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# A novel single dominant *DYNC1H1* pathogenic variant causes various upper and lower motor neuron anomalies

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Rong Mao, analysis or interpretation of data, drafting/revising manuscript
Hunter Best, acquisition of data, analysis or interpretation of data
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Xavier Hernandorena, acquisition of data, revising manuscript
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**Abstract**

**Objective:** To perform genotype-phenotype, clinical and molecular analysis in a large 3-generation family with autosomal dominant congenital spinal muscular atrophy.

**Methods:** Using a combined genetic approach including whole genome scanning, next generation sequencing-based multigene panel and targeted variant Sanger sequencing, we studied the proband and multiple affected individuals of this family who presented with bilateral proximal lower limb muscle weakness and atrophy.

**Results:** we identified a novel heterozygous variant, c.1826T>C; p.Ile609Thr, in the *DYNC1H1* gene localized within the common haplotype in the 14q32.31 chromosomal region cosegregated with disease in this large family. Within the family, affected individuals were found to have a wide array of clinical variability. Although some individuals presented the typical lower motor neuron phenotype (SMA-LED) with areflexia and denervation, others presented with muscle weakness and atrophy, hyperreflexia and absence of denervation suggesting a predominant upper motor neuron disease. In addition, some affected individuals presented with an intermediate phenotype characterized by hyperreflexia and denervation, expressing a combination of lower and upper motor neuron defects.

**Conclusion:** Our study demonstrates the wide clinical variability associated with a single *DYNC1H1* mutation and this mutation demonstrated a high penetrance within this large family.

Key words:
***DYNC1H1*,** Spinal muscular atrophies, Exome

## Introduction

Motor neuron disorders from a large spectrum of inherited diseases including spinal muscular atrophies (SMA), familial amyotrophic lateral scleroses (FALS), hereditary spastic paraplegias (HSP) and overlapping phenotypes. Each of these diseases are genetically heterogeneous and are commonly classified by their mode of inheritance, the spatial distribution of muscle weakness, the age at onset, the severity and the occasional presence of additional clinical features.[1,2] Autosomal dominant Spinal Muscular Atrophy with Lower limb predominance (SMA-LED; OMIM# 158600) is a clinically well characterized type of SMA, with autosomal dominant inheritance,

congenital or early childhood onset, lower limb predominant weakness and slow or absent progression.[3-7] Two genes have been associated with SMA-LED: *DYNC1H1* (Dynein Heavy Chain 1), coding for a major component of the Dynein-Dynactin motor complex and *BICD2* (Bicaudal D2) a molecular partner of *DYNC1H1*.[8-20] Mutations in both of these genes cause lower and upper motor neuron diseases. Some *DYNC1H1* mutations cause SMA-LED, others cause axonal Charcot Marie Tooth disease (CMT 20 ; OMIM# 614228) and some mutations cause hereditary spastic paraplegia (SPG3 ; OMIM# 182600)[9,14,16,21]. Here we studied a large 3-generation family with 21 affected members presenting bilateral lower limb weakness and muscle atrophy with neurological findings revealing a variable combination of upper and lower motor neurons defects among the individuals. Using a combined genetic approach, we identified a unique novel N-terminal tail domain heterozygous missense mutation (Ile609Thr) in the gene *DYNC1H1* in all these individuals, which suggests a significant role of modifying genes in the neuronal expression pattern of *DYNC1H1* gene mutations.

## Patients and methods

### Data Collection

Patients belong to a large three-generation pedigree with 21 affected individuals with ages ranging from 64 to 13 years (figure1). Patients with history of non-progressive bilateral pelvic girdle muscles weakness since childhood were considered affected. Medical records from 7 clinical centers in France (Tours, Limoges, Bordeaux, Rouen, Bayonne, Paris, Avignon) were reviewed for 18 affected individuals and electrophysiological studies were conducted in 16 of them. Peripheral blood DNA was obtained after informed consent from 20 affected and 15 non affected subjects.

### Next generation sequencing (NGS) based multigene panel screening

NGS was performed on the proband (II16) using DNA extracted from whole blood. Proband's DNA sample (II16) was captured using the multigene panel for Charcot Marie Tooth diseases (NSPv.20 CMT NimbleGen, developped and validated by ARUP Lab) and sequenced with 2X100 bp paired end on an Illumina 2500 according to manufacturer's recommendation. Sequence variants were called with Genome Analysis Toolkit (v.1.6) and filtered using DbSNP, 1000 Genomes Project, 6500 Exomes and the ARUP internal database. In silico analyses of variants were performed using PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.jcvi.org/), and MutationTaster (http://www.mutationtaster.org/) to predict the possible disruption of protein functions.

**DNA Sanger sequencing**

Amplicon of *DYNC1H1* exon 8 was amplified in the DNA of the 20 affected and 10 non affected individuals and sequenced using BigDye® Terminator Cycle Sequencing Kit (Applied Biosystems, Carlsbad, California) on an Applied Biosystems 3730 DNA Analyzer. Primer sequences are available upon request.

**Haplotype analysis**

A genome-wide scan analysis was performed among the DNAs of 15 patients, using 1,088 microsatellite markers with an average marker distance of 4cM (DeCode Genetics). Haplotype analysis at the candidate 14q32.2-q32.3 chromosomal region was performed in 20 affected individuals. Parametric computerized linkage analysis (MERLIN software) was made at the locus D14s979. For LOD score calculation, we used a model of rare autosomal dominant disease (prevalence 1.10,000), a 100% penetrance and a 0% phenocopy parameter. Allele frequencies at the selected locus were obtained from the online databases for Caucasian population (CEPH).

**Results**

**Various neurological phenotypes in the same family**

All the individuals examined presented childhood onset proximal weakness without deterioration of motor function over time. None of them had arthrogryposis or feet deformity at birth and all were able to walk independently at time of observation. Neurological examination and electrophysiological studies revealed remarkable differences with a variable combination of lower motor neuron disease symptoms (areflexia, distal muscle wasting, foot deformity, electrical denervation) and upper motor neuron symptoms (hyperreflexia, ankle clonus, abolished somatosensory evoked potentials). These findings are summarized in table 1. Five patients presented a pure lower motor neuron disease with a pattern of chronic denervation, corresponding to the typical SMA-LED phenotype (see patient III16 in table 2 and figure 2A). Five other patients, did not show evidence of denervation but exhibited spasticity in the lower limbs meeting the criteria of a pure hereditary spastic paraplegia (see patient II10 in table 2 and III14 in figure 2B). The other 6 patients presented an intermediate phenotype with lower and motor neuron disease symptoms (see patient III7 in table 2 and figure 2C). Mental function evaluation was not performed but most of the patients presented learning difficulties at school.

**Identification of a novel tail domain mutation in the gene *DYNC1H1***

Next generation sequencing-based multigene panel in patient III16 allowed to identify a heterozygous variant, c.1826T>C, in the coding sequence of exon 8 of gene coding for the Heavy Chain 1 of Cytoplasmic Dynein (*DYNC1H1*). This variant, not previously reported in the literature or population databases, causes a missense mutation p.Ile609Thr at the protein level in a highly conserved region among vertebrate species. The mutation maps to the N-terminal region which is the dimerization domain at the stem of *DYNC1H1*, mediating the formation of dynein heavy chain dimers and interactions with dynein intermediate light chains. Ile609Thr is predicted to be pathogenic by the computational prediction programs (SIFT, PolyPhen and MutationTaster). Whole genome sequencing in patient III16 and III3 showed the same heterozygous variant and

no other pathogenic variants were identified in the currently known dominant genes that could lead to motor neuron defect. Targeted Sanger sequencing of *DYNC1H1* exon 8 further showed the cosegregation of the variant, Ile609Thr, in the 20 affected individuals tested of this family. This variant was absent in the 10 non-affected individuals tested.

**Genetic linkage to the *DYNC1H1* gene locus on chromosome 14q32.3**

Whole genome scanning and haplotype analysis on 20 affected individuals presenting the three previously reported clinical presentations refined the locus of the disease to the same chromosomal region containing the entire sequence of gene *DYNC1H1* (14q32.3, between loci D14S1066 and D14S1007), cosegregating with an autosomal dominant pattern. Linkage analysis demonstrated a positive value with a maximum LOD score at marker D14s979 (Zmax=5.30) at the recombination fraction theta = 0.00 (data available on request).

**Discussion**

Spinal muscular atrophy with autosomal dominance inheritance is a clinically heterogeneous subgroup of hereditary motor neuropathies, involving multiple genes and various molecular pathways.[24] Among them, Spinal Muscular Atrophy with Lower limb predominance and autosomal dominant inheritance (SMA-LED) is a lower motor neuron disease recently described, characterized by almost exclusive involvement of lower limbs, proximal predominance of muscle weakness, frequent distal muscle wasting and mild or absent progression and a typical muscle MRI imaging pattern with a diffuse involvement of the quadriceps and a relative sparing of the adductor compartment[10,17] SMA–LED has been initially linked to mutations of gene *DYNC1H1*, a major component of the Dynein-Dynactin motor protein complex. The 30 reported *DYNC1H1* mutations associated to the SMA-LED phenotype,[8,9,13,14,16,17,18,19] are almost always located in the stem domain of the protein, while mutations located in the motor domain of *DYNC1H1* are reported in malformations of cortical development (MCD) and intellectual disability[15,22,23,25] without

or with limited lower motor neuron involvement. We report in this study a novel *DYNC1H1* mutation located in the stem domain, affecting both lower and upper motor neurons at various degrees, with a broad phenotypical range extending from a pure motor neuropathy to a pure spastic paraplegia. In fact, other *DYNC1H1* tail domain mutations has already been reported in patients presenting Hereditary Spastic Paraplegia (HPN)[14] and the involvement of upper motor neurons has already been evoked in SMA-LED[17] or even with MCD23 patients presenting hyperreflexia of the lower limbs. In our study a same *DYNC1H1* mutation is associated with either a pure motor neuron disease (SMA-LED), a pure upper motor neuron disease (HSP) or an intermediate phenotype. This suggests that the type of neuronal expression might be influenced by other factors than by the protein variant itself. These factors could be epigenetic or more probably genetic, as suggested by the clustering of pure HSP phenotypes in a same branch of the family studied here (a mother with her 3 sons). Note that this pleotropic effect of a unique *DYNC1H1* tail domain mutation has been reported by Tsurusacki et al, in a family with either autosomal dominant axonal CMT or SMA-LED phenotype.[9] A similar combination of upper and lower motor neuron diseases has been reported in the phenotypical spectrum related to gene *BICD2* (Bicaudal D Homolog 2) mutations[11,12] , a key adaptor protein interacting with *DYNC1H1*. *BICD2* mutations are responsible for a pure autosomal dominant spinal muscular atrophy phenotype (SMA-LED2), a pure HSP and a phenotype combining lower limbs hyperreflexia and SMA-LED2.[10,11,12] An increasing number of scientific data shows that Golgi functional and structural defects is a common pathophysiological feature of several lower and upper motor neuron diseases. In another hand, Dynein-Dynactin motor protein complex plays a key role in Golgi structure, dynamics and localization. Reported missense *DYNC1H1* tail mutations increase *BICD2-DYNC1H1* interactions, decreasing the binding of the Dynein–Dynactin motor complex to microtubules in a dominant negative manner. The subsequent impairment of cellular transport and Golgi function in *DYNC1H1* related disorders plays probably a major role in motor neurons dysfunction.[16,18,26]

Figure 1. Pedigree of the 3 generations family with autosomal dominant inheritance. Filled symbols represent the affected individuals. The specific phenotypes are color coded: red symbols are used for pure Lower motor neuron phenotype (Spinal Muscular Atrophy); blue symbols for pure upper motor neuron phenotype (Spastic Paraplegia); green symbols for combined lower and upper motor neuron phenotype; black symbols for affected individuals without medical record available.

Table 1: Clinical and electrophysiological characteristics of 16 patients of the same family. Neurogenic EMG pattern is defined by decreased or absent recruitment and large amplitude potentials. ND = not documented. Osteotendinous reflexes scale: 0 = absent, 1+= present only with reinforcement 2+= normal, 3+=brisk, 4+= markedly hyperactive with clonus.

Table 2: Summary of the clinical informations from 3 patients presenting a pure upper motor neuron phenotype (III6), a pure upper motor neuron phenotype (II10) and a combined phenotype (III7)

Figure 2. Pictures of 3 patients presenting the SMA-LED phenotype (A-III16), the HSP phenotype (B-III14) and the combined upper and lower motor neuron phenotype (C-III17). Thigh muscles wasting is more pronounced in patients III4 and III17 although pelvic girdle weakness is a common feature of all affected individuals in this family.

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**Figure 1**

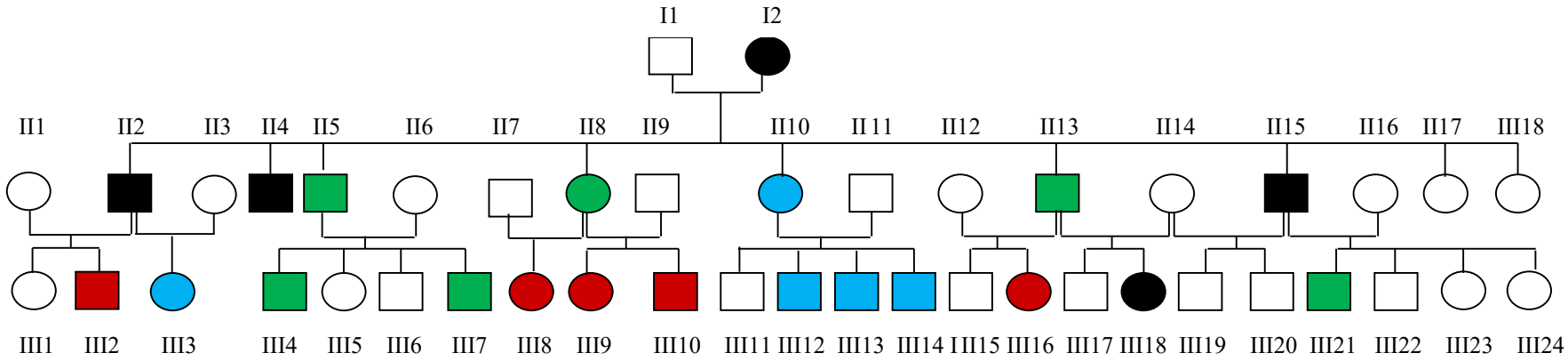
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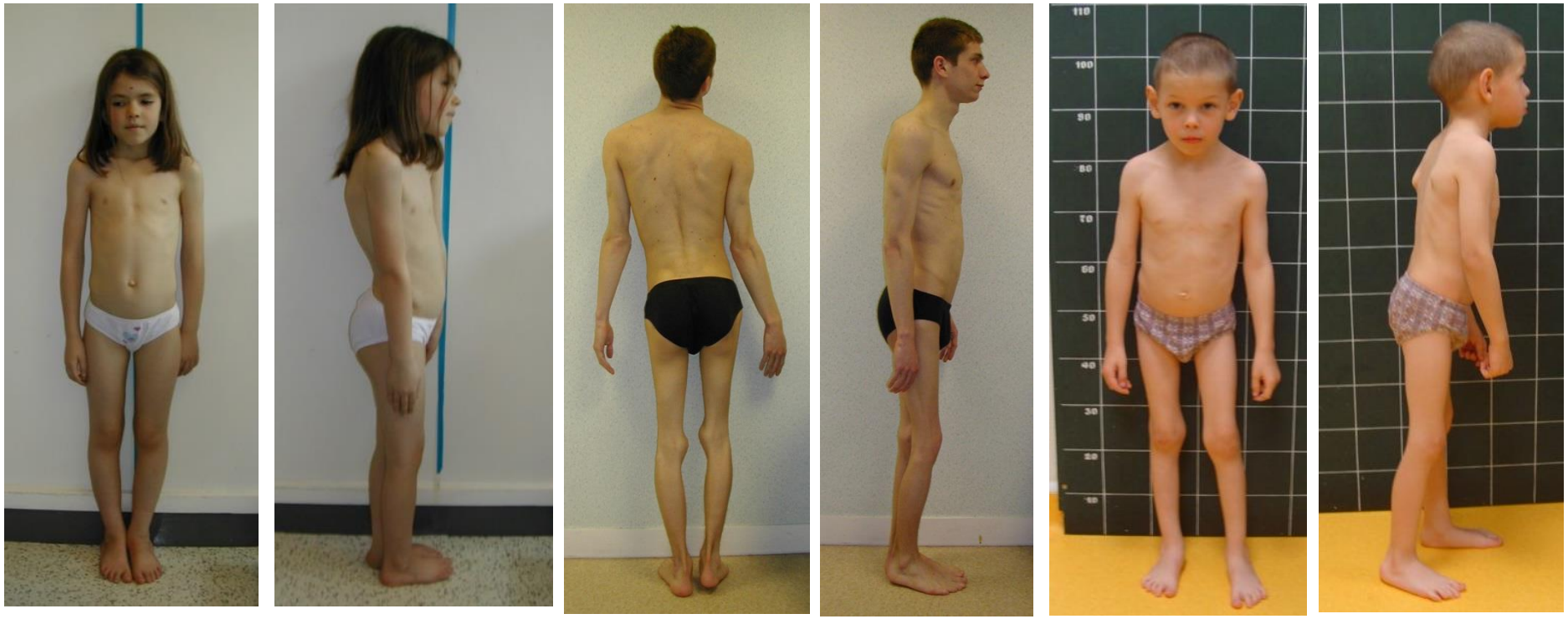
**Figure 2**

**A. Individual III16** **B. Individual III14** **C. Individual III7**



| Patients | Age at last physical examination | Distribution of muscle atrophy | Feet deformity | Knee reflexes | Ankle reflexes | Age at EMG | EMG Lower limbs | Lower limbs motor and sensory NCVs |
|---|---|---|---|---|---|---|---|---|
| II 5 | 42yo | thighs | high arched | 2+ | 4+ | 35yo | neurogenic | normal |
| II 8 | 42yo | legs | high arched | 0 | 3+ | 41yo | neurogenic | normal |
| II 10 | 46yo | legs and thighs | ND | 2+ | 4+ | 46yo | normal | normal |
| II 13 | 44yo | legs | ND | ND | ND | 44yo | normal | normal |
| III 2 | 4yo | legs | flat | 0 | 0 | 4yo | neurogenic | normal |
| III 3 | 4yo | ND | flat | 2+ | 3+ | 15yo | normal | normal |
| III 4 | 3yo | thighs and legs | flat | 2+ | 1+ | ND | ND | ND |
| III 7 | 5yo | legs and thighs | flat | 3+ | 4+ | 4yo | neurogenic | normal |
| III 8 | 17yo | ND | high arched | 2+ | 2+ | 27yo | neurogenic | normal |
| III 9 | 15yo | ND | high arched | 0 | 1+ | 2yo | neurogenic | normal |
| III 10 | 17yo | legs and thighs | ND | 0 | 1+ | 3yo | neurogenic | normal |
| III 12 | 19yo | legs and thighs | flat | 3+ | 3+ | 14yo | normal | normal |
| III 13 | 19yo | legs and thighs | flat | 3+ | 4+ | 14yo | normal | normal |
| III 14 | 23yo | legs and thighs | yes | 2+ | 4+ | 18yo | normal | ND |
| III 16 | 5yo | legs | flat | 1+ | 1+ | 12yo | neurogenic | normal |
| III 21 | 10yo | ND | high arched | 1+ | 3+ | 10yo | neurogenic | normal |

| | Patient III16 | Patient II10 | Patient III7 |
|---|---|---|---|
| Gender, age | Female, 8 yo | Female, 46 yo | Male, 5 yo |
| Development | Normal, walked at 15 months | | Hip dysplasia at birth. Walked at 18 months with frequent falls. |
| Neurological examination | Waddling gait, frequent falls, difficulties for climbing stairs and long walks. Positive Gower's sign. Bilateral flat feet hyperlaxity of ankles. Mild leg muscles atrophy. Decreased knee and ankle reflexes. No Babinsky, no ankle clonus. Mild intention tremor of the hands. No intellectual disability. | Mild limitation of walking distance. Thighs and legs muscle wasting. Brisk knee and ankle reflexes with bilateral ankle clonus. Normal superficial sensation at the lower limbs. Decreased distal vibratory sensation at the lower limbs. No upper limbs weakness or atrophy. No intellectual disability. | Unable to run. Difficulties for climbing stairs, rising from sitting on the floor and walking on heels. Bilateral flat feet, ankle valgus and Achilles tendon stiffness. Buttocks, thighs and legs muscle wasting. Brisk knee and ankle reflexes with bilateral ankle clonus. No Babinsky or Rossolimo sign. Learning difficulties. |
| Electrophysiological studies | Lower limbs electromyography and conduction studies showed decreased or absent recruitment with large amplitude potentials. Normal motor and sensory nerve conduction velocities No spontaneous fibrillation recorded | Normal lower limbs electromyography and conduction studies<br>Somatosensory evoked potentials abolished (provoked by lower limbs nerves stimulation) | Lower limbs electromyography and conduction studies showed decreased or absent recruitment with large amplitude potentials. Normal motor and sensory nerve conduction velocities |
| Imaging | ND | Brain and Spine MRI normal | ND |