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Review

What's new in congenital myopathies?

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Abstract

The congenital myopathies are defined by distinctive morphologic abnormalities in skeletal muscle. Over the past decade there have been major advances in *defining the genetic basis* of the majority of congenital myopathy subtypes, with increasing availability of genetic and prenatal diagnosis. Identification of the disease genes, in combination with a reappraisal of muscle pathology and the development of tissue culture and animal models is now providing *insights into disease pathogenesis* and, for the first time, suggesting avenues for the *development of specific therapies*. This review highlights some of the major recent advances in each of these areas and demonstrates how a morphological classification of the congenital myopathies into subgroups remains useful for future research into gene discovery and understanding of disease mechanism.

Keywords: Congenital myopathy; Nemaline myopathy; Central core disease; Centronuclear myopathy; Congenital fibre type disproportion

1. Introduction

The congenital myopathies are a heterogeneous group of neuromuscular disorders that are grouped into subtypes based on the predominant pathological feature present on muscle biopsy. The congenital myopathies can broadly be defined as follows:

- Distinctive and specific morphologic abnormalities in skeletal muscle on light and/or electron microscopy as the main pathological feature. Examples include cores, rods, and central nuclei.
- The pathological features originate within the myofibre, as distinct from the muscular dystrophies, where the primary pathology affects the stability of the sarcolemmal membrane.
- Clinical presentation with weakness and hypotonia.
- Onset typically "congenital", at birth or in the first year of life with delay in motor milestones. However, it is now recognized that there can be a wide variation in clinical severity within each subtype with childhood and adult onset.
- Genetic aetiology.

The diagnosis of a specific congenital myopathy still relies predominantly on muscle pathology. Routine laboratory investigations are rarely helpful; serum creatine kinase is usually normal and EMG is either normal, myopathic, or occasionally neurogenic. Clinically it may not be possible to distinguish a congenital myopathy from lower motor neuron disorders and congenital muscular dystrophy, although certain clinical findings and serum creatine kinase may be suggestive. Facial weakness, often associated with dysmorphism and a high palate due to its onset *in utero* ("the myopathic facies"), can often discriminate a congenital myopathy from a muscular dystrophy, anterior horn cell disorder or a peripheral neuropathy; the main differential diagnosis of congenital onset facial diplegia is congenital myotonic dystrophy. Morbidity in all forms of congenital myopathy is associated with respiratory muscle involvement, bulbar weakness and risk of aspiration, and orthopaedic complications such as scoliosis and contractures. The frequency of these complications is variable between the different subtypes, and between patients with the same histological diagnosis. Survival is usually dictated by the degree of respiratory insufficiency;

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infants and children with are particularly vulnerable during the first two years of life when they are most susceptible to complications from respiratory and bulbar weakness. Cardiac involvement is rare and intelligence is usually normal. The clinical course tends to be nonprogressive or slowly progressive.

2. Advances in genetic diagnosis

Over the past decade there have been major advances in *defining the genetic basis* of the majority of congenital myopathy subtypes. Table 1 summarises the current (March 2008) status of the genetic loci for the various subtypes of congenital myopathy and provides key references [1–30]. The progress over the last 10 years has been remarkable. In 1997, the only known loci for congenital myopathies were the ryanodine receptor for central core disease, α-tropomyosin$_{SLOW}$ for an autosomal dominant form of nemaline myopathy and myotubularin for X-linked myotubular myopathy. By the end of 2007, genes responsible for all of the major subtypes of congenital myopathy have been identified. The congenital myopathies listed in the Table 1 addendum, for which the genetic basis is unknown, represent a list of rare and poorly defined entities, in which very few, often single sporadic patients have been reported. Nevertheless, disorders such as cap disease, myosin storage myopathy and sarcotubular myopathy were once classified as "possible congenital myopathies" since only a few cases were reported – and the genes have since been identified by sequencing of candidate genes suggested by the ultrastructural features on muscle biopsy (in the case of cap disease and myosin storage myopathy) or the occurrence of a rare myopathy within a genetic isolate; Mutations in TRIM32 result in LGMD2H in the Manitoba Hutterites [30], and mutations in TRIM32 were subsequently found to result also in sarco-

Table 1
Genetic and morphological classification of congenital myopathies

Disorder	Inheritance	Gene/protein/locus	Reference
Myopathies with protein accumulations			
Nemaline myopathy	AD, AR	α-Tropomyosin$_{SLOW}$	[1,2]
	AR	Nebulin	[3]
	AD,AR	Skeletal α-actin	[4]
	AD	β-Tropomyosin	[5]
	AR	Troponin T	[6]
	AR	Cofilin	[7]
	AD	15q21-q24	[8]
Myosin storage myopathy (hyaline body myopathy)	AD	Slow/β-cardiac myosin heavy chain (MYH7)	[9]
Cap disease	AD	β-Tropomyosin	[10,11]
Reducing body myopathy	X-linked	Four and a half LIM domain 1 (FHL1)	[12]
Myopathies with cores			
Central core disease	AD, AR	Ryanodine receptor	[13–16]
Core-rod myopathy	AD	Ryanodine receptor	[17,18]
Multiminicore disease (including congenital myopathy with cores)	AD, AR	Ryanodine receptor	[19,20]
	AR	Selenoprotein N	[21]
	AD	Skeletal α-actin	[22]
Myopathies with central nuclei			
Myotubular myopathy	X-linked	Myotubularin	[23]
Centronuclear myopathy	AD	Dynamin 2	[24]
	AR	Amphiphysin 2	[25]
Myopathies with fibre size variation			
Congenital fibre type disproportion	AD	Skeletal α-actin	[26]
	AD	α-Tropomyosin$_{SLOW}$	[27]
	AR	Selenoprotein N	[28]
	X-linked	Xp22.13 to Xq22.1	[29]
Myopathies with vacuoles			
Sarcotubular myopathy	AR	TRIM32 (ubiquitin ligase)	[30]
Addendum : myopathies with unknown genetic aetiology (reviewed in [31])			
Possible disease entities (several familial cases)		Doubtful (rare sporadic cases only)	
Fingerprint body myopathy		Broad A band disease	
Tubular aggregate myopathy		Lamellar body myopathy	
Cylindrical spirals myopathy		Myopathy with excess spindles	
Myopathy with hexagonally cross-linked tubular arrays		Zebra body myopathy	
		Myopathy with mosaic fibres and interlacing sarcomeres	
		Myopathy with apoptotic changes	

AR, autosomal recessive; AD, autosomal dominant.