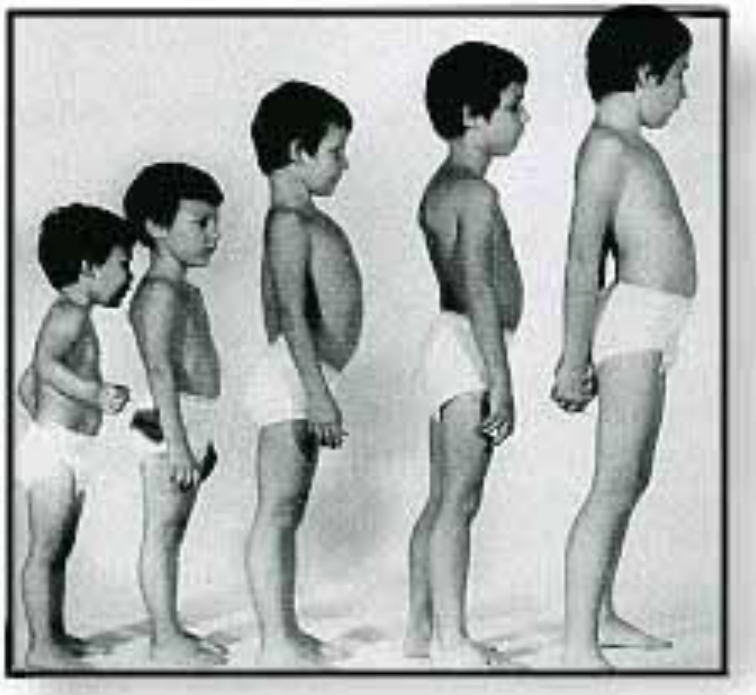
Neuromuscular disorders - Introduction



EPNS Training Course
Neuromuscular Disorders
Budapest, 6-7 April 2017

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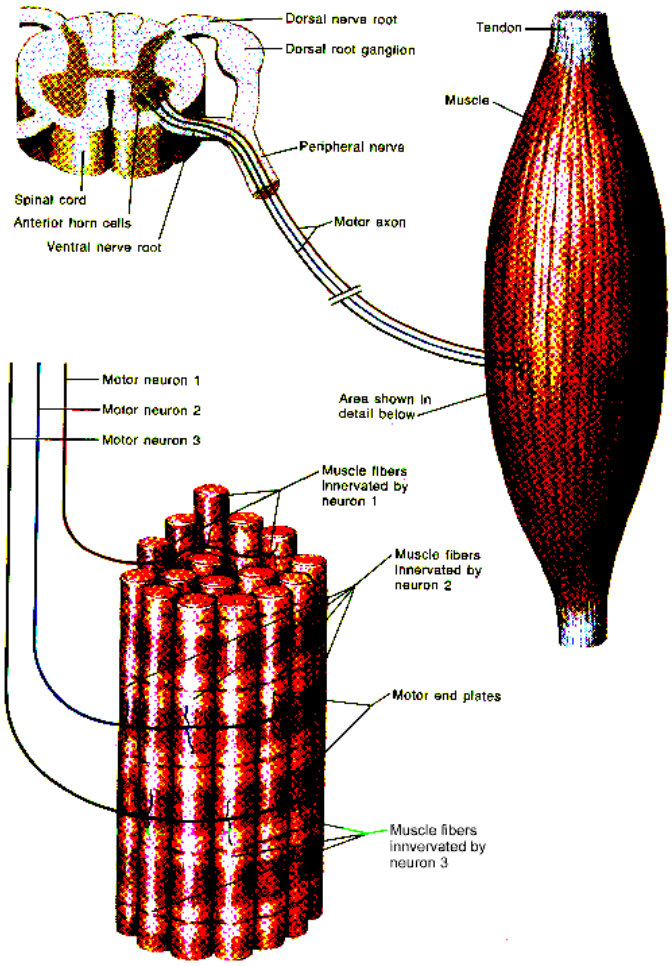
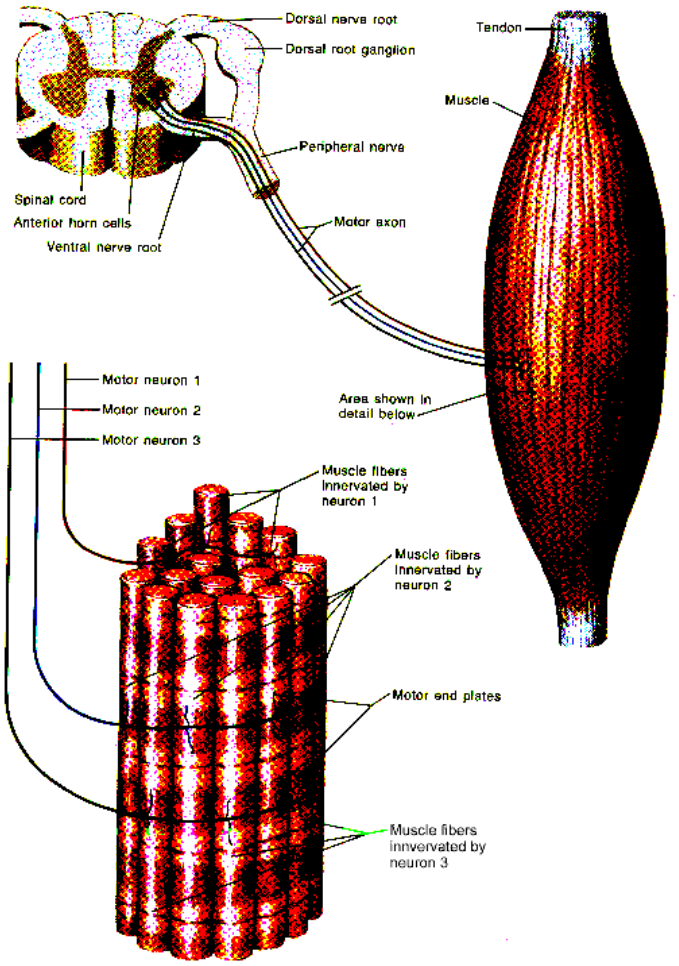
- Introduction Neuromuscular disorders (NMD)
- Diagnosis NMD

Neuromuscular disorders affect the motor unit:



Motor unit: motor neuron and its innerverated muscles

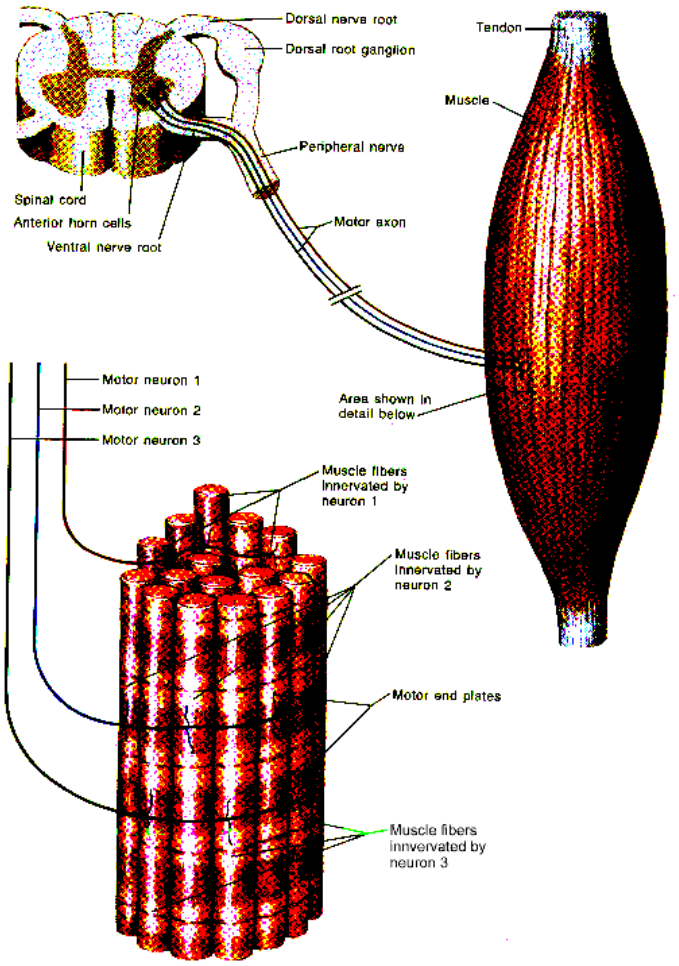
Neuromuscular disorders affect the motor unit:



Causes:

1. Infection
2. Inflammation/autoimmune
3. Hereditary, genetic

Neuromuscular disorders affect the motor unit:



Motor neuron
- SMA, polio

Axon
- Guillain-Barré, HMSN

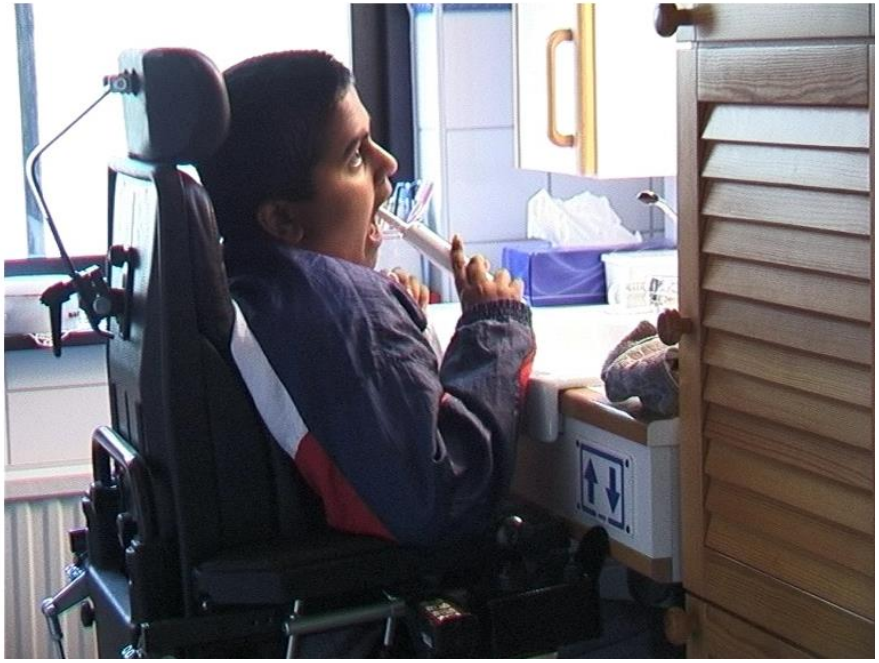
Neuromuscular junction
- Myasthenia

Muscle fiber
- Muscular dystrophies
- Myopathies

Neuromuscular disorders: how common?

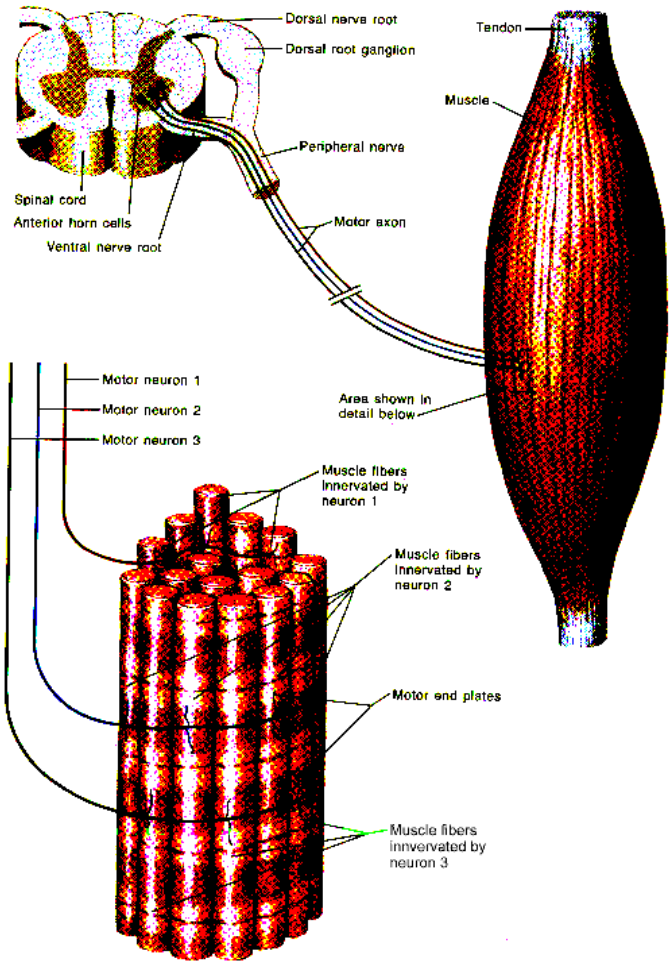
- 1:1500 (children and adults).
- Most hereditary (>200 different NMDs)

Neuromuscular disorders, symptoms:



- Muscle weakness
  - 2ary symtoms: respiratory problems, contractures, scoliosis
- myotonia, paralysis, pain, muscle cramps
- symptoms from other organs (heart, smooth muscle, CNS)

Neuromuscular disorders – diagnosis:



- ”Clinical diagnosis” (typical history/examination)
- Neurophysiology
- Muscle biopsy
- Genetic (specific gene or ”next generation sequencing”)

Clinical history

- Type of weakness/muscle dysfunction?
- Affected muscle groups?
- Start of symptoms? Progression?
- Pedigree – inheritance pattern?
- Associated symtoms (cardiac, smooth muscle, CNS, orthopaedic, other organs/sytems)?

Clinical examination:

- **Observation normal movement pattern!** (extent/distribution of weakness, muscle wasting, involuntary movements (e.g. fasciculations, twitches, tremor))
- **Walk (incl. heels & toes), run, jump** (weakness, ataxia, spasticity, other movement disorder?)
- **Gower´s maneuver** (necessity to use arms when rising from lying to standing?)
- **Tendon reflexes** (0=absent, 1=trace, 2=normal, 3=brisk, 4=nonsustained clonus, 5=sustained clonus)
- **Muscle strength** (MRC scale: 0=no voluntary movement, 1=trace of movement, 2=movement w.o. gravity, 3=movement against gravity, 4=movement against gravity and some added resistance, 5=movement against gravity and full resistance of tester)

Clinical examination:

- **Test of muscle tone**

Examine resistance of limbs to passive movements and range of movements of peripheral joints (e.g. wrists, ankles). Abnormal tone may present as:

Flaccidity – absence of muscle tone.

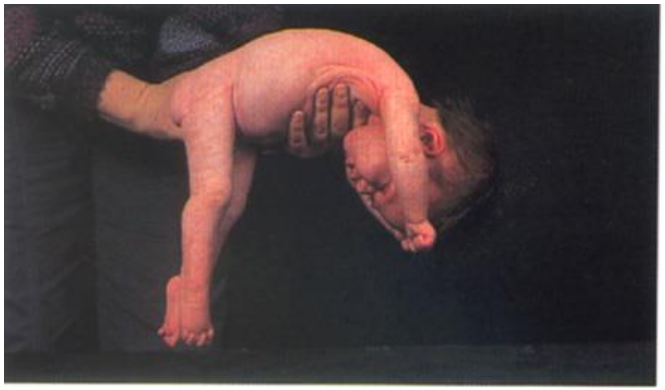
Hypotonia – decreased resistance to passive movement, usually accompanied by muscle weakness.

Hypertonia– Increased resistance to passive movement.

Spasticity – Velocity-dependent increase in tonic stretch reflexes

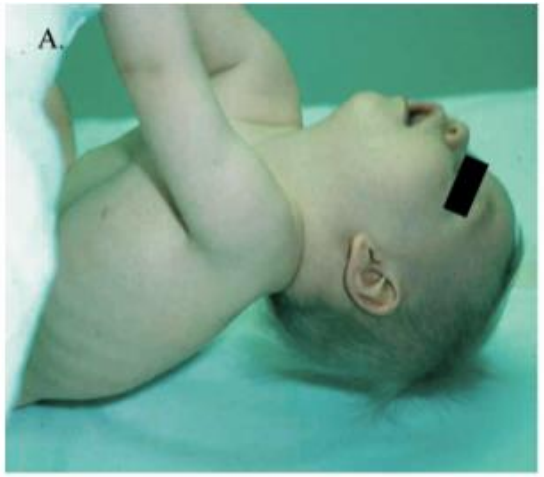
Rigidity – Simultaneous increase in muscle tone of agonist and antagosist muscles -> constant contraction

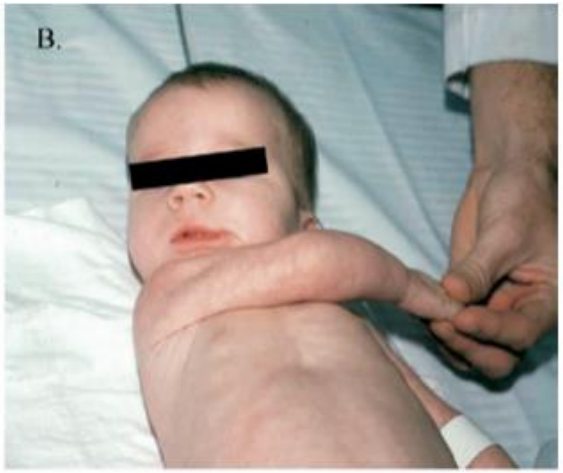
Neuromuscular disorders may present as neonatal hypotinia, ”Floppy infant”



Typical signs in floppy infant:

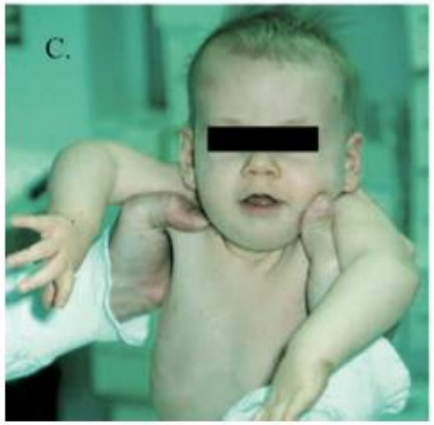
”Pull to sit”

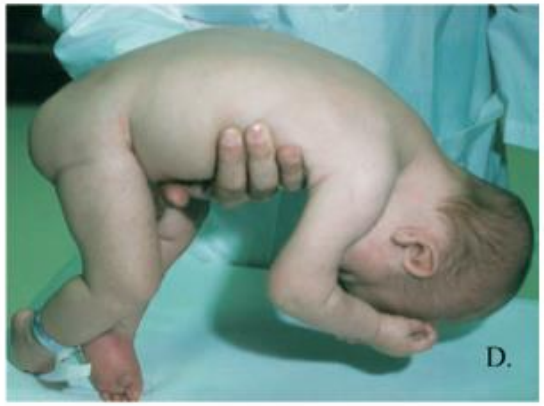




Scarf sign

Axillarhäng

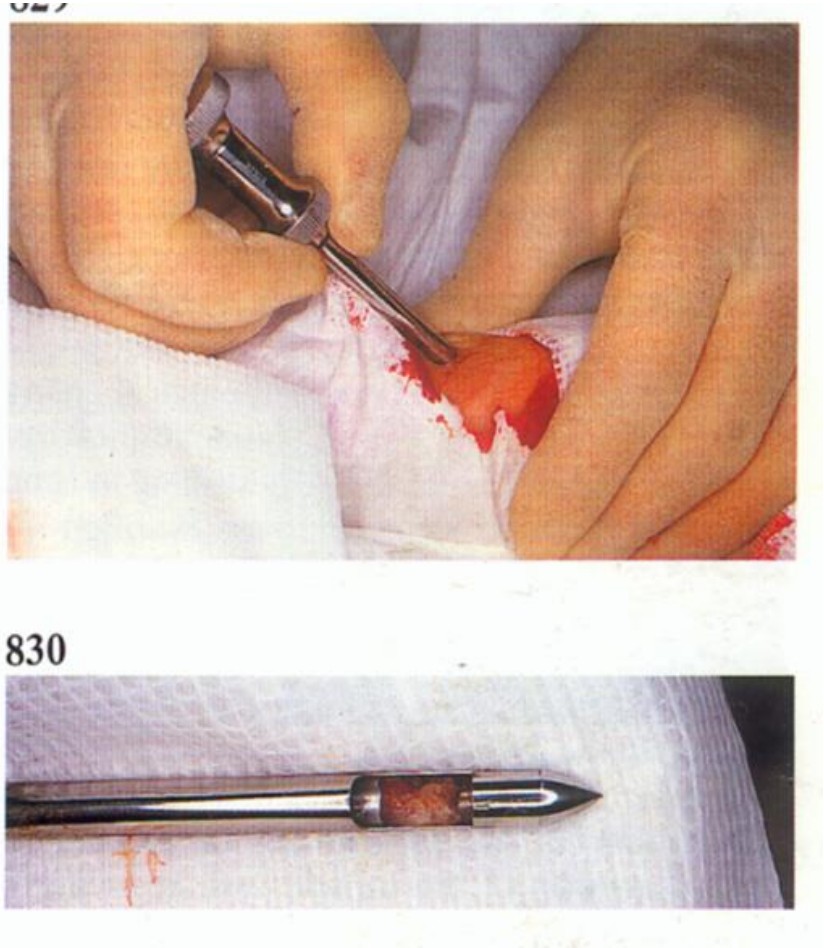




Hängande
med bukstöd

Bodensteiner, Semin Pediatr Neurol 15:10-20, 2008

Muscle biopsy



- Appropriate muscle?

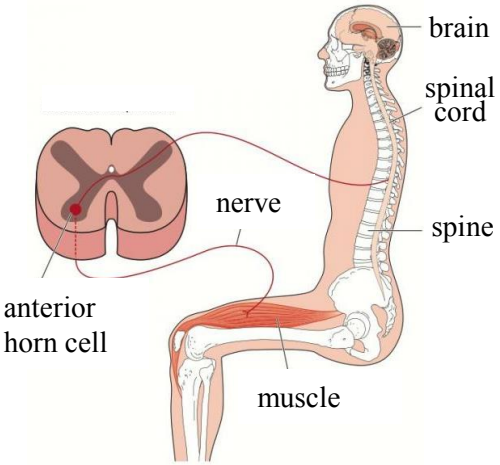
  Intermediate affection
- Local anaesthesia or general anaesthesia

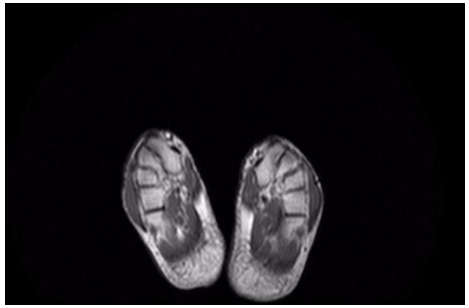
  Age, fear
- Routine histology, specific stainings

COST Action no. BM1304

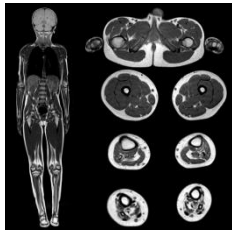
MYO-MRI
MR IMAGING & SPECTROSCOPY IN NEUROMUSCULAR DISEASE

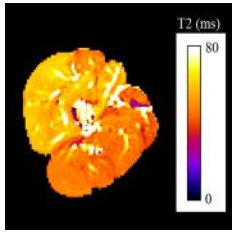
Applications of MRI & MRS techniques in neuromuscular disease: collaboration on outcome measures and pattern recognition for diagnostics and therapy development

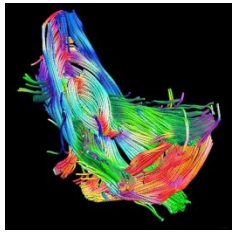


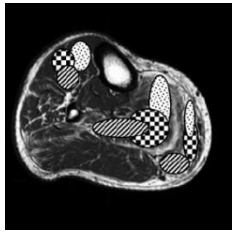


1. Improve diagnosis and our understanding of muscle pathology
   → **online atlas**
2. Develop multicentric imaging outcome measures
   → **SoPs**
3. Explore new contrasts, targets and imaging techniques for NMD
   → **clinical testing**
4. Explore strategies for muscle imaging texture analysis
   → **validated algorithms**









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Advances in genetic diagnosis: "Next generation sequencing"

Selected gene panels
Whole **exome** sequencing ("only" DNA encoding proteins, 25 000 genes)
Whole **genome** sequencing

Problems:
Cost
ENORMOUS amounts of data!
How distinguish disease causing mutation from rare polymorhisms?

NGS for diagnosis neuromuskular disorders:

Table 1. Next-generation sequencing approaches in a diagnostic setting for patients with skeletal muscle disorders

References	Disease	Number of genes	Number of samples	Detection rate (%)	Potential diagnosis (%)
Targeted resequencing					
Ankala *et al.* [10]	NMD	41	81	46	
	CMD	12	88	36	
	LGMD	11	96	26	
Savarese *et al.* [11]	NMD	93	177	29	32
Chae *et al.* [12]	EO-NMD	579	43	49	27
Evila *et al.* [13]	NMD	180	61	15	20
Kuhn *et al.* [14]	LGMD	38	58	33	
Sevy *et al.* [15]	DM	298	17	12	35
Savarese *et al.* [16▪]	LGMD	89/93	258	48	32
	CMD		164	39	30
	Others[a]		82	35	33
	Total		504	43	31
WES					
Neveling *et al.* [17]	Movement disorders	151	50	20	
Ghaoui *et al.* [18▪]	LGMD	136	60	45	
Todd *et al.* [19▪][b]	CMD	n.a.	38	47	
Bartoli *et al.* [20▪]	LGMD + DM	39	37	16	8
O'Grady *et al.* [21▪][b]	CMD	400	32	43	9

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Collaborative effort for best use "Next generation sequencing"!

Clinician Pathologist Geneticist

Thank you!