

DYNC1H1

Tutorial with Parents (October 22, 2018)

The tutorial took place in the Kennedy IDDRC office and was attended by both parents. Dr. Walkley hosted the meeting which was also attended by medical student, Adam Kopp who had prepared the written scientific review of the gene and condition. Dr. Wasserstein began the tutorial with an overview of the child's condition which was further elaborated by the parents. The child had been seen some years ago as well in CERC by Dr. Lisa Shulman. The scientific presentation occurred in two parts, with Dr. Arne Gennerich presenting a beautiful overview of motor proteins (complete with movies) and how a mutation in a dynein motor could cause such variable phenotypes. The second scientist was Dr. Bridget Shafit-Zagardo, who provided important insight into how an in vivo model system involving zebrafish could be used to model the mutation occurring in the child. Drs. Gennerich and Shafit-Zagardo each received 2019 IDDRC pilot grants to pursue studies in their labs on how disruptions of the dynein motor complex secondary to mutations in *DYNC1H1* can cause this complex disease.

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.

Charcot-Marie-Tooth disease is a spectrum of chronic motor and sensory polyneuropathies caused by mutations in various genes that are involved with myelin and/or axonal structures within peripheral nerves, and it is the most common inherited neuromuscular disorder. The most common 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. The major categories of CMT are types 1 through 7, as well as an X-linked category, CMT-X. Within each category, a letter assigns a

specific gene associated (eg CMT1A, CMT1B, etc). Broadly speaking, CMT1 affects the myelin sheaths surrounding nerve axons, CMT2 affects the axons themselves. CMT3, which comprises two disorders (Dejerine-Sottas syndrome and congenital hypomyelinating neuropathy), is a severe, early-onset peripheral neuropathy thought to be caused by an inability of Schwann cells to produce normal myelin. CMT4 is a rapidly expanding category of autosomal recessive demyelinating motor sensory neuropathies, which are rarer, more clinically severe, and less likely to result from mutations in structural myelin proteins than the autosomal dominant forms. CMT5, 6, and 7, also referred to as hereditary motor sensory neuropathy (HMSN), are referred to more commonly by their associated symptoms (HMSN 5 with autosomal dominant spastic paraparesis with sensory neuropathy, HMSN 6 with dominant or recessive optic atrophy and motor sensory neuropathy, HMSN 7 with retinitis pigmentosa and motor sensory neuropathy).

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:

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intellectual disability with neuronal migration defects. *Journal of Medical Genetics*, 49(3), 179–183. <https://doi.org/10.1136/jmedgenet-2011-100542>

Support Groups and Information:

[Charcot-Marie-Tooth Association](#)

[Cortical Malformation & Cephalic Disorder Foundation](#)

[Muscular Dystrophy Association](#)

Facebook group: DYNC1H1 Gene Mutation Family Support Group (private group, 125 members, provides information and support for families affected by DYNC1H1 mutations).

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