# Scientists identify new genes related to congenital hydrocephalus

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When babies are born with congenital hydrocephalus (CH), a condition traditionally thought to be a result of a buildup of cerebrospinal fluid (CSF) in the brain, neurosurgeons normally treat the condition by

surgically implanting a shunt that drains fluid from the brain into the abdomen.

"This neurosurgical treatment can be life-saving in some cases but is clearly suboptimal and in other patients has limited positive impact on neurodevelopment," says Dr. Kristopher T. Kahle, M.D., Ph.D., assistant professor of neurosurgery, pediatrics, and cellular & molecular physiology at Yale School of Medicine. CH affects one in 1,000 births. These children can have lifelong problems such as intellectual disability, motor deficits, and epilepsy. Meanwhile, shunts often require multiple revision surgeries due to malfunction or infection. "It's not uncommon for someone to have double-digit shunt revisions over the course of their lifetime," he says. CH costs the US healthcare system $2 billion annually.

Dr. Kahle says that not all CH cases are the same, and the condition is about more than just excess fluid within the brain. It's estimated that 40 percent of CH cases have a genetic basis, and better understanding this aspect could help doctors differentiate types of cases, prescribe appropriate treatments, and develop new interventions and medications.

In the largest whole exome sequencing study of sporadic CH to date, "Exome sequencing implicates genetic disruption of prenatal neuro-gliogenesis in sporadic congenital hydrocephalus", published in *Nature Medicine* on October 19, Dr. Kahle and a team of researchers from Yale and other collaborating institutions part of the Yale-led HYDROseq consortium sought to understand the genetic makeup of the condition more deeply. This paper followed up the Kahle lab's first paper on the subject published in Neuron in 2018.

Whole exome sequencing is an efficient and affordable type of genetic sequencing that reads the portion of DNA that gives instructions to make proteins. Those proteins go on to become the building blocks of cells.

The Yale Center for Genome Analysis and Center for Mendelian Genomics, established by Drs. Rick Lifton (previously at Yale, now at Rockefeller University) and Murat Gunel, MD, current chair of neurosurgery at Yale, are world leaders in this type of sequencing. Co-first author Sheng Chi Jin and researchers were able to identify more than six new CH genes that they are highly confident increases risk for CSF by analyzing the exomes of 381 patients, as well as some of their parents (for a total of 232 trios of parents and child).

"Strikingly, these genes are not involved in CSF production or reabsorption, but rather in very early and fundamental aspects of brain development," says Dr. Kahle. Many of these genes play a key role in regulating neural stem cell growth and differentiation. "These results might help explain why many of these patients also have epilepsy, intellectual disability, and motor defects. It's not just a fluid problem. And this may have important implications for how, when, and even if we should operate on someone with this condition."

He thinks that performing exome sequencing on such patients early on could mean some children might not get shunts but instead be treated for their specific type of CH, receiving speech therapy or occupational therapy, for instance. Also, many of these genes could also be targeted with new drugs. Dr. Kahle and his team are already working on a mouse model to target one of the genetically mutated pathways and potentially reverse CH with treatments in utero.

He says another future step will be using this information to develop molecular classifications for CH to predict which genetic mutations will lead to specific outcomes, so patients and their families may understand their prognosis better. In a related paper in JAMA Pediatrics due out in mid-November entitled, "Exome sequencing as a possible diagnostic adjunct in sporadic congenital hydrocephalus," the Kahle lab's team of researchers, including Yale MD/Ph.D. candidate Benjamin Reeves,

showed that using exome sequencing in a clinical setting helped identify newborns with a common genetic mutation causing their CH, which helped in dealing with their prognosis and therapeutics.

Many large hospitals can perform whole exome sequencing, and Dr. Kahle thinks it could become the standard of care for CH patients. More research to fully understand this condition that causes lifelong disability could make the value of genetic testing even clearer. Says Dr. Kahle, "There's more to be done. That motivates us for continued gene discovery."

**More information:** Sheng Chih Jin et al. Exome sequencing implicates genetic disruption of prenatal neuro-gliogenesis in sporadic congenital hydrocephalus, *Nature Medicine* (2020). DOI: 10.1038/s41591-020-1090-2

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