MedicalXpress

Researchers publish largest description of ST3GAL5 (GM3 Synthase) deficiency

February 5 2019

Researchers have combined the largest description of ST3GAL5 (GM3 synthase) deficiency using detailed natural history data from 104 individuals of Amish ancestry born between 1986 and 2017 with a definite or probable diagnosis of ST3GAL5 deficiency. The study examined objective measures of biochemistry, auditory function, brain development, and caregiver burden. GM3 synthase is encoded by ST3GAL5, and is essential for synthesis of the most biologically relevant gangliosides in mammals.

The study, led by clinicians, represents a collaborative effort by the Plain Community Health Consortium (PCHC). PCHC is a network of non-profit clinics across five states that diagnose and treat rare genetic disorders in children from the Anabaptist communities. In addition to the Clinic for Special Children, the PCHC clinics include Center for Special Children in La Farge, WI, The Community Health Clinic in Topeka, IN, Nemours duPont Pediatrics in Dover, DE and New Leaf Center in Eaton, OH. The study appears in this month's issue of *Molecular Genetics and Metabolism*.

The report includes a detailed clinical characterization of the ST3GAL5 deficiency phenotype, which includes somatic growth failure, progressive microcephaly, irritability, blindness, deafness, involuntary movements, intractable seizures, and psychomotor arrest. Researchers used available medical records and structured interviews as the basis for data collection within Amish populations across five states. In addition to records and interviews, electroencephalograms (EEGs), audiology

tests, irritability, and Parent Stress indexes, genealogical records, glycosphingolipid analysis, and newborn hearing screens were used to fully characterize the natural course of this rare and devastating disease.

This comprehensive study provides a rich baseline against which to judge the effectiveness of new disease-modifying therapies. ST3GAL5 deficiency is often diagnosed within hours of life, before the onset of neurological damage, which has motivated efforts to develop pre-symptomatic therapies. Liver transplantation might provide some benefit to children with the ST3GAL5 deficiency, but is contingent on the passage of GM3 through the blood-brain barrier. ST3GAL5 gene replacement holds promise but faces two significant obstacles. Current adeno-associated viral (AAV) gene vectors deliver to only a minority of central neurons. Strategies for better AAV design or repeat dosing may circumvent this problem. Mice have been useful in understanding human ST3GAL5 deficiency but pose challenges for pre-clinical treatment studies. Pigs more closely model human neurodevelopment and may prove more suitable for studying ganglioside-deficient brain diseases. While the study's initial findings suggest that these therapies might be successful for ST3GAL5 deficiency, researchers note that in-depth studies are warranted to determine the best potential treatments for ST3GAL5 deficiency.

More information: Lauren E. Bowser et al, Recessive GM3 synthase deficiency: Natural history, biochemistry, and therapeutic frontier, *Molecular Genetics and Metabolism* (2019). DOI: 10.1016/j.ymgme.2019.01.013

Provided by Clinic for Special Children