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Case report

A missense mutation in *DYNC1H1* gene causing spinal muscular atrophy – Lower extremity, dominant

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ABSTRACT

Spinal muscular atrophy (SMA) is a hereditary neuromuscular disorder, which causes progressive muscle weakness and in severe cases respiratory failure and death. Although the majority of the SMA cases are autosomal recessive, there is an autosomal dominant variant of SMA that primarily affects the lower extremities, known as 'spinal muscular atrophy – lower extremity, dominant' (SMALED). Mutations in the Dynein Cytoplasmic 1 Heavy Chain 1 (*DYNC1H1*) gene were the first to be associated with SMALED. Here we report a family with SMALED caused by a pathogenic heterozygous missense c.1809 A > T, p. glu603Asp mutation in *DYNC1H1*. The main clinical features were congenital hip displacement, talipes, delayed motor development, wasting and weakness in lower limbs with relative sparing of upper extremities and very slow disease progression.

SMALED is extremely rare and only a handful of families have been reported. Over the years other phenotypes including Charcot Marie Tooth type 2 and hereditary mental retardation with cortical neural migration defects have also been reported to be caused by *DYNC1H1* mutations.

This report aims to increase our awareness of SMALED and various other phenotypes associated with mutations in this gene.

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Abbreviations: SMA, spinal muscular atrophy; SMALED, spinal muscular atrophy – lower extremity, dominant; *DYNC1H1*, Dynein Cytoplasmic 1 Heavy Chain 1 gene; EMG, electromyography.

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1. Introduction

Spinal muscular atrophy (SMA), a hereditary neuromuscular disorder, is characterised by degeneration and loss of motor neurons in the anterior horn of the spinal cord resulting in progressive muscle weakness and, in severe cases respiratory failure and death [1]. The majority of the SMA cases are autosomal recessive and caused by homozygous deletion or mutation of the *SMN1* gene. However, there is an autosomal dominant variant of SMA that affects primarily the lower extremities, known as spinal muscular atrophy – lower extremity, dominant (SMALED) [2].

Mutations in several genes have been associated with SMALED, including Dynein Cytoplasmic 1 Heavy Chain 1 (*DYNC1H1*), protein bicaudal D homolog 2 (*BICD2*) and transient receptor potential cation channel subfamily V member 4 (*TRPV4*) [3–5]. Here we describe a family with SMALED caused by a pathogenic missense mutation in *DYNC1H1*. Mutations in this gene were the first to be identified as a cause of SMALED [3]. This gene encodes the force generating subunit of the cytoplasmic dynein motor complex, which participates in a wide variety of cellular functions, such as shuttling of cellular constituents towards the minus ends of the microtubules and numerous aspect of mitosis. These functions make the dynein motor complex a critical player in neurogenesis and migration [6].

2. Case description

The proband (Fig. 1A, III 2) presented to our neurology clinic with a waddling gait and lower limb weakness since childhood. He was born breech at 37 weeks and had bilateral congenital hip dislocation as well as talipes equinovarus requiring multiple surgeries in his childhood. He managed to walk unaided at the age of 18 months. He often stumbled or tripped due to his lower limb weakness and could only walk short distances. Examination revealed an excessive lumbar lordosis, and bilateral marked quadriceps wasting, pes cavus, tight-tendo Achilles, and knee contractures. He had lower limb weakness, particularly hip flexion and knee extension. Deep tendon reflexes were reduced at the knee and absent at the ankle. There were no abnormal sensory signs and the examination of the upper limb extremities was normal.

Laboratory test showed normal serum total creatine kinase. Nerve conduction studies showed normal sensory and motor amplitudes and conduction velocities, and electromyography (EMG) revealed chronic neurogenic changes. Magnetic resonance imaging of the thighs demonstrated severe focal muscle atrophy affecting both quadriceps musculature, especially vastus lateralis, vastus intermedius and rectus femoris. To a lesser extent, hip adductor muscles were also affected. Hamstring compartments were relatively preserved and there was no sign of active inflammation. (Fig. 1B).

The probands father (II 3) and brother (III 1) also had similar phenotype. Both had congenital hip dislocations and talipes equinovarus. They also had prominent proximal muscle wasting in the lower extremities (Fig. 1C). The EMG of II3 showed chronic neurogenic changes in upper limbs as well as lower limbs. The clinical features of these subjects and other family members are summarised in the Table 1.

The pedigree was suggestive of an autosomal dominant disorder (Fig. 1A). The proband was tested with a panel of 56 genes associated with inherited peripheral neuropathies, using Agilent SureSelectXT^2 custom target enrichment system and Next Generation Sequencing, and found to harbour a heterogeneous missense variant in exon 8 of the *DYNC1H1* gene, c.1809 A > T, p.Glu603Asp (NM_001376.4). Screening of other family members confirmed segregation in affected individuals. p.Glu603, located in the tail domain of the protein, is highly conserved across species (Fig. 1D). Recently a different mutation, p.Glu603Val (NM_001376.4) in the same location has also been reported to cause SMALED [7].

3. Discussion

We identified a family with SMALED caused by a missense mutation in *DYNC1H1*. The main clinical features were congenital hip displacement, talipes, delayed motor development, wasting and weakness in lower limbs with relative sparing of upper extremities and very slow disease progression. Others have reported similar SMALED phenotype associated with *DYNC1H1* mutations [2,3,7–14]. Symptoms tend to manifest at birth or infancy, and typically by the first decade of life. The severity of the symptoms may vary. A mother with a pathogenic *DYNC1H1* mutation only had difficulty with squatting and quadriceps wasting, which was revealed by a muscle computed tomography scan, whereas her two sons had typical SMALED phenotype [8]. Quadriceps is the commonest muscle group that is affected, but distal lower limb muscles can also be affected. Although the upper extremities are often spared, there are some reports of upper limb wasting and weakness. Scapular winging is one of the common upper limb features. The EMG of the upper limb muscles also showed neurogenic changes in one of our cases (II 3). Besides wasting and weakness, arthrogryposes in the lower limb is another common feature, particularly congenital hip dislocation and talipes equinovarus. Spine deformity, especially lumber hyperlordosis is also prevalent. Therefore, it is not surprising that gait development is delayed and eventually most of them learn to walk unaided, but often have a waddling gait. Rarely, they may also have intellectual disability and epilepsy [12,15]. MRI brain is scarcely performed in SMALED to assess cortical abnormalities.

Lower limb predilection in *DYNC1H1* mutation associated SMA is thought to reflect a localised pattern of anterior horn cell loss. The static or very slowly progressive clinical course together with congenital arthrogryposes suggest that the clinically significant loss of anterior horn cells occurs prenatally and is largely completed by birth. SMALED caused by *DYNC1H1* mutations is not a fatal condition and the lack of autopsy examination makes it difficult to prove these hypotheses.

There are other phenotypes that have been associated with *DYNC1H1* mutations. Weedon et al. reported *DYNC1H1* mutations in a large family with Charcot Marie Tooth type 2 [16]. Early onset, delayed motor development, distal lower limb wasting and weakness and pes cavus deformity were the core

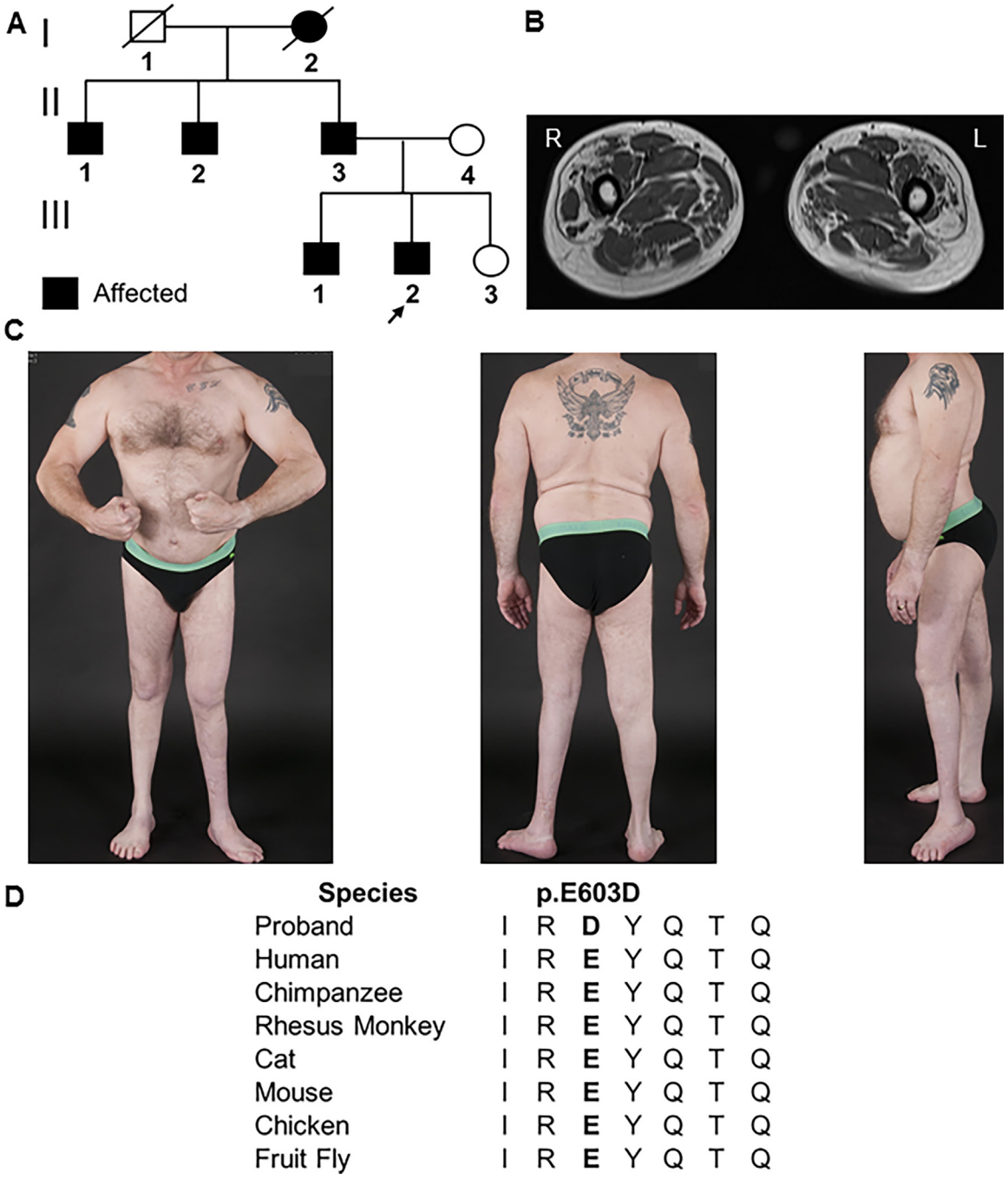

Fig. 1 – (A) Pedigree structure; I 1 and I 2 died before they could be tested for mutations. II 1 and II 2 refused genetic testing. (B) The muscle MRI of the proband showed severe quadriceps wasting. (C) Severe lower limb wasting in the proband's father. (D) Amino acid sequence of the mutation site is conserved across many species.

features of the affected family members, which were consistent with Charcot Marie Tooth. Upper limb involvement was less frequent. Also, intact fine touch, vibration sensation and proprioception, frequent proximal lower limb muscle involvement, spinal deformity, hip problems and a broad-based waddling gait were some of the atypical features that were present in many members of the family. In addition, few had delay in speech development and intellectual disability [16]. Therefore, after revaluating the phenotype reported in the original paper, we suggest that this phenotype resembles SMALED, an early onset static or slow progressive motor neuropathy rather than Charcot Marie Tooth.

Hereditary mental retardation with cortical neural migration defects is another phenotype that has been associated with *DYNC1H1* mutations [15,17,18]. Besides variable degrees of cognitive impairment, they have severe

Table 1 – Clinical features of all affected family members.

Patient	Age (Y)	Phenotype
I 2	82	She had lower limb muscle wasting and weakness. She walked with a waddling gait.
II 1	60	He had lower limb muscle wasting and weakness. He also had learning difficulties and epilepsy.
II 2	59	He had bilateral talipes equinovarus, congenital hip dislocation and scoliosis. He had lower limb weakness and difficulties with walking.
II 3	58	He had bilateral talipes equinovarus and congenital hip dislocation requiring surgeries. He also had bilateral pes cavus, wasting of muscles (particularly quadriceps), reduced reflexes, but normal sensation in the lower limbs and walked very slowly with a waddling gait.
III 1	32	He had similar features as II 3.
III 2	30	He had similar features as II 3.

brain abnormalities and focal or generalised epilepsy. Cataract and dimorphism have also been reported in this phenotype [19,20]. A proportion may have arthrogryposes and limb weakness or deformity [15,17,18]. They often have global developmental delay. Histopathological examination of two foetal brains with *DYNC1H1* mutations revealed fronto-parietal polymicrogyria, corpus callosum and cortico-spinal tracts dysgenesis, brainstem and cerebellar abnormalities as well as severe disruption of cortical lamination. Immunohistochemical studies showed cell proliferation defects and migration failure of the postmitotic neuroblast towards the cortical plate [21]. There is no clear genotype-phenotype correlations observed, but SMALED causing mutations more commonly occur around the tail domain whereas hereditary mental retardation with cortical neural migration phenotype causing mutations are more frequent around the motor domain [7].

4. Conclusions

Mutations in *DYNC1H1* have two main phenotypes: early onset static or slow progressive motor neuropathy with lower limb predilection and hereditary mental retardation with cortical neural migration defects. Some individuals may have overlapping features of both phenotypes. There are only handful families with SMALED described in the literature. We report a pedigree with a *DYNC1H1* mutation. Further studies are required to appreciate the full extent of clinical presentations as well as the natural history of disorders associated with mutations in *DYNC1H1*.

Consent

Written consent has been obtained.

Conflict of interest

None declared.

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