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Clinical Letter

An *ACSL4* Hemizygous Intragenic Deletion in a Patient With Childhood Stroke

Caitlin A. Chang, MD [a], Julie Lauzon, MD, MHSc [a, b], Adam Kirton, MD, MSc [b, c], Bob Argiropoulos, PhD [a, b, d, *]

[a] Department of Medical Genetics, Alberta Children's Hospital, Calgary, Alberta, Canada
[b] Alberta Children's Hospital Research Institute for Child and Maternal Health, Alberta Children's Hospital, Calgary, Alberta, Canada
[c] Department of Pediatrics and Clinical Neurosciences, Pediatric Neurology, Alberta Children's Hospital, Calgary, Alberta, Canada
[d] Genetic Laboratory Services, Cytogenetics Laboratory, Alberta Children's Hospital, Calgary, Alberta, Canada

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We describe a male with a maternally inherited 9.75-kb intragenic deletion of *ACSL4*. Fewer than 25 individuals have been reported with ACSL4-related X-linked intellectual disability (XLID). This individual highlights a unique presentation of *ACSL4*-related XLID and reveals additional pathways for investigation.

Patient description

This boy was born at term via an uncomplicated spontaneous vaginal delivery. Initial development was normal. He presented with acute-onset left hemiparesis at 16 months due to an acute arterial ischemic stroke (AIS) in the right basal ganglia. Tests for parainfluenza and adenovirus were positive. Vascular tortuosity was present. Additional evaluation for stroke risk factors, including lumbar puncture, echocardiogram, and examination of blood for thrombophilia and inflammatory markers were negative.

At three years, severe communication delays were evident. Behavioral difficulties included frequent outbursts, irritability, and tantrums. There were no limitations in gross or fine motor functioning. At 4.5 years, he developed seizures characterized by eye deviation and automatisms. At age five years, a microarray was performed to evaluate severely delayed language, intellectual, social, and behavioral development. He was nondysmorphic on clinical genetics assessment.

Chromosome microarray (via the Cytosure ISCA 8 × 60 K v2.0 platform) on peripheral blood detected a 9.75-kb copy number loss within chromosome Xq23, encompassing exons 1 to 6 of *ACSL4*: arr [GRCh37] Xq23(108919564_108929311)x0. Microarray analysis in the mildly delayed mother identified a mosaic heterozygous deletion of the same region (level of mosaicism 9.7%).

Follow-up imaging two years post-AIS revealed no significant change from the previous study.

Discussion

ACSL4 (MIM 300157) was the first gene shown to be involved in nonsyndromic intellectual disability (ID) and fatty acid

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Publication of a single patient's clinical findings does not require REB review as per second edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2).

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* Communications should be addressed to: Dr. Argiropoulos; Cytogenetics Laboratory; Calgary Genetic Lab Services; 28 Oki Drive NW; Calgary, AB, T3B 6A8, Canada.
E-mail address: cchang2015@meds.uwo.ca (B. Argiropoulos).

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metabolism.[1] Males with *ACSL4* point or splice-site mutations present with behavioral issues, mildly affected electroencephalogram, and severely delayed speech.[2,3] Four families have been reported with large contiguous deletions or rearrangements involving *ACSL4*, presenting with ID and clinical findings relating to the loss or disruption of neighboring genes.[4-7]

ACSL4 encodes a long-chain acyl-CoA synthetase that converts free long-chain fatty acids into fatty acyl-CoA esters. Marked reduction in enzymatic activity *in vitro* leads to deranged fatty acid metabolism in neurons, alterations in dendritic spine, and attenuation of neuronal differentiation, implicating its loss in abnormal neuronal development.[1,2,8,9]

Our patient had typical features of *ACLS4* disruption, with ID and lack of dysmorphic features. His initial presentation with childhood stroke may represent an expansion of the phenotype. In patients with stroke and developmental delay out of proportion to expected findings, chromosomal microarray is an appropriate next-line investigation.

We hypothesize that *ACSL4* deficiency may have influenced our patient's predisposition to, as well as recovery from childhood-onset stroke. Arteriopathy is the leading cause of childhood AIS with both genetic and environmental associations (reviewed by McCrea et al., 2019).[10] *ACLS4* plays an important role in arachidonate metabolism and may act to the regulate secretion of arachidonic acid-derived lipid mediators from the arterial wall. Sustained ACLS4 downregulation in arterial smooth muscle cells *in vitro* reduces synthesis of prostaglandin E_2, a prostaglandin with vasodilator effects.[11] Downstream effects of ACSL4 may include regulation of smooth muscle cells proliferation, release of inflammatory mediators, or other processes in the vascular wall.[11]

There are several limitations to our report. No other individuals with a deletion encompassing only *ACSL4* have been reported in the literature, and the patients with point mutations or large contiguous gene deletions have not been reported to have had cerebrovascular events or vascular imaging. Therefore the presence of AIS in our patient may be incidental. Additional vascular imaging studies in patients with *ACLS4* disruptions may help to clarify whether there is a true underlying association with vascular tortuosity or childhood stroke.

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