De novo variants in *SNAP25* cause a spectrum of developmental and epileptic encephalopathy

Konrad Platzer1, Wendy K. Chung2, Zöe Powis3, Eva Brilstra4, Marie McDonald5, Mohamed Mikati6, Megan T. Cho6, Ashley C. Taylor7, Alexandrea Wadley7, Jennifer A. Sullivan5, Vandana Shashi5, Johannes R. Lemke1

1 Institute of Human Genetics, University of Leipzig Hospitals and Clinics, Leipzig, Germany
2 Department of Pediatrics, Columbia University Medical Center, New York, NY, USA.
3 Ambry Genetics, Aliso Viejo, CA, USA.
4 Department of Genetics, Utrecht University Medical Center, Utrecht, The Netherlands
5 Division of Genetics, Department of Pediatrics, Duke University, Durham, NC, USA
6 Division of Pediatric Neurology, Department of Pediatrics, Duke University, Durham, NC, USA
7 GeneDX, Gaithersburg, MD, USA.
8 Section of Genetics, Department of Pediatrics, University of Oklahoma, Oklahoma City, OK, USA.
9 Division of Medical Genetics, Department of Pediatrics, Duke University edical Center, Durham, North Carolina, USA.

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Abstract

Introduction: Synaptosomal-associated Protein-25 (SNAP25), predominantly expressed in the brain, is part of the SNARE complex (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) required for proper presynaptic vesicle docking and fusion. Heterozygous *de novo* variants in *SNAP25* have previously been separately reported in three individuals with intellectual disability (ID), epileptic encephalopathy, ataxia and congenital myasthenia.

Results: We have collected detailed phenotypic data on at least four additional cases with *de novo* variants in *SNAP25*. Combined with the three publishes cases, all seven individuals presented with ID with three of them classified as severe, three as moderate and one as mild. Five individuals developed seizures with a spectrum of epileptic spasms, focal and generalized seizures. Four remained refractory to therapy. Three individuals did not attain walking skills by age eleven years or later. Movement disorders of dystonia or choreoathetosis were seen in two individuals. Brain imaging revealed two individuals showing generalized volume loss. In addition, one case presented with signs of a leukoencephalopathy. Further symptoms include microcephaly, ataxia, cortical visual impairment, congenital myasthenia

and congenital hip dysplasia and contractures. All causative variants constitute *de novo missense* variants located in the t-SNARE coiled-coil homology domain 1 & 2, both showing a significantly reduced number of *missense* variation in controls, indicating a selective constraint.

Conclusion: *De novo* variants in *SNAP25* cause a spectrum of developmental and epileptic encephalopathy. Further patients and studies are needed to improve our understanding of the phenotypic spectrum and elucidate the effects of the variants on protein function.