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Review

Myopathies associated with β-tropomyosin mutations

H. Tajsharghi [a,*], M. Ohlsson [a], L. Palm [b], A. Oldfors [a]

[a] Department of Pathology, Institute of Biomedicine, University of Gothenburg, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden
[b] Department of Paediatrics Malmoe, Skane University Hospital, SE-205 02 Malmoe, Sweden

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Abstract

Mutations in *TPM2*, encoding β-tropomyosin, have recently been found to cause a range of muscle disorders. We review the clinical and morphological expression of the previously reported mutations illustrating the heterogeneity of β-tropomyosin-associated diseases and describe an additional case with a novel mutation.

The manifestations of mutations in *TPM2* include non-specific congenital myopathy with type 1 fibre predominance, nemaline myopathy, cap disease and distal arthrogryposis. In addition, Escobar syndrome with nemaline myopathy is a manifestation of homozygous truncating β-tropomyosin mutation.

Cap disease appears to be the most common morphological manifestation. A coarse intermyofibrillar network and jagged Z lines are additional frequent changes. The dominant β-tropomyosin mutations manifest either as congenital myopathy or distal arthrogryposis. The various congenital myopathies are usually associated with moderate muscle weakness and no congenital joint contractures. The distal arthrogryposis syndromes associated with *TPM2* mutations include the less severe forms, with congenital contractures mainly of the hands and feet and mild or no muscle weakness. The dominant *TPM2* mutations include amino acid deletions/insertions and missense mutations. There is no clear relation between the type of mutations or the localisation of the mutated residue in the β-tropomyosin molecule and the clinical and morphological phenotype.
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1. Introduction

Tropomyosins comprise a family of actin-binding proteins encoded by four different genes (*TPM1*, *TPM2*, *TPM3* and *TPM4*). Each gene uses alternative splicing, alternative promoters and differential processing to encode multiple striated muscle, smooth muscle and cytoskeletal transcripts [1–3].

Tropomyosin (Tm) is central in the control of calcium-regulated striated and smooth muscle contraction by its interaction with actin and the troponin complex, as well as the stability of actin filaments. It is also essential for various functions of cell processes including cell motility, cell division and cytokinesis through interaction with the β- and γ-actin cytoskeletons [3].

In humans, the striated muscle isoform α-Tm_{fast} (encoded by *TPM1*) is predominantly expressed in cardiac muscle and fast, type 2, muscle fibres. β-tropomyosin (encoded by *TPM2*) is mainly expressed in slow, type 1 and, to some extent, in fast muscle fibres and cardiac muscle. α-Tm_{slow} or γ-Tm (encoded by *TPM3*) is predominantly expressed in slow muscle fibres and is also expressed in the heart [1]. In addition, TPM1-κ is a newly discovered, striated muscle α-Tm_{fast} isoform which is solely expressed in cardiac tissue in humans, rats, and chickens but not in the mouse [4,5].

Two δ-Tm alternative splicing transcripts are encoded by *TPM4* [6]. In humans, δ-Tm is expressed in different tissues such as the kidneys, placenta and endocrine tissues (http://www.proteinatlas.org/ENSG00000167460).

* Corresponding author.
E-mail address: homa.tajsharghi@pathology.gu.se (H. Tajsharghi).

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TPM2 encodes for two major splice variants; β-tropomyosin (β-Tm) (accession number for transcript variant 1: NM_213674.1 and GI: 47519592) and tropomyosin-1 (Tm-1) (accession number for transcript variant 2: NM_003289.3 and GI: 47519615). β-Tm is associated with α-actin in the thin filaments of the sarcomeres of striated muscle. Tm-1 is ubiquitously expressed and associated with cytoskeletal β- and γ-actins [3].

Mutations in *TPM1* are associated with familial hypertrophic cardiomyopathy [7], whereas mutations in *TPM3* are a common cause of congenital fibre type disproportion [8]. In addition, rare cases of nemaline myopathy and cap have been associated with *TPM3* mutation [9–12].

Recently, different dominant mutations in the gene encoding β-Tm (*TPM2*) have been identified in association with a range of clinical and morphological phenotypes, including unspecific congenital myopathy, nemaline myopathy, cap disease and distal arthrogryposis (DA) [13–19]. In addition, Escobar syndrome associated with nemaline myopathy has been found in association with the total absence of β-Tm [20].

In this article, we present a review of the literature on myopathies associated with *TPM2* mutations illustrating the heterogeneity of the morphological and clinical expression of *TPM2* mutations.

2. Disease manifestations of *TPM2* mutations

2.1. Nemaline myopathy

Nemaline myopathy is characterised by the accumulation of nemaline rods in a large proportion of the muscle fibres best visualised in Gomori trichrome staining. The nemaline rods are expansions and deposits of Z disk and thin filament material, largely composed of α-actinin and actin [21]. The biopsies often exhibit type 1 fibre predominance, or, in extreme cases, type 1 fibre uniformity. The muscle weakness most typically affects proximal muscles, neck flexors and facial muscles, but distal muscle involvement is common later in the clinical course of the disease. Respiratory and feeding problems are common features, both in the neonatal period and throughout life. Skeletal involvement includes congenital contractures, scoliosis, spinal rigidity and foot deformities [22]. Cardiomyopathy has only occasionally been described [23,24]. The clinical severity ranges from severe cases with neonatal onset and early death to adult-onset cases with only mild muscle weakness. Based on the severity of the clinical phenotypes, age of onset and additional features, nemaline myopathy can be divided into six different forms: severe, typical, intermediate, mild, adult onset and other forms [25].

Nemaline myopathy is associated with mutations in at least seven genes: skeletal muscle α-actin (*ACTA1*), β-tropomyosin (*TPM2*), α-tropomyosin slow (*TPM3*), nebulin (*NEB*), troponin T1 (*TNNT1*), cofilin (*CFL2*) and *KBTBD13* [9,13,26–30]. Mutations in *ACTA1* and *NEB* appear to be the most frequent cause of the disease. *NEB*, an occasional *TNNT1* mutation and several *ACTA1* mutations show recessive inheritance [27,28,31–35]. The majority of the cases with dominant mutations occur as sporadic cases due to *de novo* mutations [22,36] (http://waimr.uwa.edu.au/). In addition, nemaline myopathy may occur secondary to monoclonal gammopathy [37].

Nemaline myopathy associated with *TPM2* mutations has been described in two cases with two different heterozygous dominant missense mutations (Table 1: Q147P and E41K) [13,14]. The clinical phenotype was described as mild in patient 1 (Q147P), a female who died at the age of 51 years from respiratory insufficiency. She presented with walking difficulties at 12 years of age and in adulthood she had an asymmetric limb muscle weakness, together with mild facial and neck flexor weakness, and used a wheelchair from the age of 48 years (Table 2). Patient 2 (E41K), a 66-year-old female, had a moderate phenotype with transient respiratory insufficiency in the neonatal period, followed by delayed motor milestones. At the age of 32 years, clinical examination showed moderate muscle weakness predominantly in proximal muscles, neck flexors, facial muscles and foot extensors, together with lumbar hyperlordosis. At the age of 57 years, the muscle weakness was located in both proximal and distal muscles. She had facial diplegia, with a long, narrow face, high-arched palate, micrognathia and dysphagia. She suffered from respiratory insufficiency and received ventilatory support at night. No cardiac involvement was seen and she was still able to walk without support. Morphological features included type 1 fibre predominance in both cases and nemaline rods accumulating in the subsarcolemmal region, with a distribution similar to the regions of myofibrillar disorganisation seen in cap disease (Fig. 1).

2.2. Cap disease

Cap disease was first defined by Fidzianska in 1981 as a rare congenital myopathy with well-demarcated, peripherally located cap-like structures (Fig. 2A) consisting of disarranged myofibrils with enlarged Z disks (Fig. 2B) [38,39]. The caps lack or show reduced thick filaments and reduced myosin ATPase activity (Fig. 2C) but high reactivity for many sarcomeric proteins including actin, nebulin, tropomyosin, troponin T and desmin (Fig. 2D) [15]. The clinical features are similar to those of typical nemaline myopathy, with infantile onset of hypotonia and muscle weakness. Cap disease has so far been associated with mutations in three different genes: *TPM2*, *TPM3* and *ACTA1* [11,12,14–16,19,40], all of which are also associated with nemaline myopathy.

The majority of published cases of cap disease were caused by *TPM2* mutations, all heterozygous and either causing single amino acid substitutions, deletions or insertions (Table 1: E41K, K49del, G53dup, E139del, N202K) [14–16,19]. All the patients but one had hypotonia at birth and delayed motor milestones. A 35-year-old female, patient 3 (E41K), showed at the age of 26 years both

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