PLATFORM PRESENTATIONS

Grand Plenary Abstracts

GR.1

Different functional consequences result in different phenotypes in CLCN4-related developmental and epileptic encephalopathy

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doi: 10.1017/cjn.2023.70

Background: Variants in *CLCN4* are implicated in neurodevelopmental disorder, X-linked intellectual disability, and epileptic encephalopathy. *CLCN4* encodes ClC-4, which is hypothesized to play a role in ion homeostasis and intracellular trafficking. ClC-4 relies on its formation of heterodimers with ClC-3, which possesses signals for target organelles. Methods: Case-Series. Then, we performed heterologous expression, patch-clamp electrophysiology, confocal microscopy, and protein biochemistry experiments to characterize our patients' ClC-4 variants. Results: All three male patients had developmental and epileptic encephalopathy. Patients #1 and #2 had normal-appearing brains on MRI and no dysmorphic features. Patient #3 had: microcephaly, microsomia, complete agenesis of the corpus-callosum; and, cerebellar and brainstem hypoplasia. Patient #1 had recurrent status epilepticus separated by months of seizure freedom, while Patient #2 and #3 had brief, daily seizures. The p.Gly342Arg variant impaired the heterodimerization capability of ClC-4. The p.Ile549Leu and p.Asp89Asn variants exhibited early transport-activation, with p.Asp89Asn favouring higher transport-activity of ClC-4. Conclusions: We extend the phenotypic spectrum of *CLCN4* variants and demonstrate the pathological functional-consequences of three previously unclassified variants. The p.Gly342Arg variant lead to a loss-of-function phenotype; however, the p.Ile549Leu and p.Asp89Asn variants likely caused gain-of-function phenotypes. Targeted animal or induced pluripotent stem-cell models are needed to further understand epileptogenic mechanisms of *CLCN4* variants.

GR.2

A deep intronic FGF14 GAA repeat expansion causes late-onset cerebellar ataxia

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doi: 10.1017/cjn.2023.71

Background: The late-onset cerebellar ataxias (LOCAs) have until recently resisted molecular diagnosis. Contributing to this diagnostic gap is that non-coding structural variations, such as repeat expansions, are not fully accessible to standard short-read sequencing analysis. Methods: We combined bioinformatics analysis of whole-genome sequencing and long-read sequencing to search for repeat expansions in patients with LOCA. We enrolled 66 French-Canadian, 228 German, 20 Australian and 31 Indian patients. Pathogenic mechanisms were studied in post-mortem cerebellum and induced pluripotent stem cell (iPSC)-derived motor neurons from 2 patients. Results: We identified 128 patients who carried an autosomal dominant GAA repeat expansion in the first intron of the *FGF14* gene. The expansion was present in 61%, 18%, 15% and 10% of patients in the French-Canadian, German, Australian and Indian cohorts, respectively. The pathogenic threshold was determined to be $(GAA)_{\geq 250}$, although incomplete penetrance was observed in the $(GAA)_{250\text{-}300}$ range. Patients developed a slowly progressive cerebellar syndrome at an average age of 59 years. Patient-derived post-mortem cerebellum and induced motor neurons both showed reduction in *FGF14* RNA and protein expression compared to controls. Conclusions: This intronic, dominantly inherited GAA repeat expansion in *FGF14* represents one of the most common genetic causes of LOCA uncovered to date.

GR.3

Socioeconomical disparities in acute ischemic stroke revascularization interventions in Ontario, Canada

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doi: 10.1017/cjn.2023.72

Background: Lower socioeconomic status is associated with worse outcomes after stroke. We evaluated the differences in acute revascularization treatments in patients with acute ischemic stroke (AIS) who were materially deprived compared to those who were not. Methods: In a population-based cohort study, we used linked administrative data to identify community-dwelling adults hospitalized for AIS between 2017-2022 in Ontario, Canada. The main exposure was neighborhood-level material deprivation quintiles. Multivariable logistic regression was used to obtain the adjusted odds ratio (aOR) of receiving revascularization treatments