UKE Paper of the Month (UKE-Webpage: Wissenschaftler > Aktuelles aus der Forschung)

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Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes

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Abstract: N-methyl-D-aspartate (NMDA) receptors mediate excitatory neurotransmission in the mammalian brain. Two glycine-binding NR1 subunits and two glutamate-binding NR2 subunits each form highly Ca^{2+}-permeable cation channels which are blocked by extracellular Mg^{2+} in a voltage-dependent manner. Either *GRIN2B* or *GRIN2A*, encoding the NMDA receptor subunits NR2B and NR2A, was found to be disrupted by chromosome translocation breakpoints in individuals with mental retardation and/or epilepsy. Sequencing of *GRIN2B* in 468 individuals with mental retardation revealed four *de novo* mutations: a frameshift, a missense and two splice-site mutations. In another cohort of 127 individuals with idiopathic epilepsy and/or mental retardation, we discovered a *GRIN2A* nonsense mutation in a three-generation family. In a girl with early-onset epileptic encephalopathy, we identified the *de novo GRIN2A* mutation c.1845C>A predicting the amino acid substitution p.N615K. Analysis of NR1-NR2A^{N615K} (NR2A subunit with the p.N615K alteration) receptor currents revealed a loss of the Mg^{2+} block and a decrease in Ca^{2+} permeability. Our findings suggest that disturbances in the neuronal electrophysiological balance during development result in variable neurological phenotypes depending on which NR2 subunit of NMDA receptors is affected.

Statement: "This is the first time that single gene mutations in subunits of NMDA receptors, the most important excitatory neurotransmitter channels in the brain, could be linked to monogenic disorders such as mental retardation and epilepsy. Our findings support the idea that any disturbance in the number and/or composition of NMDA receptors has profound effects on neuronal development and activity in humans. The publication has been selected as "LATEST HIGHLIGHT" by Nature Genetics that underscores the importance of our results. This was an interdisciplinary work between the Institutes of Human Genetics at the University Medical Center Hamburg-Eppendorf, the University Hospital Essen, the University of Erlangen-Nuremberg, the Research Group Molecular and Cellular Neurophysiology at the University of Darmstadt, and the Centre de Génétique Humaine, University of Liège (Belgium)."

This work was performed at the University Medical Center Hamburg-Eppendorf (UKE) at the Institute of Human Genetics in the groups of Dr. Georg Rosenberger and Professor Dr. Kerstin Kutsche. Kerstin Kutsche holds a professorship at UKE since 2004 and Georg Rosenberger is an independent group leader since two years. Both authors have strong research interests in the field of neurological diseases, such as mental retardation, epilepsy, autism, and brain malformations, and aim to find the causative genes. This work was supported by a grant from the Deutsche Forschungsgemeinschaft (FOR 885/IRP5).