CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

De Novo Mutations in Genes Regulating Neural Stem Cell Fate in Human Congenital Hydrocephalus

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Introduction

CH is a major cause of childhood morbidity and mortality, affecting 1 in 1,000 live births [1] and representing up to 3% of all pediatric hospital charges in the U.S. [2]. Accordingly, CH is a major financial burden on health care systems worldwide [3], and costs the U.S health care system alone greater than $2 billion annually [2, 4]. Over the last few decades, there has been little progress in the prevention or treatment of hydrocephalus. Current therapy consists of life-long, catheter-based CSF shunting and endoscopic third ventriculostomy with or without choroid plexus cauterization, invasive surgeries with high rates of failure and morbidity [5]. Understanding critical genetic drivers underlying human CH holds promise for the development of targeted therapies.

Methods

We exome sequenced DNA isolated from 125 patient-parent trios (affected patient and unaffected parents) and an additional 52 probands for a total of 177 non-L1CAM primary CH. Exome-sequencing data from these 440 individuals was then analyzed to identify rare, de novo and transmitted mutations contributing to CH. Candidate mutations were subsequently confirmed by Sanger

Results

Exome sequencing identified three novel genes with significant burden of rare damaging de novo or transmitted mutations: TRIM71 (p = 2.15 x 10-7), SMARCC1 (p = 8.15 x 10-10), and PTCH1 (p = 1.06 x 10-6). Additionally, two de novo duplications were identified at the SHH locus, encoding the PTCH1 ligand (p = 1.2 x 10-4). Together, these mutations explain 10% of studied congenital hydrocephalus cases. Strikingly, all four genes are required for neural tube development and regulate ventricular zone neural stem cell fate.

Conclusions

These results implicate impaired neurogenesis and not active CSF accumulation in the pathogenesis of a subset of CH patients, with potential diagnostic, prognostic, and therapeutic ramifications.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the genetic basis of hydrocephalus and recognize the pressing need for studies that aim to advance our primitive understanding of genetic and molecular determinants of this disorder, 2) Understand and appreciate the ability of large cohort, exome sequencing and bioinformatics analyses to elucidate the pathogenesis of heterogeneous disorders, 3) Identify novel, effective treatment targets in hydrocephalus in the light of novel, recurrent mutations in genes required for neural tube development and neural stem cell programming.

[Default Poster]

References

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