

# Muscle diseases with damaged sarcomeres - causes and consequences

Akademisk avhandling

av

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Avhandlingen baseras på följande delarbeten:

- I** **Ohlsson M**, Tajsharghi H, Darin N, Kyllerman M, Oldfors A. Follow-up of nemaline myopathy in two patients with novel mutations in the skeletal muscle alpha-actin gene (*ACTA1*). *Neuromuscul Disorder* 2004;14:471-475.
- II** Tajsharghi H, **Ohlsson M**, Lindberg C, Oldfors A. Congenital myopathy with nemaline rods and cap structures caused by a mutation in the beta-tropomyosin gene (*TPM2*). *Arch Neurol* 2007;64(9):1334-1338.
- III** **Ohlsson M**, Quijano-Roy S, Darin N, Brochier G, Lacène E, Avila-Smirnow D, Fardeau M, Oldfors A, Tajsharghi H. New morphologic and genetic findings in cap disease associated with  $\beta$ -tropomyosin (*TPM2*) mutations. *Neurology* 2008;71:1896-1901.
- IV** **Ohlsson M**, Fidzianska A, Tajsharghi H, Oldfors A. *TPM3* mutation in one of the original cases of cap disease. *Neurology* 2009;72:1961-1963.
- V** **Ohlsson M**, Brådvik B, Lindberg C, Tajsharghi H, Martinsson M, Oldfors A. Familial myopathy with early respiratory failure and sharing of a large haplotype at chromosome 2q31. Manuscript.

## Muscle diseases with damaged sarcomeres - causes and consequences

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Muscle diseases, also called myopathies, are usually defined as diseases where the pathology is confined to the muscle itself. This excludes diseases caused by structural abnormalities in the peripheral nerve, from the anterior horn cell to the neuromuscular junction. Much effort has been made to elucidate the pathogenesis of skeletal muscle diseases that result from mutations in sarcomeric and associated proteins, highlighting their importance in normal muscle structure and function. The short-term goals in this field are to determine the remaining causative genes behind the skeletal muscle diseases and to learn more about the pathogenesis behind these diseases. The long-term goals are to develop more specific therapy in the future.

In paper I we investigated two children with nemaline myopathy and identified two *de novo* heterozygous mutations not previously described in the skeletal  $\alpha$ -actin gene (*ACTA1*). The marked variability in clinical features in spite of similar muscle pathology in early childhood was demonstrated. The severe muscle atrophy with replacement of fat and connective tissue found in one of the patients demonstrated that nemaline myopathy might be progressive in some cases.

In paper II we investigated a mother and daughter with similar clinical but different morphological features, nemaline myopathy and cap disease. We identified a heterozygous missense mutation in the  $\beta$ -tropomyosin gene, *TPM2*, the first mutation to be found in cap disease. We concluded that candidate genes in cap disease ought to be found within the genes encoding for sarcomeric proteins, especially those previously associated with nemaline myopathy and that mutations in *TPM2* might be a common cause of cap disease.

In paper III we investigated three unrelated patients and identified three *de novo* heterozygous mutations in *TPM2*: a three-base pair deletion in-frame, a three-base pair duplication in-frame, and a missense mutation. The hypothesis that mutations in *TPM2* are a common cause of cap disease was confirmed. In muscle biopsy specimens, a coarse-meshed and irregular intermyofibrillar network was found. These specific pathological findings may be clues towards a correct diagnosis and indicate that the pathogenesis involves defective assembly of myofilaments.

In paper IV we had the opportunity to investigate one of the original cases of cap disease. In this patient we found a *de novo* heterozygous missense mutation in *TPM3*. The observation that cap disease, like nemaline myopathy, is associated with mutations in *TPM2* as well as in *TPM3* and shows similar clinical presentation supports our concept that cap disease is related to nemaline myopathy and all genes encoding components of the sarcomeric thin filament should be considered as candidate genes in patients with cap disease.

In paper V we investigated seven individuals from two apparently unrelated families with a dominantly inherited adult-onset myopathy with early respiratory failure. All patients had muscle weakness in the pelvic girdle, neck flexors and trunk muscles together with prominent calf hypertrophy. Muscle histopathological features included eosinophilic deposits and extensive myofibrillar lesions with marked Z-disk alterations. Genetic analysis with array data using SNP markers demonstrated that the affected individuals shared a large haplotype on chromosome 2q31, including the giant titin gene (*TTN*). Further studies include the investigation of the *TTN* gene and other genes of interest in this region.

This study has deepened the understanding of inherited myopathies associated with damaged sarcomeres by describing new mutations in causative genes, which in the end could lead to new therapy strategies.

**Key words:** Congenital myopathies, nemaline myopathy, cap disease, hereditary myopathy with early respiratory failure, myofibrillar myopathy, *ACTA1*, *TPM2*, *TPM3*, *TTN*.