Am J Hum Genet. 2026 Feb 5;113(2):362-379. doi: 10.1016/j.ajhg.2025.12.011.
Epub 2026 Jan 15.

Bi-allelic variants in neuronal adhesion molecule astrotactin 1 gene ASTN1 cause diverse neurodevelopmental disorders

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PMID: 41544630
DOI: 10.1016/j.ajhg.2025.12.011

Abstract

ASTN1 encodes astrotactin 1, a neuronal-glial ligand in the developing brain that promotes neuronal migration along radial glia in brain structures with laminar organization, such as the cerebral cortex, hippocampus, and cerebellum. In mouse models, disruption of Astn1 results in neuronal migration deficits, a mild reduction in cerebellar volume, and balance and coordination deficits. In humans, bi-allelic ASTN1 variants have been identified in nine individuals with neurodevelopmental disorders (NDDs) with or without brain malformations. ASTN1 additionally interacts with astrotactin 2 (ASTN2) to implement neuronal migration; ASTN2 deletions associate with NDDs with reduced penetrance. Here, we describe eighteen individuals with NDDs from twelve unrelated families with bi-allelic, ultra-rare, predicted damaging variants in

ASTN1 and one individual with heterozygous variants in both ASTN1 and ASTN2. We expand the clinical phenotypic descriptions of ASTN1-related NDDs, which range from mild to profound developmental delay or intellectual disability and can be associated with autism, attention-deficient hyperactivity disorder (ADHD), and epilepsy. Other recurrent abnormalities include dysmorphic facial features, hypotonia, spasticity, and ataxia. Additionally, we add to the neuroradiographic phenotype of this condition, which can be normal, mildly dysmorphic (a thin corpus callosum and cerebellar dysgenesis), or severely dysmorphic (polymicrogyria and lissencephaly). Remarkably, three genetic models of multilocus pathogenic variation (MPV), including tri-allelic, double heterozygous, and double homozygous due to distributive absence of heterozygosity (AOH), were observed. This ASTN1 allelic series characterizes the consequences of perturbations in radial-glia-guided neuronal migration in humans, the phenotypic spectrum of ASTN1-related NDDs, and the contribution of MPV to the genetic basis of NDDs.

Keywords: ASTN1; ASTN2; autism; cerebellum; distributive AOH; epilepsy; intellectual disability; multilocus pathogenic variation; neurodevelopmental disorders; neuronal migration.

Conflict of interest statement

Declaration of interests The authors declare no competing interests.

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