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Study sheds light on how psychiatric risk gene disrupts brain development

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Scientists are making progress towards a better understanding of the neuropathology associated with debilitating psychiatric illnesses like bipolar disorder and schizophrenia. New research, published by Cell Press in the July 15 issue of the journal *Neuron*, reveals mechanisms that connect a known psychiatric risk gene to disruptions in brain cell proliferation and migration during development.

A research group led by Dr. Li-Huei Tsai from the Massachusetts Institute of Technology had recently discovered that the psychiatric risk gene, Disrupted in Schizophrenia-1 (DISC1), is an essential regulator of the proliferation of early brain cells (known as neural progenitor cells) via inhibition of a molecule called GSK3? and modulation of the Wnt signaling pathway. Disruptions in the Wnt pathway, which is critical for embryonic development, have previously been linked with developmental defects and with various human diseases.

"Our recent finding was particularly interesting because one of the actions of lithium, the most common mood disorder drug, is to inhibit GSK3?." explains Dr. Tsai. "Although DISC1 was one of the first psychiatric illness risk genes to be identified and we know that it plays a key role in brain development, the mechanisms by which DISC1 is regulated remain unknown." In this study, Dr. Tsai and colleagues built on earlier work and investigated how DISC1 is regulated during cortical development by looking for novel DISC1-interacting proteins.

The researchers discovered a key interaction between DISC1 and a

protein called Dixdc1 which is the mammalian version of a nonmammalian Wnt signaling molecule. Dixdc1 and DISC1 interacted to regulate neural progenitor proliferation via modulation of Wnt/GSK3? signaling. Interestingly, although DISC1 and Dixdc1 were both essential for neural migration, the Wnt/GSK3? pathway was not required for migration. It appears as if Dixdc1 integrates DISC1 into Wnt-dependent and -independent signaling pathways.

"Our findings identify the novel Wnt signaling pathway gene, Dixdc1, as a critical regulator of DISC1 function during cortical development. This discovery suggests that Dixdc1 and DISC1 are involved in Wnt signaling at many levels in the nervous system and that mutations in DISC1 likely contribute to disease pathology by disrupting Wnt signaling during neural development and in the adult brain," concludes Dr. Tsai. "Future studies are needed to determine whether other candidate psychiatric risk genes also interact with Wnt signaling."

More information: Singh et al.: “Dixdc1 Is a Critical Regulator of DISC1 and Embryonic Cortical Development.” Publishing in Neuron 67, 33-48, July 15, 2010. DOI 10.1016/j.neuron.2010.06.002

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