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Expanding the phenotypic spectrum associated with mutations of *DYNC1H1*

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Abstract

Autosomal dominant mutations of *DYNC1H1* cause a range of neurogenetic diseases, including mental retardation with cortical malformations, hereditary spastic paraplegia and spinal muscular atrophy. Using SNP array, linkage analysis and next generation sequencing, we identified two families and one isolated proband sharing a known spinal muscular atrophy, lower extremity predominant (SMALED) causing mutation *DYNC1H1* c.1792C>T, p.Arg598Cys, and another family harbouring a c.2327C>T, p.Pro776Leu mutation. Here, we present a detailed clinical and pathological examination of these patients, and show that patients with *DYNC1H1* mutations may present with a phenotype mimicking a congenital myopathy. We also highlight features that increase the phenotypic overlap with *BICD2*, which causes SMALED2. Serial muscle biopsies were available for several patients, spanning from infancy and early childhood to middle age. These provide a unique insight into the developmental and pathological origins of SMALED, suggesting *in utero* denervation with reinnervation by surrounding intact motor neurons and segmental anterior horn cell deficits. We characterise biopsy features that may make diagnosis of this condition easier in the future.

Keywords: *DYNC1H1*; Myopathy; Diagnosis by sequencing; Exome sequencing; SMALED

1. Introduction

Spinal muscular atrophies (SMAs) are a group of hereditary disorders caused by aberrant development and/or early loss of spinal cord motor neurons [1]. The major cause of SMA is the 'classical' autosomal recessive 5qSMA, caused almost exclusively by homozygous deletion of exons 7 and 8 of the survival of motor neuron 1 (*SMN1*) gene on chromosome 5q [2,3] (OMIM 253300, 253550, 253400, and 271150). Less common and less well-characterised are the autosomal dominant forms of SMA, which are milder than 5qSMA, and static or slowly progressive rather than rapidly progressive [4]. One subtype of non-5qSMA is SMA, lower extremity predominant (SMALED), which is characterised by congenital onset of static or slowly progressive muscle weakness and atrophy in the lower limbs, delayed gross motor milestones, and little to no sensory impairment [5,6]. Mutations in dynein, cytoplasmic 1, heavy chain 1 (*DYNC1H1*, *OMIM* #600112) were the first described cause of SMALED (OMIM #158600) [6–9], shortly followed by bicaudal D homolog 2 (*Drosophila*) (*BICD2*, OMIM #609797), causing SMALED2 (OMIM #615290) [10–13]. These genes encode interacting proteins that form part of the microtubule transport system

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[14]. The challenge of the small neuronal cell body sustaining a large cell compartment makes neurons heavily reliant on the microtubule transport system, which functions in neuron development, morphology and survival [15,16]. Several genes involved in microtubule transport are known to cause neurological diseases with varying degrees of phenotypic overlap [10,14,17].

DYNC1H1 forms a dimer that is the core of the dynein motor complex, which traffics cargo along microtubules in a retrograde fashion [16,18]. The long tail domain at the N-terminus interacts with intermediate-light and light dynein chains to form a cargo-binding complex [19], and contains the dimerisation domain. The C-terminus holds six ATPase domains and a microtubule-binding stalk [18]. The majority of 'pure' SMALED causing mutations are in the dimerisation domain (amino acids 300–1140), although SMALED with cortical malformations can be caused by mutations in the stem, neck and motor domains (p.Arg264Gly, p.Arg1603Thr and p.Glu3048Lys respectively [9,20]), and SMALED with learning disabilities by the motor domain mutation p.Glu2616Lys [17]. *BICD2* encodes an adaptor protein, which links a variety of cellular cargos to the dynein–dynactin motor complex [21]. Recently, two studies showed evidence that BICD2 also promotes activation of the dynein motor [22,23].

Next generation sequencing (NGS) provides an unbiased method for genetic diagnosis in neuromuscular disease, as opposed to the previous candidate gene based approach. This technique enables new phenotypes to be associated with known disease genes, expanding phenotypic spectra and blurring the boundaries of disease classification [24]. This applies to *DYNC1H1* and *BICD2*. *DYNC1H1* was first associated with disease in 2011 [7]. SMALED is now known to variably include cognitive impairment, attention deficit hyperactivity disorder (ADHD), cortical malformations [9] and arthrogryposis [17,20]. Additional phenotypes include hereditary spastic paraplegia (HSP) with thin corpus callosum [25], cortical malformations including polymicrogyria [9,26,27], and congenital cataracts with gut dysmotility [28]. Similarly, *BICD2* mutations were first described to cause SMALED and HSP [10–12], but are now known to also cause SMA with cerebellar developmental disorder, arthrogryposis multiplex *congenita* and polymicrogyria [14], and distal myopathy [29]. The phenotypic spectra associated with *BICD2* and *DYNC1H1* have therefore been increasingly seen to overlap. With this cohort, we further the phenotypic expansion of *DYCN1H1* mutations.

We describe two families (AUS1 and TUR1) and one isolated proband (P4) with neuromuscular disease caused by a previously reported *DYNC1H1* mutation (c.1792C>T, p.Arg598Cys) [17,20,25,30], and one family (AUS2) with a previously reported *DYNC1H1* c.2327C>T, p.Pro776Leu mutation [31]. Families AUS1 and AUS2 and the isolated proband P4 are from Australia. AUS1 is a large multi-generational family. Family TUR1 is from Turkey. Families AUS1 and TUR1 had an initial diagnosis of congenital myopathy based on clinical and pathological signs, while AUS2 and P4 were diagnosed with distal arthrogryposis. Diagnosis by sequencing [32,33] caused a re-evaluation of the clinical and pathological features of these families. Muscle biopsies had been obtained from several family members over multiple time points from family AUS1, providing unprecedented characterisation of the pathology of this disease. We also present features from the earliest SMALED patient biopsy to date, taken at 1 year old.

2. Patients and methods

This study was approved by the UWA Human Research Ethics Committee and all patients gave informed consent.

2.1. Patient details

AUS1 is a non-consanguineous Caucasian family from Australia with ten affected individuals (aged 1 to 69 years) over three generations (Fig. 1A). Muscle biopsies were taken from four family members at various ages (AUS1:II:2, AUS1:III:2, AUS1:IV:7, AUS1:IV:8), as shown in Fig. 2.

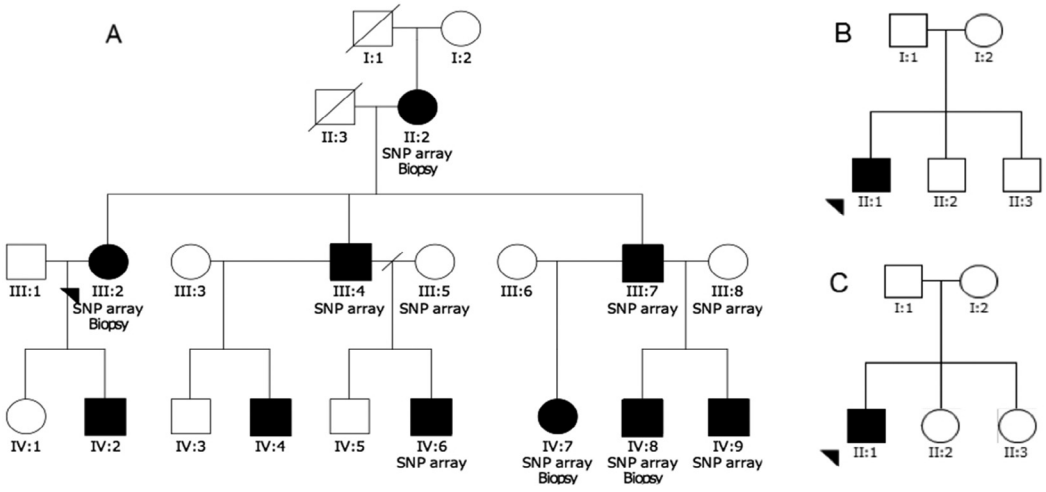

Fig. 1. Pedigrees of three families described in this study showing segregation of the DYNC1H1 mutations. (A) Pedigree of family AUS1, a multi-generational Australian family in which affected individuals harboured the c.1792C>T, p.Arg598Cys substitution. Individuals in which a muscle biopsy was performed, or for whom a SNP-array was performed, are indicated. (B) Pedigree of family AUS2, an Australian family with the c.2327C>T, p.Pro776Leu mutation. (C) Pedigree of family TUR1, a Turkish family with one affected male patient harbouring c.1792C>T, p.Arg598Cys.