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CONFIRMATION OF THE NEURONAL NETWORK HYPOTHESIS OF INTELLECTUAL DISABILITY IN SEVERAL MOUSE MODELS

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Intellectual disability (ID)/mental retardation is characterized by strong heterogeneity in its causes and cognitive and behavioral manifestations. Despite this heterogeneity, all forms of ID show the key deficit of a global deficiency in all cognitive abilities. This raises the question whether the common cognitive deficit in ID may be the result of a common underlying brain deficiency. Many forms of ID or mouse models that mimic ID have been found to show abnormalities in neuron numbers, cortical layering, dendritic arborization, dendritic spine densities or altered spine morphologies. In addition, many genes that cause ID upon mutation are involved in the regulation of neuronal network connectivity during development of the brain. These observations led to a "Neuronal Network Hypothesis" of ID, which states that the cognitive deficit in all forms of ID is caused by abnormal development of neuronal connectivity (Ramakers, 2002; TINS 25: 191-199). This hypothesis emphasizes structural synaptic connectivity rather than functional deficiencies, such as altered neurotransmission or action potential conductance changes, as primary cause of ID. To test the Network Hypothesis, we quantified dendritic arborization and spine properties in several genetic mouse models of ID. Brains from knock-out mice for OPHN1, ARHGEF6 and GDI1 and wild type litter mates were stained at 12 weeks with the Golgi method and dendritic properties were quantified using image analysis. All three mouse models showed significant alterations in structural network connectivity in hippocampal area CA1. As the abnormalities were different in each mouse model, it is suggested that any deviation from an optimal degree of network connectivity results in deficient cognitive ability.