**DYNC1H1**

**Patient Description:**
This is a boy with global developmental delay first noted at about one year of age. Currently 11 years old, his predominant concerns relate to motor planning, coordination, learning, and hyperactivity. He is in an intensive special ed program with multiple hours of therapies each week.

Additional details on mutation: c.9052C>T (p.P3018S)
De novo, not previously reported as a pathogenic variant, but interpreted as likely pathogenic because it’s not observed in large population cohorts, it’s a non-conservative aa substitution likely to impact secondary protein structure, and in silico models predict pathogenicity. Apparently is autosomal dominant.

**Disease/Syndrome Features:**
Heterozygous, missense mutations in *DYNC1H1* cause a varied group of disorders including Charcot-Marie-Tooth disease type 2 (CMT2), spinal muscular atrophy with predominant involvement of the lower extremities (SMA-LED), malformations of cortical development (MCD), and severe intellectual disability. There is some phenotypic overlap between these conditions, as for example in the learning difficulties reported in several individuals with CMT2 or SMA-LED and *DYNC1H1* mutations.

Charcot-Marie-Tooth disease, a chronic motor and sensory polyneuropathy, is the most common inherited neuromuscular disorder. CMT is divided into type 1, which affects the myelin sheaths surrounding nerve axons, and type 2, which affects the axons themselves. Clinical features of CMT include distal muscle weakness and atrophy as well as loss of sensation, depressed tendon reflexes, and a particular foot shape termed pes cavus. A missense mutation in *DYNC1H1* has been shown to cause CMT2 in a family with 23 affected individuals. Members of this family had clinical features including delayed motor milestones, abnormal gait, reduced sensations, and early-onset slowly progressive distal lower limb weakness and wasting. Upper limb involvement was rare and individuals usually remained ambulatory into adulthood. Severely affected family members also noted neuropathic lower limb pains [Weedon 2011].

*DYNC1H1* missense mutations have also been identified in several families with SMA-LED, a rare form of dominantly inherited SMA that principally targets the legs and presents with weakness in early childhood. Despite sharing several features with CMT2, SMA-LED is distinguished by the absence of sensory findings either on examination or by electrophysiology study. Families with SMA-LED and *DYNC1H1* mutations experience a static or minimally progressive disease [Harms 2012].

In addition to these familial syndromes, whole exome sequencing has identified *de novo* mutations in *DYNC1H1* as a cause of intellectual disability [Vissers 2010, de Ligt 2012, Willemsen 2012]. Specifically, mutations in *DYNC1H1* appear to be an important cause
of MCD, a family of disorders that includes lissencephaly, pachygyria, polymicrogyria, and microcephaly. These disorders are associated with severe cases of intellectual disability and involve a disturbance in the coordinated developmental proliferation, migration, or differentiation of specific neuronal populations. Posterior pachygyria is the cortical malformation most commonly associated with *DYNC1H1* mutations, but many patients had additional abnormalities, and two had patterns of both pachygyria and polymicrogyria [Poirier 2013].

**Protein/Pathway:**
*DYNC1H1*, dynein cytoplasmic 1 heavy chain 1, encodes a large component of the cytoplasmic dynein complex. Dyneins are a family of cytoskeletal motor proteins that convert ATP to mechanical energy in order to move along microtubules within cells. There are two major classes of dyneins, axonemal and cytoplasmic, and cytoplasmic dyneins are involved in numerous cellular processes including retrograde axonal transport, nuclear positioning, Golgi localization, and autophagy. Cytoplasmic dynein’s role in mitotic and post-mitotic motility as well as in the regulation of neuronal homeostasis help explain the variety of neuropathies and CNS malformations observed in patients with *DYNC1H1* mutations.

Pairs of the dynein heavy chain homodimerize via N-terminal tail domains to form the core of the dynein complex. *DYNC1H1* also encodes binding sites for peripheral components and a C-terminal motor domain with seven AAA domains and a microtubule-binding domain. Missense mutations in the tail domain cause the mouse phenotypes *Legs at odd angles, Cramping I*, and *Sprawling*, which display defective retrograde transport leading to neurodegeneration and errors in neuronal migration and axon growth [Hafezparast 2003].

Dynein complexes purified from SMA-LED patient fibroblasts heterozygous for the I584L *DYNC1H1* mutation showed several features of impaired activity. For example, while they bound microtubules in the absence of ATP, binding was decreased in the presence of ATP. Additionally, complexes showed decreased stability as assayed by sucrose gradient fractionation [Harms 2012]. Many cases of the MCD lissencephaly are associated with mutations in *PAFAH1B1*, which encodes a protein involved in microtubule homeostasis and interacts with *DYNC1H1*.

**Publications:**


Poirier, K., Lebrun, N., Broix, L., Tian, G., Saillour, Y., Boscheron, C., … Chelly, J. (2013). Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nature Genetics, 45*(6), 639–647. https://doi.org/10.1038/ng.2613


**Support Groups and Information:**
- Charcot-Marie-Tooth Association
- Cortical Malformation & Cephalic Disorder Foundation
- Muscular Dystrophy Association