# Lower Extremity Weakness from a Rare Mutation

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# Disclosures

- Loeb: None
- Elliott: None

# History

- 28 year old woman presenting for history of lower extremity weakness since birth.
- Reported history of spinal muscular atrophy based on a “muscle biopsy” (?EMG) around age 2-3 years old
- Weakness has been mostly stable since onset and seems symmetric

# Additional history

- Denies weakness in her arms
- Able to walk without assistance
- Occasionally use forearm crutches
- Uses manual wheel chair for long distances
- No sensory complaints but with long distances, will develop cramps and tingling

# Additional history

- No trouble speaking, swallowing, no double vision, no shortness of breath or orthopnea, no bladder/bowel issues
- No cramps or muscle twitches
- No history of cataract or cardiac involvement
- Able to perform her activities of daily living

# Developmental history

- Born at term
- Delayed motor milestones
- Walked with assistance (walker/crutches) at age 5
- Trouble with athletics
- Never able to run or jump
- Trouble with stairs

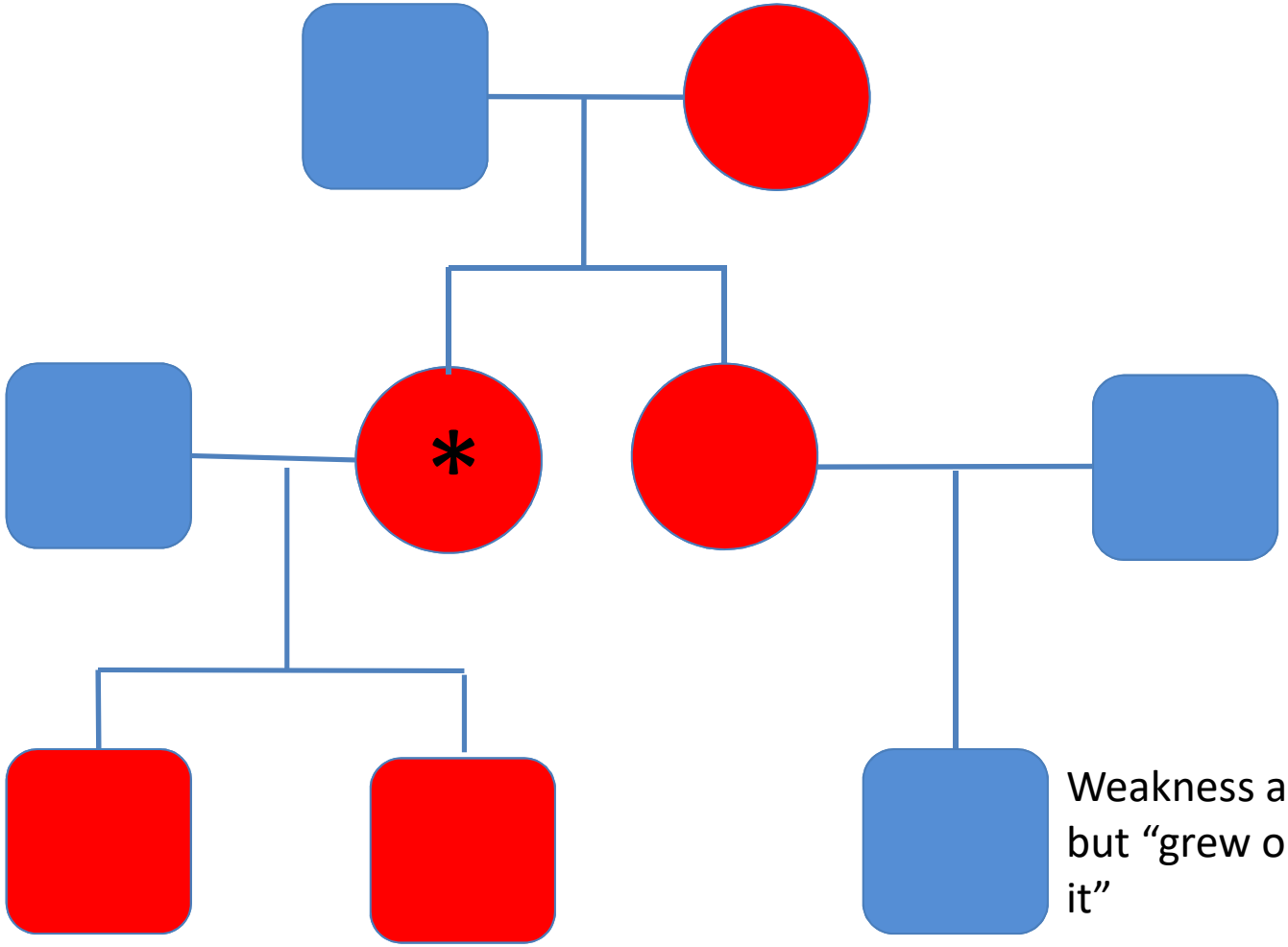
# Other

- Meds: Esomeprazole
- PMH/PSH: Anemia, GERD/C-Section
- ALL: none
- SH: Lives with husband and kids, prior smoking history, occasional alcohol use, no drug use

# Family History

- Mother: “identical” weakness, started at age 12
- Son 7yo: club feet, developed scoliosis, weakness, requires forearm crutches
- Son 6yo: weakness, requires forearm crutches
- Sister:  weakness, cognitive delay, epilepsy

# Pedigree




Weakness as child, but “grew out of it”

# Examination

- General: well appearing, high arched feet, no contractures
- Mental status: AOx3, normal language function
- Cranial Nerves: intact
- Motor: tone is normal, mild LE atrophy, neck flexors (4+/5) shoulder abduction 5-/5, elbow flexors 5/5, elbow extensors 5-/5, Wrist extensors 5/5, finger abd 5/5, **hip flexors 4-/5, knee extensors 4/5, knee flexors 4/5**, ankle DF 5-/5, ankle PF 5/5. No grip myotonia, no fasciculations
- Reflexes biceps 2, triceps 1, brachi 1, knees 2, ankles 0
- Sensory: intact to PP, LT, vibration, proprioception
- Coordination: intact to finger to nose
- Gait: Able to walk unassisted, wide based, hyperlordotic

# Summary of presentation

- Autosomal dominant pattern (or XD, or mito)
- Static vs very slowly progressive
- Proximal > distal
- Lower extremity >>upper extremity
- Normal sensory examination

# Localization

- Where could you localize this?

# Localization

- Muscle
- Motor Neuron
- Nerve
- Neuromuscular junction

- Additional laboratory findings to help localization?

# Laboratory

- Creatine kinase was 159 U/L

# NCS/EMG

**Nerve Conduction Studies**
**Motor Summary Table**

| Stim Site | N R | Onset (ms) | O-P Amp (mV) | Neg Area (mVms) | Neg Dur (ms) | Site1 | Site2 | Delta-0 (ms) | Dist (cm) | Vel (m/s) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Right Median Motor (APB)** | | | | | | | | | | |
| Wrist | | 2.8 | 13.8 | 41.81 | 5.31 | Wrist | APB | 2.8 | 7.0 | |
| Elbow | | 6.7 | 13.8 | 41.79 | 5.47 | Elbow | Wrist | 3.9 | 25.0 | 64 |
| **Right Peroneal Motor (EDB)** | | | | | | | | | | |
| Ankle | | 2.8 | 3.9 | 11.29 | 5.47 | Ankle | EDB | 2.8 | 8.0 | |
| B Fib | | 7.8 | 2.9 | 9.19 | 7.19 | B Fib | Ankle | 5.0 | 28.0 | 56 |
| Poplt | | 9.2 | 2.6 | 8.70 | 7.19 | Poplt | B Fib | 1.4 | 8.0 | 57 |
| **Right Tibial Motor (AHB)** | | | | | | | | | | |
| Ankle | | 3.6 | 12.7 | 24.86 | 5.31 | Ankle | AHB | 3.6 | 8.0 | |
| Knee | | 10.0 | 9.7 | 22.99 | 6.72 | Knee | Ankle | 6.4 | 34.0 | 53 |
| **Right Ulnar Motor (ADM)** | | | | | | | | | | |
| Wrist | | 2.8 | 12.9 | 39.28 | 5.47 | Wrist | ADM | 2.8 | 7.0 | |
| B Elbow | | 5.8 | 12.8 | 39.51 | 5.94 | B Elbow | Wrist | 3.0 | 23.0 | 77 |
| A Elbow | | 7.5 | 11.6 | 31.61 | 5.78 | A Elbow | B Elbow | 1.7 | 12.0 | 71 |

## Anti Sensory Summary Table

| Stim Site | NR | Peak (ms) | O-P Amp (µV) | Site1 | Site2 | Delta-0 (ms) | Dist (cm) | Vel (m/s) |
|---|---|---|---|---|---|---|---|---|
| **Right Sural Anti Sensory (Lat Mall)** | | | | | | | | |
| Calf | | 3.2 | 19.9 | Calf | Lat Mall | 2.6 | 14.0 | 54 |

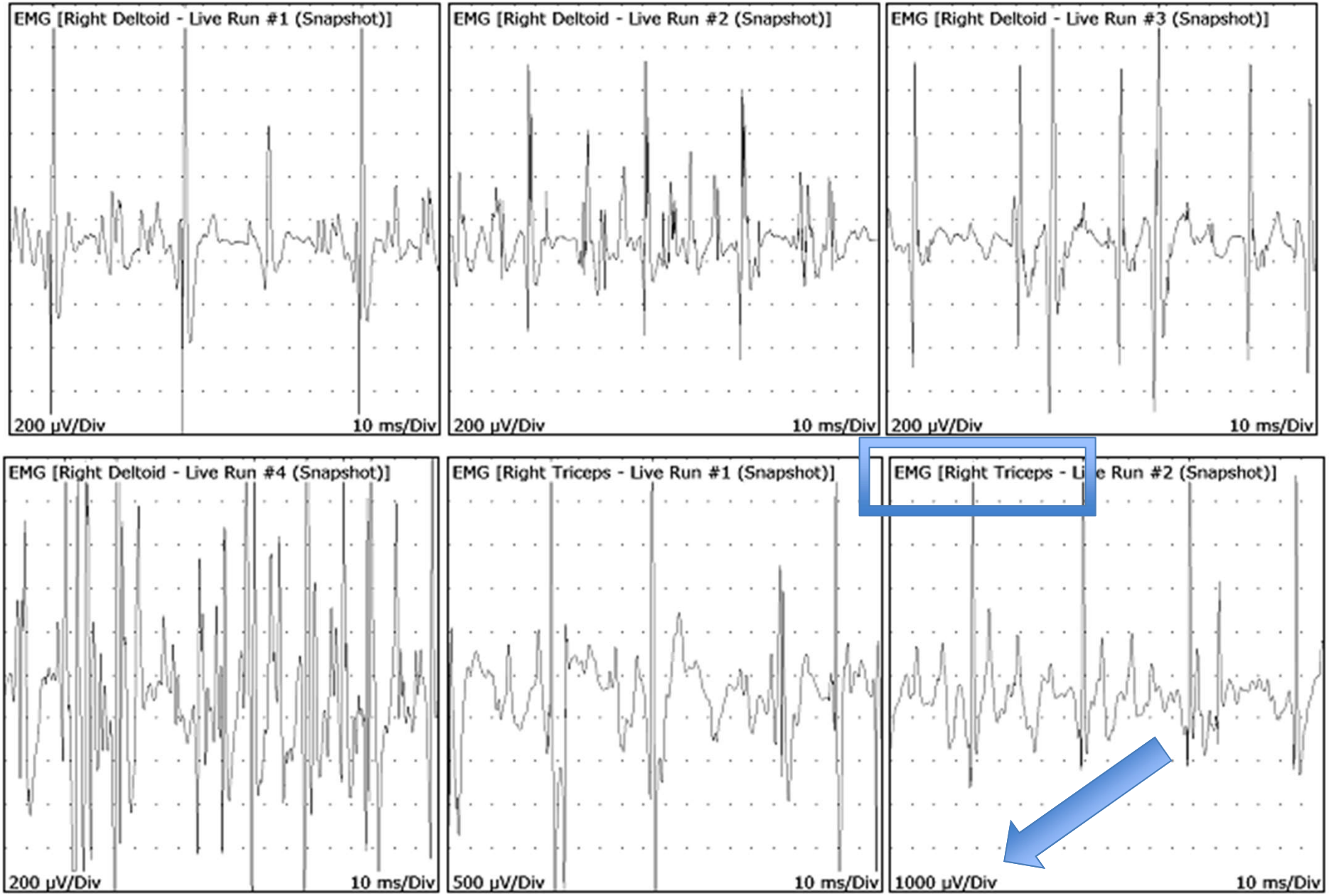
## Comparison Summary Table

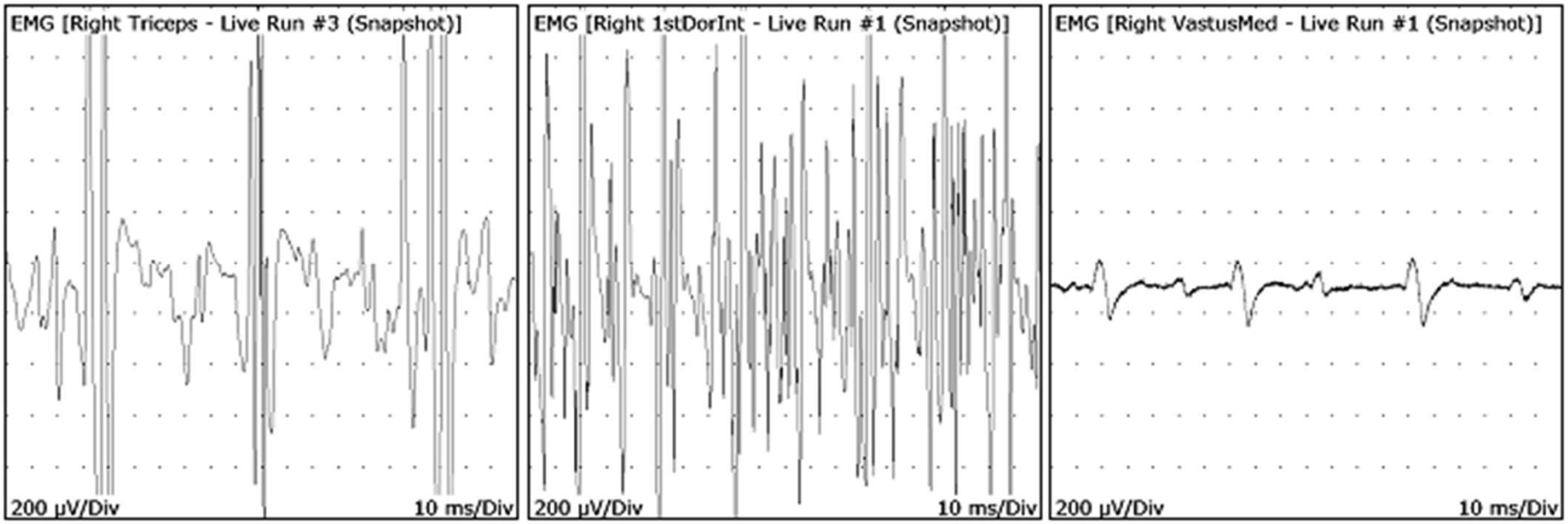
| Stim Site | NR | Peak (ms) | O-P Amp (µV) | Site1 | Site2 | Delta-P (ms) |
|---|---|---|---|---|---|---|
| **Right Median/Ulnar Palm Comparison (Wrist - 8cm)** | | | | | | |
| Median Palm | | 1.6 | 130.7 | Median Palm | Ulnar Palm | 0.0 |
| Ulnar Palm | | 1.6 | 42.3 | | | |

**EMG**

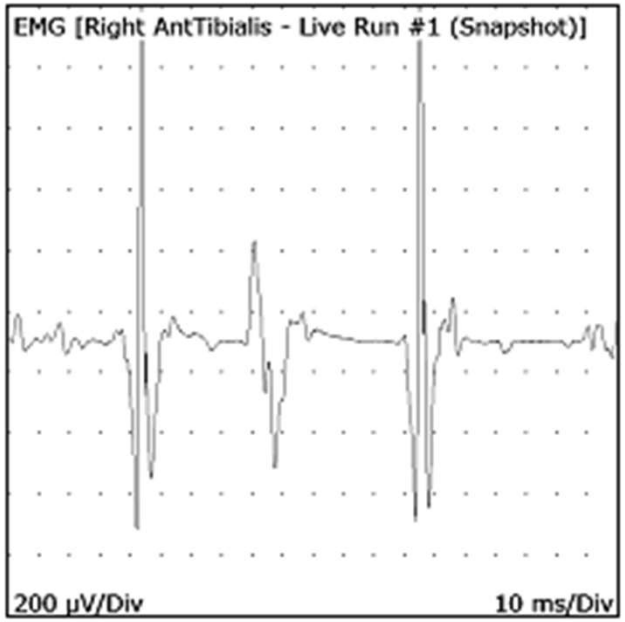
| Side | Muscle | Nerve | Root | PSW | Fibs | Fasc | Poly | Amp | Dur | Ins Act | Activa | Recrt | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Right | Deltoid | Axillary | C5-6 | Nml | Nml | Nml | Many | **Incr** | Nml | **Incr** | **Decr** | Nml | |
| Right | Triceps | Radial | C6-7-8 | Nml | Nml | Nml | None | **Incr** | Incr | Nml | **Decr** | **Decr** | **up to 7 mv** |
| Right | 1stDorInt | Ulnar | C8-T1 | Nml | Nml | Nml | None | **Incr** | Nml | Nml | Nml | Nml | **not well tolerated** |
| Right | VastusMed | Femoral | L2-4 | Nml | Nml | Nml | None | --- | --- | Nml | **Decr** | **Sev Decr** | **distant mup firing fast** |
| Right | AntTibialis | Dp Br Fibular | L4-5 | Nml | Nml | Nml | None | **Incr** | **Incr** | Nml | Decr | Decr | |

# RIGHT UPPER EXTRMITY






# Where is the lesion?



# Spinal Muscular Atrophy

- Genetic disorder of the anterior horn cell
- Autosomal recessive with variable severity
- Homozygous mutation 5q13 survival motor neuron
- Symmetric proximal weakness with areflexia

# Laboratory data

## SMA TESTING

**NEGATIVE**

This test did not identify any deletions of exon 7 in the *SMN1* gene. While this analysis did not identify any pathogenic or likely pathogenic deletions associated with spinal muscular atrophy (SMA), the diagnosis cannot be completely ruled out due to variants not detected by this assay or variants in another gene.

| Interpretive Results Table - qPCR | | | | |
|---|---|---|---|---|
| **Interpretation** | **SMN1 Copy Number** | **SMN2 Copy Number** | **Inheritance** | **Pub Med ID** |
| Negative | 2 copies | 2 copies | Autosomal Recessive | |

# Non-5q SMA

- Very diverse group of diseases
- Variable modes of inheritance
- Early/late onset & distal/proximal weakness

# Autosomal dominant, early onset

- Scapuloperoneal SMA
  - TRPV4 mutation
  - Proximal/distal weakness, static
  - Laryngeal weakness
  - Contractures of the knees, ankles

# Autosomal dominant, early onset

- SMALED1
  - DYNC1H1
  - LE atrophy
  - LE weakness
  - Normal/near nl arm strength
  - **Normal reflexes**
  - **No contractures**
- SMALED2
  - BICD2
  - LE atrophy
  - Weakness LE>UE, prox>dist
  - Variable reflexes
  - **Contractures**

# Mitochondrial Sequencing

| | |
|---|---|
| Test(s) requested: | Mitochondrial Disorders / Sequence Analysis and Deletion Testing of the Mitochondrial Genome |
| **Result:** | **NEGATIVE: No Pathogenic Variant Was Identified.** |
| | No pathogenic variant known to be associated with a disorder of mitochondrial metabolism was identified by this analysis of the entire mitochondrial genome in this patient. |
| Interpretation: | No pathogenic variant associated with a disorder of mitochondrial metabolism was identified by this analysis of the entire mitochondrial genome; therefore, we cannot confirm a diagnosis of a mitochondrial disorder in this individual. The combination of full sequence analysis plus deletion testing is expected to identify a mitochondrial DNA pathogenic variant in approximately 40% of adults and 10-20% of pediatric patients with a primary mitochondrial disorder (Chinnery, P. 2006; Koenig, MK 2008; Zeviani and Di Donato 2004). |

# Whole Exome Sequencing

| Gene | Disease | Mode of Inheritance | Variant | Coding DNA | Zygosity | Inherited From | Classification |
|---|---|---|---|---|---|---|---|
| DYNC1H1 | DYNC1H1-Related Disorder | Autosomal Dominant | p.R251C | c.751 C>T | Heterozygous | Unknown | Pathogenic Variant |

DYNC1H1 Mutation: p.R251C (c.751 C>T)

# DYNC1H1

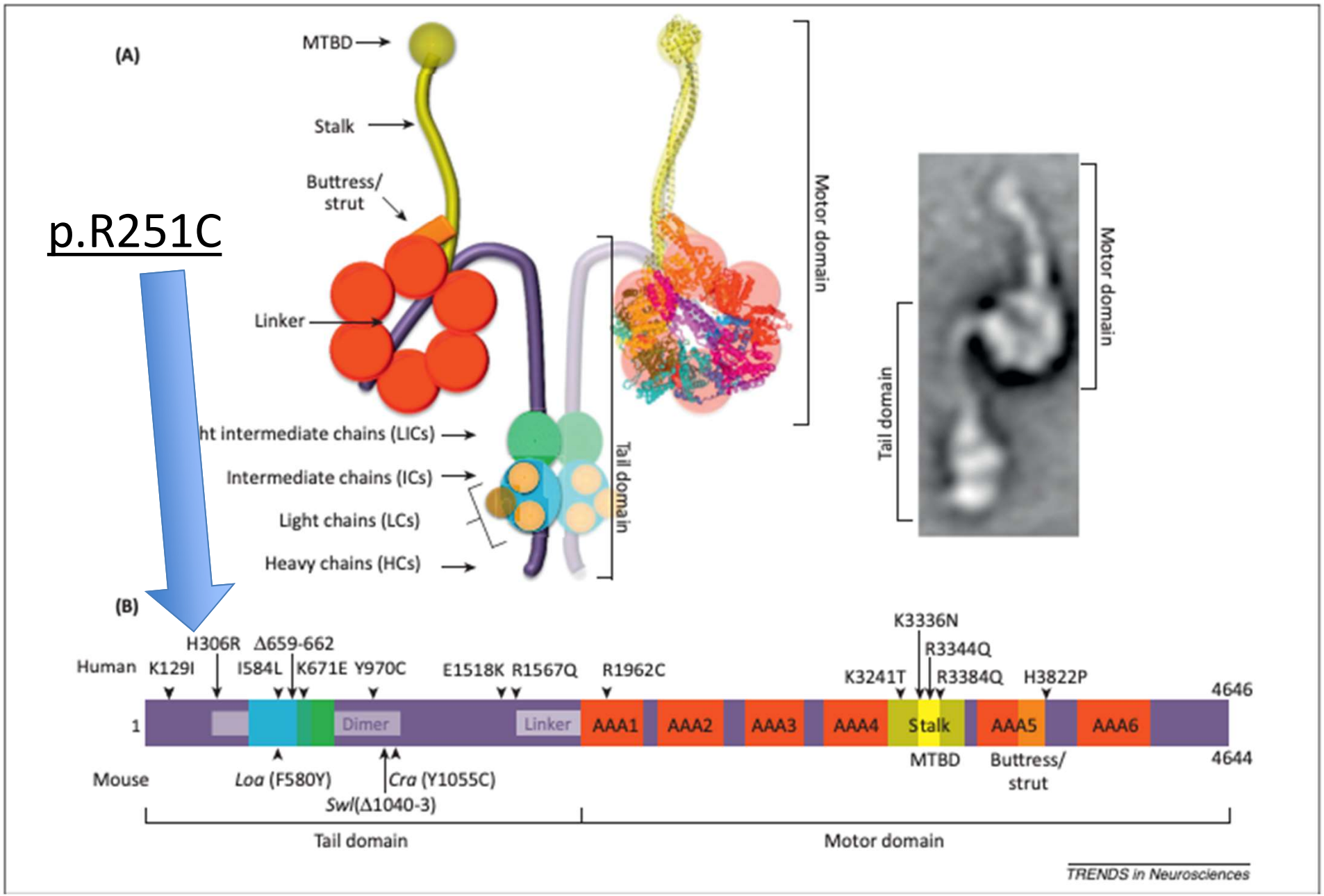
Dynein, cytoplasmic 1, heavy chain 1

- Dynein: large family of motor proteins complexes
- Runs along microtubules toward the cell body
- Tail and motor domain
- Cargo carried via tail domain
- Retrograde transport, migration, cell division, other

# DYNC1H1

- Three clinical phenotypes
  - **SMA-LED1**
  - CMT2O
  - Malformation of cortical development (MCD)
  - Overlapping syndrome

- Phenotypic variability
  - SMA-LED 1 & CMT2O & MCD
    - DYNC1H1
  - SMA-LED 2 & late onset HSP
    - BICD2
  - Scapuloperoneal SMA & CMT2C
    - TRPV4



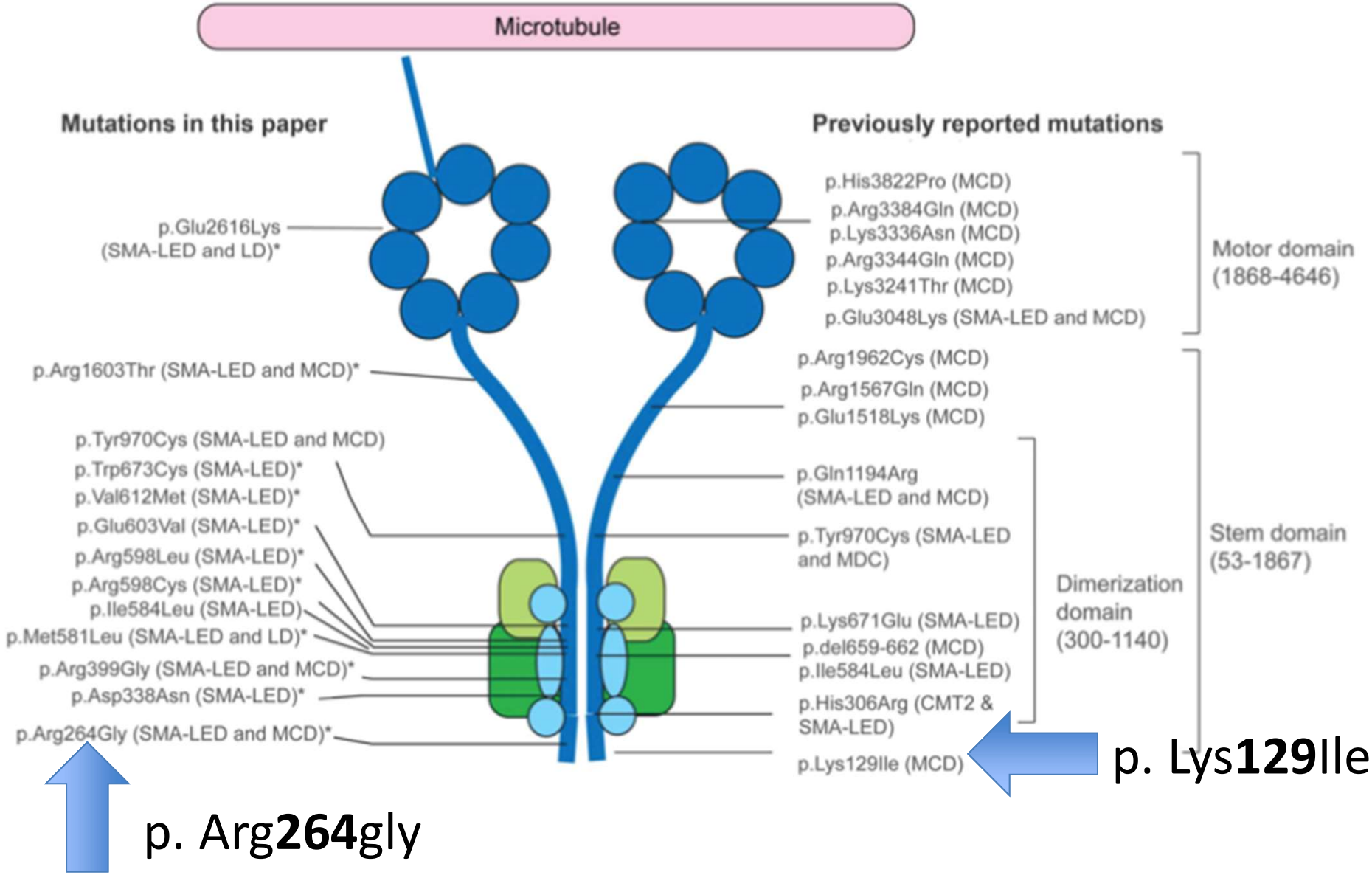

Schiavo G, et al. Trends Neurosci. 2013 36(11):641-651.

# DYNC1H1

- Tail domain mutations producing SMALED
- Motor domain mutations producing cortical migration defects
- Heterozygous DYNC1H1 mutation
  - [p.H306R (c.917A>G)]
  - CMT2O and SMALED1

Tsurusaki Y, et al. Neurogenetics. 2012 Nov;13(4):327-32.

Weedon MN, et al. Am J Hum Genet. 2011 Aug 12;89(2):308-12.




Scoto, M. et al. Neurology 2015;84:668–679

# Clinical overlap

- Wide range of clinical features in DYNC1H1-related mutations
- Isolated CNS malformations
- Motor neurons
- Sensory/motor nerves

# Acknowledgements


- Thank you Dr. Elliott

# References


- Harms MB, Allred P, Gardner R Jr, et al. Dominant spinal muscular atrophy with lower extremity predominance: linkage to 14q32. Neurology 2010; 75: 539-546.
- Scoto M, Rossor AM, Harms MB, et al. Novel mutations expand the clinical spectrum of DYNC1H1-associated spinal muscular atrophy. Neurology. 2015 Feb 17;84(7):668-679.
- Peeters K, Chamova T, Jordanova A. Clinical and genetic diversity of SMN1-negative proximal spinal muscular atrophies. Brain. 2014 Nov;137(Pt 11):2879-2896.
- Yoshioka M, Morisada N, Toyoshima D, et al. Novel BICD2 mutation in a Japanese family with autosomal dominant lower extremity-predominant spinal muscular atrophy-2. Brain Dev. 2018 Apr;40(4):343-347
- Roberts AJ, Kon T, Knight PJ, Sutoh K, Burgess SA. Functions and mechanics of dynein motor proteins. Nat. Rev. Mol. Cell Biol. 2013;14:713-726.
- Schiavo G1, Greensmith L, Hafezparast M, Fisher EM. Cytoplasmic dynein heavy chain: the servant of many masters. Trends Neurosci. 2013 Nov;36(11):641-651.
- Scoto M, Rossor AM, Harms MB. et al. Novel mutations expand the clinical spectrum of DYNC1H1-associated spinal muscular atrophy. Neurology 2015;84:668-679.
- Fiorillo C, Moro F, Yi J, et al. Novel Dynein DYNC1H1 neck and motor domain mutations link distal spinal muscular atrophy and abnormal cortical development. Hum Mutat 2014; 35: 298–302.
- Tsurusaki Y, Saitoh S, Tomizawa K, Sudo A,. A DYNC1H1 mutation causes a dominant spinal muscular atrophy with lower extremity predominance. Neurogenetics. 2012 Nov;13(4):327-332.
- Weedon MN, Hastings R, Caswell R, et al. Exome sequencing identifies a DYNC1H1 mutation in a large pedigree with dominant axonal Charcot-Marie-Tooth disease. Am J Hum Genet. 2011 Aug 12;89(2):308-312.
- Neveling K., Martinez-Carrera L.A., Hölker I.,et al. Mutations in BICD2, which encodes a golgin and important motor adaptor, cause congenital autosomal-dominant spinal muscular atrophy. Am. J. Hum. Genet. 2013;92:946–954
- Synofzik M, Martinez-Carrera LA, Lindig T, et al. Dominant spinal muscular atrophy due to BICD2: a novel mutation refines the phenotype. J Neurol Neurosurg Psychiatry 2014; 85: 590–2.