

Exome sequencing establishes dysregulation of neural progenitor cell fate as a critical mechanism in human congenital hydrocephalus

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Congenital hydrocephalus (CH), thought to arise from failed cerebrospinal fluid (CSF) homeostasis, is treated with lifelong surgical CSF shunting with substantial morbidity. CH pathogenesis is poorly understood. Our recent genomics study of 180 probands with CH identified four novel CH genes, each implicated in regulating neural stem cell fate (Furey et al., Neuron, 2018). Nonetheless, less than 10 percent of studied cases are solved by these genes.

To expand our understanding of CH genetics, we doubled the size of our cohort via robust domestic and international collaborations and exome sequenced a total of 361 radiographically confirmed CH probands, including 216 case-parent trios, 14 familial cases, and 2 brain tissue-germ line paired samples.

Exome sequencing revealed multiple new causative mutations in genes we previously identified (e.g., *TRIM71* and *SMARCC1*), along with at least four novel CH genes, each of which is known to regulate ventricular zone NPC cell fate. Strikingly, three of these novel CH genes encode interacting enzymes of a signal transduction pathway targetable with available drugs.

These findings implicate new genes in CH and demonstrate related pathophysiology among sporadic and familial patients. These findings have implications for diagnosis, prognosis, and treatment, and suggest that in a subset of patients the risk of adverse neurodevelopmental outcomes may be unaltered whether or not shunting is performed.