The Phenotypic Continuum of ATP1A3-Related Disorders

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Study Question
What is the phenotypic spectrum in individuals with pathogenic variants of the ATP1A3 gene?

What Is Known and What This Paper Adds
Variants in the ATP1A3 gene have been associated with a broad spectrum of predominantly neurologic disorders. This phenotypic variability makes it challenging to assess the pathogenicity of an ATP1A3 variant found in an undiagnosed patient. The results of this study indicate that individuals with an ATP1A3 gene variant experience a phenotypic continuum of paroxysmal events, hyperkinesia, neuropsychiatric symptoms, and cognitive impairment.

Methods
This study comprised 2 parts. The first part was a cohort study of 24 patients with a pathogenic or likely pathogenic ATP1A3 variant who were recruited through the Deciphering Developmental Disorders study (ddduk.org/) and an international network of clinical collaborators. Genomic diagnosis was made through whole-exome sequencing or diagnostic gene panel. Phenotypic details were collected using a standardized clinical proforma. The UpSetR package in R was used to visualize intersections of signs and symptoms. The second part was a review of articles published between January 2004 and August 2021, which include the term ATP1A3 to record all pathogenic ATP1A3 variants published with corresponding phenotypes. Articles were identified through a PubMed search. CADD scores were calculated and compared for pathogenic (published and study cohort) and benign or likely benign (published in ClinVar) variants, and a constraint analysis was performed.

Results and Study Limitations
For the cohort study, 24 patients carrying 21 different ATP1A3 variants were included. Patients usually experienced 2–3 different types of paroxysmal events. All experienced cognitive impairment. Other common neurologic features included microcephaly (n = 7; 29%), ataxia (n = 13; 54%), dystonia (n = 10; 42%), and hypotonia (n = 7; 29%), and 16 (67%) had neuropsychiatric diagnoses. No 2 patients shared the same combination of clinical features, but 11 (46%) had a phenotype combining paroxysmal events, hyperkinesia, neuropsychiatric symptoms, and cognitive impairment. Pathogenic and likely pathogenic missense variants from our cohort and cases reported in the literature had significantly higher CADD scores (26.5 [SD: 2.04] vs 7.7 [SD: 5.27], p < 3.49e-85) than benign variants.

Most pathogenic/likely pathogenic variants lie within 6 regions of constraint that include key protein domains such as the transmembrane helices and the cytoplasmic P and N domains. Study limitations include retrospective collection of phenotypic data. In addition, phenotypic information available for published cases is variable and sometimes limited.

Study Funding and Competing Interests
This study did not receive targeted funding. The authors report no competing interests. Go to Neurology.org/N for full disclosures.
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