Documents

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Abstract
Alternating hemiplegia of childhood (AHC) is a rare neurodevelopment disorder that is typically characterized by debilitating episodic attacks of hemiplegia, seizures, and intellectual disability. Over 85% of individuals with AHC have a de novo missense variant in ATP1A3 encoding the catalytic α3 subunit of neuronal Na+/K+ ATPases. The remainder of the patients are genetically unexplained. Here, we used next-generation sequencing to search for the genetic cause of 26 ATP1A3-negative index patients with a clinical presentation of AHC or an AHC-like phenotype. Three patients had affected siblings. Using targeted sequencing of exonic, intronic, and flanking regions of ATP1A3 in 22 of the 26 index patients, we found no ultra-rare variants. Using exome sequencing, we identified the likely genetic diagnosis in 9 probands (35%) in five genes, including RHOBTB2 (n = 3), ATP1A2 (n = 3), ANK3 (n = 1), SCN2A (n = 1), and CHD2 (n = 1). In follow-up investigations, two additional ATP1A3-negative individuals were found to have rare missense SCN2A variants, including one de novo likely pathogenic variant and one likely pathogenic variant for which inheritance could not be determined. Functional evaluation of the variants identified in SCN2A and ATP1A2 supports the pathogenicity of the identified variants. Our data show that genetic variants in various neurodevelopmental genes, including SCN2A, lead to AHC or AHC-like presentation. Still, the majority of ATP1A3-negative AHC or AHC-like patients remain unexplained, suggesting that other mutational mechanisms may account for the phenotype or that cases may be explained by oligo- or polygenic risk factors. © The Author(s), under exclusive licence to European Society of Human Genetics 2023.

Index Keywords
adenosine triphosphatase (potassium sodium), complementary DNA, sodium channel Nav1.2, adenosine triphosphatase (potassium sodium); adult, ANIK3 gene, Article, ATP1A3 gene, CHD2 gene, child, childhood, clinical article, cohort analysis, controlled study, exome, female, follow up, gene, gene frequency, genetic variability, genotype, HEK293T cell line, hemiplegia, heterozygosity, high throughput sequencing, human, human cell, male, pathogenicity, phenotype, RHOBTB2 gene, whole exome sequencing, article, diagnosis, DNA flanking region, drug therapy, etiology, intellectual impairment, nerve cell differentiation, risk factor, seizure, sibling

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