein CAPRIN1 in the brain can lead to impairments, including autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), and language disorders.

Furthermore, the scientists identified a specific mutation in the CAPRIN1 gene (CAPRIN1P512L) that leads to an abnormal accumulation of proteins, causing unsteady gait and muscle weakness (myasthenia). The two studies have been published in the journals *Brain* and *Cellular and Molecular Life Sciences*.

These new insights were made possible by exome analyses, in which scientists observe which genes are altered in a cell. The team also used the GeneMatcher database—a platform on which researchers and physicians exchange information about mutations in genes and diseases associated with them.

The research team identified twelve patients who had [mutations](#) in the CAPRIN1 gene. In them, only half of the amount of protein was produced. Lisa Pavinato, a doctoral researcher in the team of Professor Dr. Alfredo Brusco at the University of Turin and DAAD-scholarship holder with Professor Dr. Brunhilde Wirth at the University of Cologne, discovered a connection between the deficient production of the protein and certain neurological impairments.

The affected persons all had speech disorders, 82 percent had ADHD, and 67 percent were affected by [autism spectrum disorders](#) and other neurodevelopmental disorders. The function of CAPRIN1 was

confirmed in laboratory experiments with human induced pluripotent stem cells in which the CAPRIN1 gene was switched off using the CRISPR/Cas9 technology, creating the conditions from which the affected individuals suffered.

Cells with a CAPRIN1 mutation develop shortened processes and faulty circuits that show reduced [electrical activity](#) compared to the healthy neurons without the mutation. In contrast, control neurons without the CAPRIN1 mutation form long processes, developing into complex networks.

Furthermore, the team also discovered changes in translation, one of the most important cellular processes for error-free cell formation and function. In fact, due to the faulty translation, the mutant neurons began to degenerate and form clumps after a few days. The results of this research have been published in the article "CAPRIN1 haploinsufficiency causes a neurodevelopmental disorder with language impairment, ADHD and ASD" in *Brain*.

In the second study, GeneMatcher was used to identify three children from different families with a newly developed point mutation at a specific position of the CAPRIN1 gene: an amino acid exchange from proline to leucine at position 512.

All three children show the same symptoms of early-onset movement disorders (ataxia), impaired speech motor skills (dysarthria), memory disorders, and myasthenia. Andrea delle Vedove, a doctoral researcher in the team of Professor Wirth, showed that this specific mutation leads to many protein clumps in neuronal cells similar to other neurodegenerative diseases such as Parkinson's, Alzheimer's or ataxia. In addition, the activity of the nerve cells was reduced.

The study "CAPRIN1P512L causes aberrant protein aggregation and

associates with early-onset ataxia" has appeared in *Cellular and Molecular Life Sciences*.

"The new research results are important not only for the affected patients and their families, who often spend years searching for answers to understand the cause of their disease, but also for physicians, who can now make faster and more accurate diagnoses," said Professor Dr. Brunhilde Wirth, Director of the Institute of Human Genetics at University Hospital Cologne, who led the studies together with national and international teams.

More information: Lisa Pavinato et al, CAPRIN1 haploinsufficiency causes a neurodevelopmental disorder with language impairment, ADHD and ASD, *Brain* (2022). [DOI: 10.1093/brain/awac278](https://doi.org/10.1093/brain/awac278)

Andrea Delle Vedove et al, CAPRIN1P512L causes aberrant protein aggregation and associates with early-onset ataxia, *Cellular and Molecular Life Sciences* (2022). [DOI: 10.1007/s00018-022-04544-3](https://doi.org/10.1007/s00018-022-04544-3)

Provided by University of Cologne

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