Cadherin 13 Deficiency Impacts the Formation of the Serotonergic System and Cognitive Function.

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About 5% of children and adults worldwide suffer from attention deficit / hyperactivity disorder (ADHD), to which both genetic and environmental factors contribute. Among all the risk genes, Cadherin 13 (Cdh13) has been linked to embryonic brain development as a negative regulator of axonal growth. Loss of Cdh13 led to an increased number of serotonergic (5-HT) neurons in the dorsal raphe (DR), the largest serotonergic nucleus that provides a substantial proportion of the serotonin innervation to the forebrain. In mice, the effect was observed at embryonic (E) day 13.5 and later persists into adulthood. In this study, we examined the effect of Cdh13 deficiency on (1) the topographical organization of the DR 5-HT neurons, (2) the 5-HT innervation in target brain regions and (3) the behavioral phenotypes in Cdh13-deficient mice.
Immunofluorescence staining revealed that the increased number of 5-HT neurons was essentially concentrated at the lateral wings of DR, and that the density of the innervation was altered in the thalamus. Furthermore, using a conditional knock-out (cKO) mouse model, we demonstrated that knocking out of Cdh13 in the serotonergic system alone was enough to make the molecular alterations that had been observed in the constitutive mouse line. Additionally, cKO mice displayed cognitive alterations in terms of impulsive-like behaviors, delayed learning and attentional control compared to their control littermates. This is the first direct evidence of Cdh13 involvement in the development of DR 5-HT circuitries and sheds light on the pathogenesis of neurodevelopmental disorders.

Keywords: ADHD, Cdh13, neurodevelopmental disorder, neural circuits, serotonergic system

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