MYOD1 involvement in myopathy

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Introduction

Myogenic Differentiation 1 (*MYOD1*) encodes a transcription factor that plays an important role in myogenic determination into mature skeletal muscle [1]. The first loss-of-function mutation of *MYOD1* in humans was described in three siblings with perinatal lethal fetal akinesia [2]. Here, we describe an individual with a loss-of-function mutation in the *MYOD1* gene and a congenital myopathy with mild motor developmental delay, ptosis and breathing and feeding difficulties.

Case report

The patient, an 8-year-old girl, presented a history of respiratory infections, hypotonia, ptosis, motor delay and failure to thrive, resulting in the placement of a gastrostomy by the age of 2 years. Bilevel positive airway pressure during naps and night-time sleep was started for severe nocturnal hypercapnia. Muscular function improved with age and remained stable with mildly decreased endurance and balance. Pulmonary imaging showed bilateral high diaphragmatic domes without pulmonary hypoplasia (Appendix S1) and diaphragmatic hypomobility on fluoroscopy. Abdominal ultrasonography at 2 years revealed bilateral small kidney (−2 SD) without other anomalies. The patient had a homozygous nonsense variant (c.697G > T; p.Glu233*) that segregated with the phenotype (parents and unaffected siblings are heterozygous carriers). Informed consent was obtained.

Discussion

In the present case, we can observe that the most severely affected musculature is the diaphragm. The lung hypoplasia observed in the patient could be due to the absence of mechanical forces originated by the proper functioning of the diaphragm. Similar conclusions were drawn from studies in a mouse model of *Myod1* and *Dmd* deficiency [3,4].

In 2016, the first *MYOD1* mutation in humans was reported by Watson *et al.* [2] in three siblings with perinatal lethal fetal akinesia. Although the severity of the phenotype is different there are still many similarities with the present individual (clinical comparison in Table 1). All patients present with triangular facies, generalized muscle weakness, renal anomalies and alterations in diaphragmatic function with respiratory insufficiency of variable degree. The previously described pathogenic variant introduces a stop codon in exon 1 within the basic motif of the bHLH protein domain and probably leads to nonsense-mediated decay with absence of MYOD1 protein. In contrast, the new stop codon in the index patient is localized within 13 bp of the exon 2/exon 3 junction (Appendix S1), and is thus predicted not to lead to nonsense-mediated decay [5].

Through this work, we thus contribute to a better understanding of the *MYOD1* myopathy phenotypic spectrum.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Myogenic Differentiation 1 involvement in myopathy.

References

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*Posthumously.

Table 1 Clinical comparison of the four individuals with Myogenic Differentiation 1 homozygous mutations

		Watson *et al.* (2016)		
	Present individual	III.1	III.2	III.4
Gender	Female	Male	Male	Female
Family history				
Consanguinity	+	+	+	+
Pre-natal and perinatal history				
Pre-natal anomalies	–	Cystic hygroma polyhydramnios	Polyhydramnios	Cystic hygroma
Birth	At term	35 + 5	35 + 1	37
Growth	Normal birth weight	Low birth weight	Low birth weight	Low birth weight
Apgar	ND	1-1	1-1	1-1
Neonatal death	–	+	+	+
Cranio facial symptoms				
Triangular face	+	+	+	+
Downslanted palpebral fissures	+	+	ND	ND
Ptosis	+	ND	ND	ND
Proptosis	+	ND	ND	ND
Mandible	Prognathia	Small chin	Small chin	Small chin
Palate	High-arched	Cleft	Cleft	Cleft
Dental malocclusion	+	NA	NA	NA
Respiratory symptoms				
Respiratory insufficiency due to muscle weakness	+	+	+	+
Diaphragm	High domes	Right-sided eventration	Very high domes	Extremely high domes
Pulmonary hypoplasia	–	+	+	+
Ventilatory support	Nocturnal BiPAP	Ventilator dependent		
Musculoskeletal symptoms				
Generalized muscle weakness	+	+	+	+
Fatigable weakness of swallowing muscles	+	ND	ND	ND
Clinodactyly/digit overlapping	+	+	+	–
Cutaneous symptoms				
Congenital, generalized hypertrichosis	+	ND	ND	ND
Genitourinary symptoms				
Cryptorchidism	NA	Bilateral	Unilateral	NA
Renal anomaly	Small kidneys (–2 SD)	Bilateral renal pelvis distension	Unilateral hydronephrosis	Renal hypoplasia

BiPAP, bilevel positive airway pressure; NA, not applicable; ND, not done; +, present; –, absent.