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Autosomal dominant nemaline myopathy with intranuclear rods due to mutation of the skeletal muscle *ACTA1* gene: Clinical and pathological variability within a kindred

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Abstract

Nemaline Myopathy with Intranuclear Rods is a rare variant of nemaline myopathy, due in almost all instances to mutation of *ACTA1*, the gene encoding skeletal muscle α-actin. We describe the novel autosomal dominant occurrence in a three-generation kindred, and review previously reported cases. Onset of myopathic symptoms in our kindred was in infancy or early childhood. Beyond infancy, limb muscle weakness was non-disabling and minimally progressive. A tall thin face and facial myopathy were prominent features in the affected adults. By light microscopy, muscle biopsies ranged from almost normal, to chronic myopathy with sarcoplasmic and intranuclear rods. A heterozygous GTG–ATG mutation (Val163Met) was found in exon 4 of *ACTA1* in affected individuals. Actin is normally present within the nucleus in only trace amounts. Mutation at postion 163 may result in intranuclear rods by virtue of its close proximity to a nuclear export signal within the actin molecule.

Keywords: Nemaline myopathy; Intranuclear rods; Intranuclear rod myopathy; Congenital myopathy; *ACTA1*; α-actin

1. Introduction

Nemaline myopathy (NM) was first reported in 1963 in independent papers by Shy [1] and Conen [2]. Patients with NM usually present with hypotonia and weakness in the neonatal or childhood periods, but presentation in adulthood is also recognised. The histological hallmark of NM is the presence of nemaline bodies or rods (Greek *nema* = thread) within muscle fibres.

Since 1995, mutations in the following genes have been found to cause NM: TPM3 (encoding α-tropomyosin$_{SLOW}$) [3], *ACTA1* (encoding skeletal muscle α-actin) [4], NEB (encoding nebulin) [5], TPM2 (encoding β-tropomyosin) [6], and TNNT1 (encoding slow skeletal muscle troponin T) [7]. Each of these proteins is a structural member of the muscle thin filament.

The presence of *intranuclear* rods in NM was first reported in 1969 by Jenis et al. [8]. The patient was a 2-week-old girl with hypotonia and severe diffuse weakness who died at age 2 months. At autopsy, each of the seven muscles studied contained a combination of intranuclear and sarcoplasmic rods. The term Intranuclear Rod Myopathy was subsequently applied to this entity [9]. However, on clinical, pathological and genetic grounds, it is best viewed as a variant of NM, and we prefer the term nemaline myopathy with intranuclear rods (NM-IR). Further cases of NM-IR have since been described (Table 1). All mutations thus far reported in NM-IR have involved *ACTA1*. Few intranuclear rods were found in a patient with myopathy,

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Table 1
Published cases of Nemaline Myopathy with Intranuclear Rods to date, and the current series

Clinician or lead author	No.	Age onset/sex	Inheritance	Clinical features	Grade [20]	CK	EMG	Course	Mutation (all *ACTA1*)	Muscle biopsy
Jenis [8]	1	Birth/F	Spor	Hypotonia, respir insuff, diffuse severe weakness, areflexia	IC	NS	NS	Died 2 mo	NS	SR (8–32% of fibres different muscles), IR (11–80% of nuclei different muscles)
Engel WK [21]	2	55 year/M	Spor	Diffuse muscle atrophy and weakness, fasciculation	AO	N	Fibrillation, mixture small myopathic + large MUP	Died 62 y	NS	Grouped + scattered atrophic fibres, rare necrotic fibres, SR, IR
	3	37 year/M	Spor	Diffuse muscle atrophy and weakness	AO	N	Fibrillation + brief, small motor units	Died 41 year	NS	Atrophic fibres, ↑int nuclei, rare necrotic fibres, SR (∼15% of fibres), IR
Fukunaga [22]	4	25 year/M	?AR	Tall face, ptosis, ophthalmoparesis, HAP, severe diffuse weakness, areflexia	AO	N	Short duration MUP, 'high amplitude spikes'	Alive at 35 y	NS	Fibre splitting, abnormal mitochondria, SR (20% of fibres), IR (∼2% of nuclei)
Norton [23]	5	Birth/M	Spor	Hypotonia, areflexia, death from pneumonia	IC	↑	Fibrillation	Died 9 mo	NS	Disruption myofibrils, SR, IR
Paulus [24]	6	61 year/F	Spor	Atrophy and weakness cervical, truncal, limb muscles	AO	N	'Myopathic'	Alive 63 y	NS	Fibre atrophy, ↑int nuclei, type 1 fibre predom, fibrosis, SR (55% of fibres), IR (31% of fibres)
Rifai [25]	7	Birth/F	Spor	Hypotonia, contractures, HAP, respir insuff, areflexia	SC	↑↑	'Decreased recruitment of MUP'	Died 6 days	NS	Fibre atrophy, large myonuclei, basophilic fibres, ↑int nuclei, type 1 fibre predom, SR, IR
Barohn [26]	8	Birth/F	Spor	Hypotonia, respir insuff, areflexia	SC	↑↑	NS	Died 5 wk	NS	Type 1 fibre predom, SR (30% of fibres), IR (80% of nuclei)
Goebel [9]	9	Birth/M	Spor	Hypotonia, arthrogryposis, HAP, respir insuff, severe diffuse weakness, areflexia, cardiac hypertrophy	SC	N	'Myopathic'	Alive 2 year	NS	Fibre atrophy, type 1 fibre predom, loss of filaments, SR, IR (35% of nuclei)
	10	Birth/F	Spor	Hypotonia, contractures knees, respir insuff, severe diffuse weakness, areflexia	SC	↑	ND	Died 3.5 mo	NS	↑variability fibre diameter, type 1 fibre predom, loss of filaments, SR, IR (70% of nuclei)
Goebel [15]/ Nowak [4]	11	Birth/M	Spor	Hypotonia, HAP, diffuse weakness, areflexia, cardiomyopathy	TC	NS	'Neurogenic' or normal	Alive at 7.5 year	GTG→CTG Val163Leu	2 muscles: fibre atrophy, fibrosis, type 1 fibre predom, IR, occasional SR, masses of thin filaments
	12	Birth/F	Spor	Hypotonia, bulbar and respir insuff, cardiomegaly	SC	↑	'Myopathic'	Died 4 month	GTG→TTG Val163Leu	↑variability fibre diameters, fibrosis, type 1 fibre predom, masses of thin filaments, IR