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

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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.