Nemaline myopathy - an overview

Carina Wallgren-Pettersson

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Group of congenital myopathies

- Inborn muscle disorders
- Names based on structural abnormalities in muscle fibers
- Abnormalities seen on special stains only

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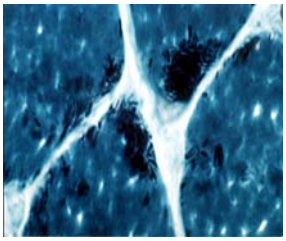
Definition of nemaline myopathy

- Muscle weakness
- Nemaline bodies (rods) in muscle fibers
- Absence of other known conditions sometimes associated with the presence of nemaline bodies



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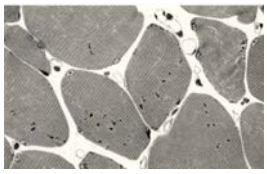
Nemaline bodies



Greek word ”*nema*” means ”thread”

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Muscle weakness may cause other features

- High-arched palate
- Joint deformities
- Flat or deformed chest
- Scoliosis
- Breathing difficulties

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Nemaline myopathy does not influence

- Brain
- Heart
- Smooth muscle
- Lungs (at least not to begin with)
- Nerves (at least not to begin with)

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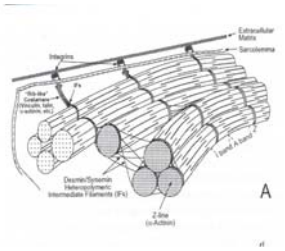
Muscle made up of muscle fibers



- Fibers of voluntary muscle are striated
- Each fiber made up of myofibrils
- Proteins of the myofibril make up the sarcomere

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Faulty genes in nemaline myopathy encode proteins of the sarcomere

- Five genes identified
- Two major ones: nebulin and actin
- A sixth gene believed to exist

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Exact cause of weakness not yet clarified

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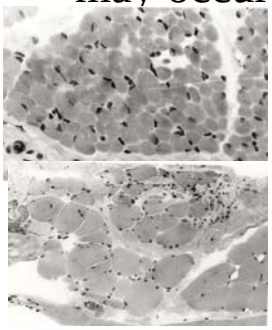
Changes in muscle tissue may occur over time



Some fibers may grow to compensate for loss of others

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Patterns of weakness

Head lag because of neck flexor weakness

Minimal facial expressions caused by weakness of facial muscles

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Patterns of weakness

- Foot deformity because of muscle weakness of the lower leg
- Postoperative result not the desired one
- Scoliosis caused by weakness of the muscles of the trunk
- Early surgery may be warranted

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Typical form of nemaline myopathy

Getting up from the floor using support or the so-called Gowers' maneuvre

- Some movement at birth
- Milestones delayed but reached
- Non-progressive or only slowly progressive course

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Severe form of nemaline myopathy

- Unable to breathe or move at birth
- Contractures or fractures at birth
- Some of these children do well later

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Mild form of nemaline myopathy

- Childhood onset
- No facial weakness
- No "foot drop"

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Remaining forms of nemaline myopathy

- Intermediate (between severe and typical)
- Adult-onset form
- "Other forms" with unusual associated features

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Modes of inheritance

- Recessive – gene from both unaffected parents
- Dominant – gene from affected parent
- In real life, many patients are the only affected person in their family and it may be difficult to know the mode of inheritance if the causative mutation has not been identified
- Genetic counseling should be offered

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No-one to blame for carrying faulty gene

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Care of persons with nemaline myopathy

Multidisciplinary team work

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All require physiotherapy

- Maintain muscle strength
- Maintain range of movements
- Maintain mobility
- Prevent scoliosis and back pain
- Maintain breathing, assist coughing
- Maintain independence in activities of daily living

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Two main issues

Breathing
Curvature of spine

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Breathing

- Treatment for swallowing difficulties
- Chest physiotherapy, assisted coughing
- No smoking
- Vigorous treatment of infections

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Breathing continued

- Regular assessment needed (vitalography)
- More detailed assessment if lung volume smaller than 60 % of normal (polysomnography)

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Look out for symptoms of too shallow breathing

- Headache
- Nausea
- Drowsiness
- Difficulty getting going
- Don’t want breakfast
- Drop in energy levels and concentration
- Bad mood
- Frequent night-time awakenings
- Nightmares
- Night sweating

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Use of mechanical aids

- To maintain quality of life
- To maintain independence

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Mechanical aids

- Some may require a wheelchair, usually in their teens
- Some may need mechanical ventilation, usually by mask

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Surgery

- Avoid unless really necessary
- To prevent scoliosis damaging breathing
- Anaesthesia carefully administered
- Immediate postoperative mobilisation with the help of a physiotherapist

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Occupation

- Free from physical strain
- Free from tobacco smoke and other toxic agents
- Free from high risk of infection

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Pregnancy and delivery

- Many patients are mothers
- Careful management and planning
- Neurologist, obstetrician and anesthesiologist working together

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Nemaline myopathy

Carina Wallgren-Pettersson

The ENMC International Consortium
on Nemaline Myopathy

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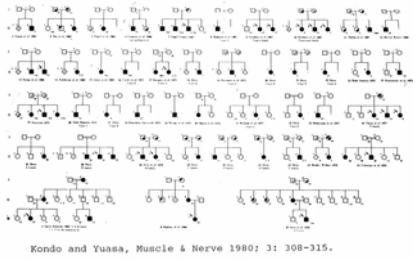
Nemaline myopathy in the eighties:
thought to be ONE dominantly inherited
disorder caused by ONE gene



Kondo and Yuasa, Muscle & Nerve 1980; 3: 308-315.

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1991: First gene localized on
chromosome 1 by Nigel Laing

Collaborative effort started

Seven families with typical form:
genetic linkage study

Clear from family history that I was
looking for a recessive gene

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1995: second gene localized in chromosome 2

First gene,
identified by Nigel Laing's group:
α-tropomyosin

Rare cause of nemaline
myopathy

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1st nemaline workshop in 1996

Participants from 7 countries

The ENMC International Consortium

for Nemaline Myopathy since 1996

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Members of the ENMC International Consortium on Nemaline Myopathy

United Kingdom
Prof. Victor Dubowitz
Prof. Caroline Sewry
Dr. Heinz Jüngbluth

Australia
Dr. Kathryn North
Dr. Edna Hardeman
Dr. Anthony Akkari
Dr. Kristen Nowak
Dr. Peter Gunning

France
Dr. Norma Romero
Dr. Marc Fiszman

Germany
Dr. Siegfried Labeit
Prof. Hans H. Goebel

Canada
Dr. Avril Castagna

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Dr. Baziel van Engelen

Spain
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Finland
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Dr. Olli Carpén

Italy
Dr. Berardino Porfirio
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Dr. Alan H. Beggs
Prof. Susan Iannaccone

Brazil
Dr. Mariz Vainzof

Sweden
Prof. L-E Thornell

Japan
Prof. Ikuya Nonaka

Co-convenors
Dr. Carina Wallgren-Pettersson, Finland
Prof. Nigel G. Laing, Australia

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Aims of Consortium work

- Understand how nemaline myopathy arises
- Develop diagnostic methods
- Pave the way for therapeutic trials

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Ongoing projects

- Remaining genes
- Diagnostic methods
- Protein forms and function in different muscles
- Cellular models
- Mouse models
- Experimental trials

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Consortium results

- Four of the five causative genes
- Clinical classification
- International database: clinical and biopsy details
- International reference database
- Comparisons between mutations and clinical features
- Mouse models: TPM3 and actin
- Plans for: Further genes, mutational databases, further pathogenetic studies, nebulin mouse model

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1999-2000: 3 new genes

Two main genes cause nemaline myopathy

- Skeletal α-actin
- Nebulin
- Both published in1999

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My research group

- Kati Donner, PhD student
- Vilma-Lotta Lehtokari, PhD student
- Maria Sandbacka, Researcher
- Hanne Ahola, Research Ass.
- Marilotta Turunen, Research Assistant
- Salla Ranta, MSc Student
- Affiliated: Katarina Pelin, PhD

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The giant nebulin gene

- Identified by Katarina Pelin in my group
- One of the biggest genes in man
- Consists of no less than 183 coding parts
- We now know the structure of the entire gene
- Mutations are found all across the gene
- Samples sent for mutation detection from around the world
- Developing diagnostic tests is a challenge

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Some 50 mutations identified in the nebulin gene

- Most of them are expected to make the protein shorter
- Still, the far end of the protein is found in the patient's muscle
- Need to find out about different forms of the protein in different muscle fibers
- One mutation in the Ashkenazim identified by Anderson and co-workers (2004)

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Mutations in β-tropomyosin

Identified in two families

by Kati Donner

in my group

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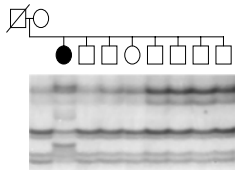
Missense mutation changing glutamine to proline in exon 4 in a patient from the Netherlands



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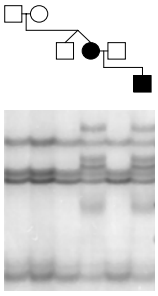
Missense mutation changing glutamic acid to lysine in exon 3 in a Bosnian family



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Other ongoing projects

- Attempt to find 6th gene using samples from consanguineous families with severe form
- Understanding how mutations in the nebulin and β-tropomyosin genes cause nemaline myopathy
- Understanding "haplotype blocks" in the nebulin gene

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MyoD conversion to get "muscle tissue" without muscle biopsy

- Fibroblasts out of skin biopsies
- Grown in culture flasks
- Converted into myoblasts using MyoD (myogenic determination gene)
- Produce muscle-like tissue

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Is nemaline myopathy different depending on the causative gene ?

Nebulin versus actin mutations

Typical nemaline myopathy: nebulin mutations	Typical nemaline myopathy: actin mutation
Severe nemaline myopathy: nebulin mutations	Severe nemaline myopathy: actin mutation

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Can mutation detection be guided by family history?

- Dominant inheritance: actin more likely
- Recessive inheritance: nebulin more likely
- One affected only, seriously ill as newborn: actin more likely

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Can mutation detection be guided by clinical features?

- Typical form: nebulin more likely
- Differences in distribution of muscle weakness
- Histological differences in some cases

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Same mutation - different severity:

Modifying genome?

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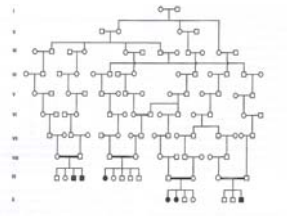
Mutations in the troponin T1 gene in an Amish kindred



- Johnston and co-workers, 2000
- Special form of nemaline myopathy
- No other mutations identified in this gene

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How many genes will there be?

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NEMALINE MYOPATHY GENES

- Nebulin (*NEB*): Numerous recessive mutations (Pelin et al. 1999)
- Actin (*ACTA1*): Numerous dominant and recessive mutations (Nowak et al. 1999)
- α-Tropomyosin (*TPM3*)
  - One dominant mutation (Laing et al. 1995)
  - One recessive mutation (Tan et al. 1999)
- β-Tropomyosin (*TPM2*)
  - Two dominant mutations (Donner et al. 2000)
- Troponin T (*TNNT1*)
  - One recessive mutation amongst the Old Order Amish (Johnston et al. 2000)

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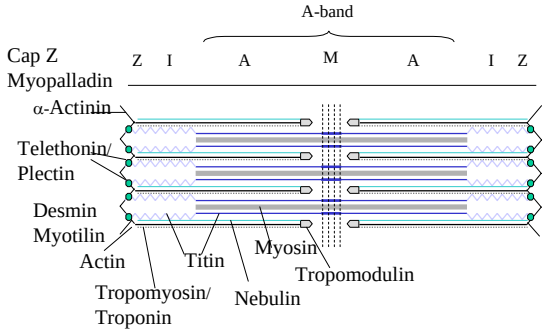
Sarcomeric defects cause structural abnormalities?



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Identification of the gene allows for

- Diagnostic tests to be developed
- Mode of inheritance to be determined
- Prenatal diagnosis if requested

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Prerequisites for developing therapies

- Identification of gene
- Characterization of protein
- Elucidation of protein function
- Understanding disease process

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Why is it difficult to develop therapies even where disease processes are known?

- Muscle tissue forms early in fetal development
- Stable tissue comprising 40 % of body volume
- Protein missing or faulty in all muscle fibers
- Immune reaction against previously unknown protein

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