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Titel des Beitrags:

De Novo Variants in GRIA4 Lead to Intellectual Disability with or without Seizures and Gait Abnormalities.

Abstract:

Using trio whole-exome sequencing, we have identified de novo heterozygous pathogenic variants in GRIA4 in five unrelated individuals with intellectual disability and other symptoms. GRIA4 encodes an AMPA receptor subunit known as GluR4, which is found on excitatory glutamatergic synapses and is important for learning and memory. Four of the variants are located in the highly conserved SYTANLAAF motif in the transmembrane protein M3, and the fifth is in an extra-cellular domain. Molecular modeling of the altered protein showed that three of the variants in the SYTANLAAF motif orient toward the center of the pore region and most likely lead to disturbance of the gating mechanism. The fourth variant in the SYTANLAAF motif most likely results in reduced permeability. The variant in the extracellular domain potentially interferes with the binding between the monomers. On the basis of clinical information and genetic results, and the fact that other subunits of the AMPA receptor have already been associated with neurodevelopmental disorders, we suggest that pathogenic de novo variants in GRIA4 lead to intellectual disability with or without seizures, gait abnormalities, problems

of social behavior, and other variable features.

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