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AUTOSOMAL RECESSIVE, SEVERE MENTAL RETARDATION RESEMBLING PITT-HOPKINS SYNDROME IS CAUSED BY DEFECTS IN TWO NOVEL GENES TARGETING A COMMON SYNAPTIC PROTEIN IN *DROSOPHILA*

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We identified homozygous and compound heterozygous deletions and mutations in two genes in four patients with severe mental retardation and variable features including epilepsy and breathing anomalies, which phenotypically overlapped with Pitt-Hopkins syndrome. Heterozygous copy number variations and single nucleotide polymorphisms in both of these distantly related genes have previously been reported in association with developmental language disorders, autism spectrum disorder, epilepsy and schizophrenia, thus pointing to a shared molecular basis underlying different neuropsychiatric disorders. While one of the encoded proteins was already known to play a role in synapses, evidence for such a function of the other protein was so far lacking. Using *Drosophila* as a model we now demonstrate, that the orthologues of both genes localize to synapses and can reorganize them by influencing density of active zones, the synaptic domain of neurotransmitter release. Moreover, we show that both proteins converge on a common presynaptic molecular target protein. Thus, the similar phenotypes resulting from defects in both genes in humans may result from an analogous shared synaptic mechanism.