"A 38 year old female with muscle weakness……"

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History

- A 38-year-old woman presented with painless proximal muscle weakness since she was 5 years old. It was largely attributed to her being overweight.
- She also reported dysphagia and generalized fatigue.
- Diplopia to far vision for 2 years. Ophthalmologic exam normal.
- No pain in extremities, skin changes, shortness of breath, exercise induced muscle cramps, hearing impairment, palpitations, seizures and speech difficulty.

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History

- Medications: Vitamin supplements.
- Family History: Mother had proximal muscle weakness.
  Brother with big calf muscles.
  Grandfather had dysphagia.
  Two sons (10 and 6-year old) with no weakness.
- PMH: OCD and Raynaud's phenomena.

Physical Examination

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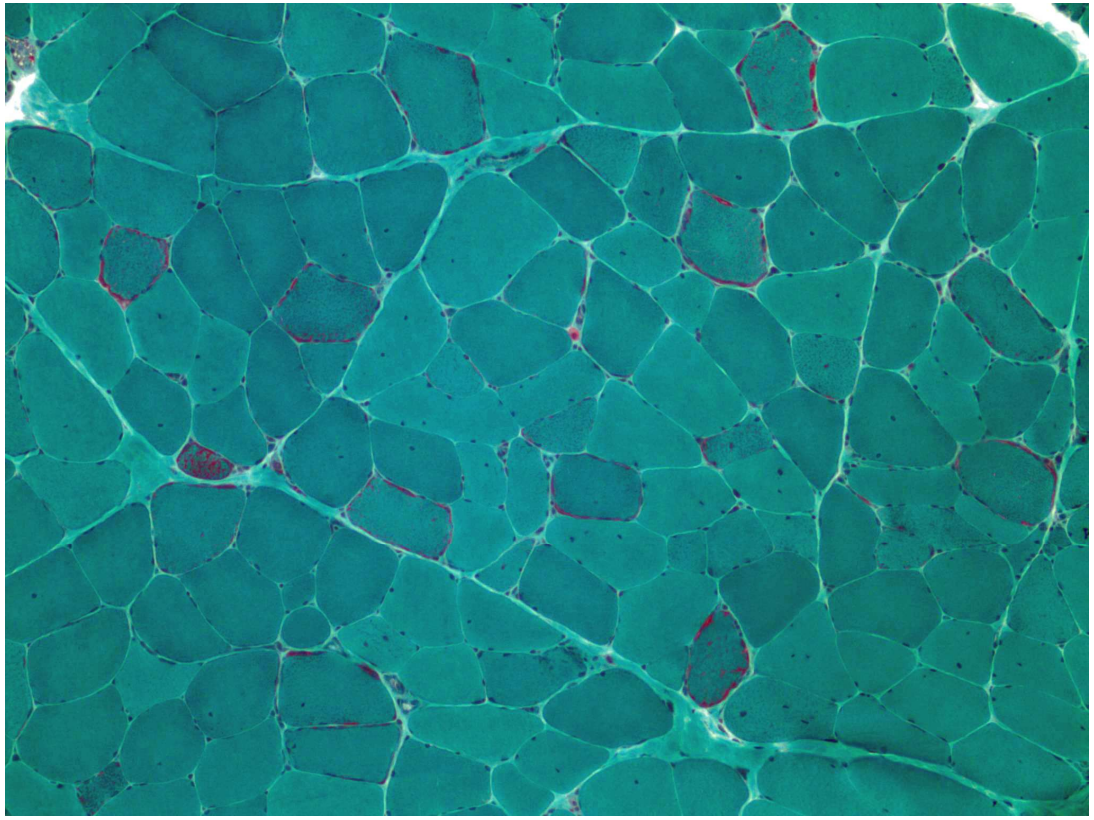
Labs and Imaging

- **CBC, CMP and TSH** were unremarkable. **CK** was elevated to 503 U/L.
- **Autoimmune panel** including ANA, dsDNA, SSA, SSB, Sm, RNP, scl-70, centromere B, Ribosomal P were negative.
- **MRI pelvis and thighs without contrast:** symmetric fatty infiltration of pelvic and thigh muscles with reduced muscle bulk.
- **Electromyography:** No myogenic or neurogenic pattern.

Muscle Biopsy revealed mitochondrial myopathy

- Modified Gromori Trichrome stain showing ragged red fibers.



Magnified Trichrome stain (400X)

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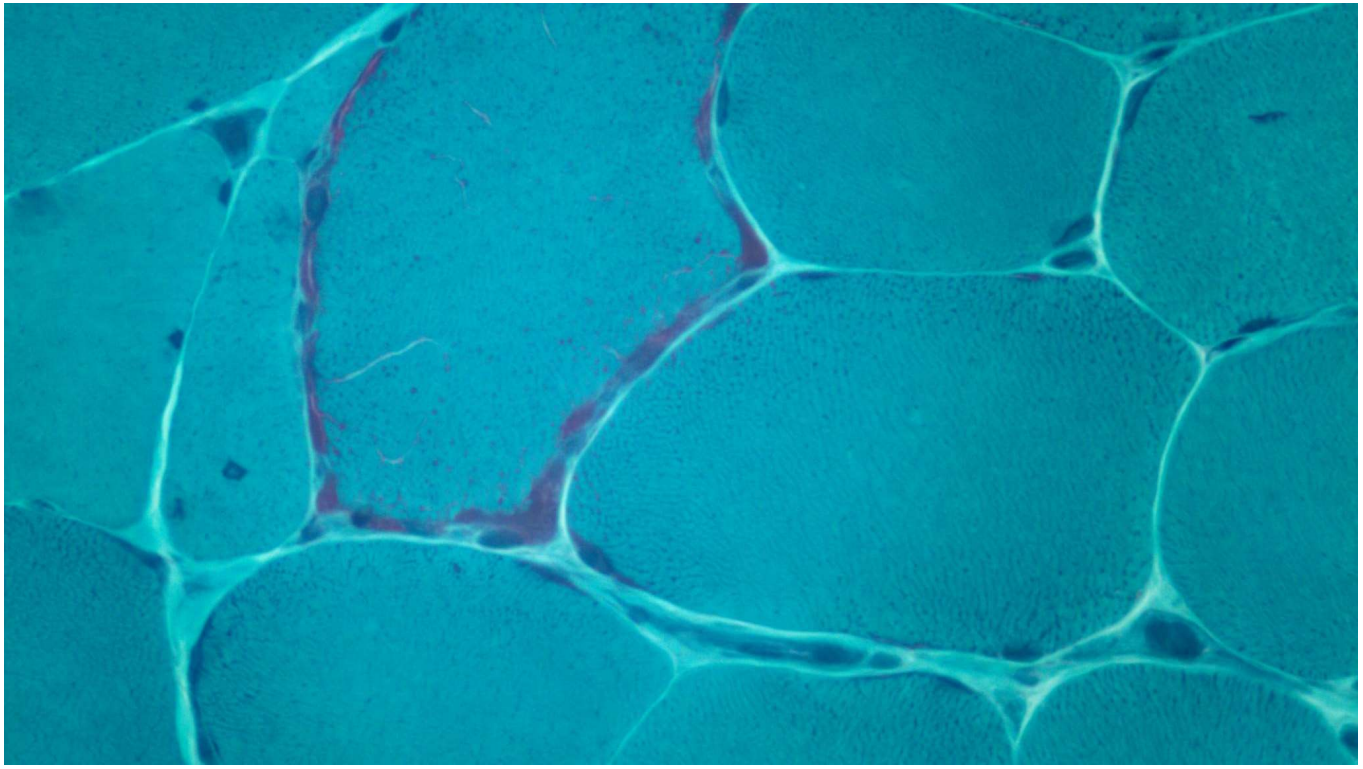
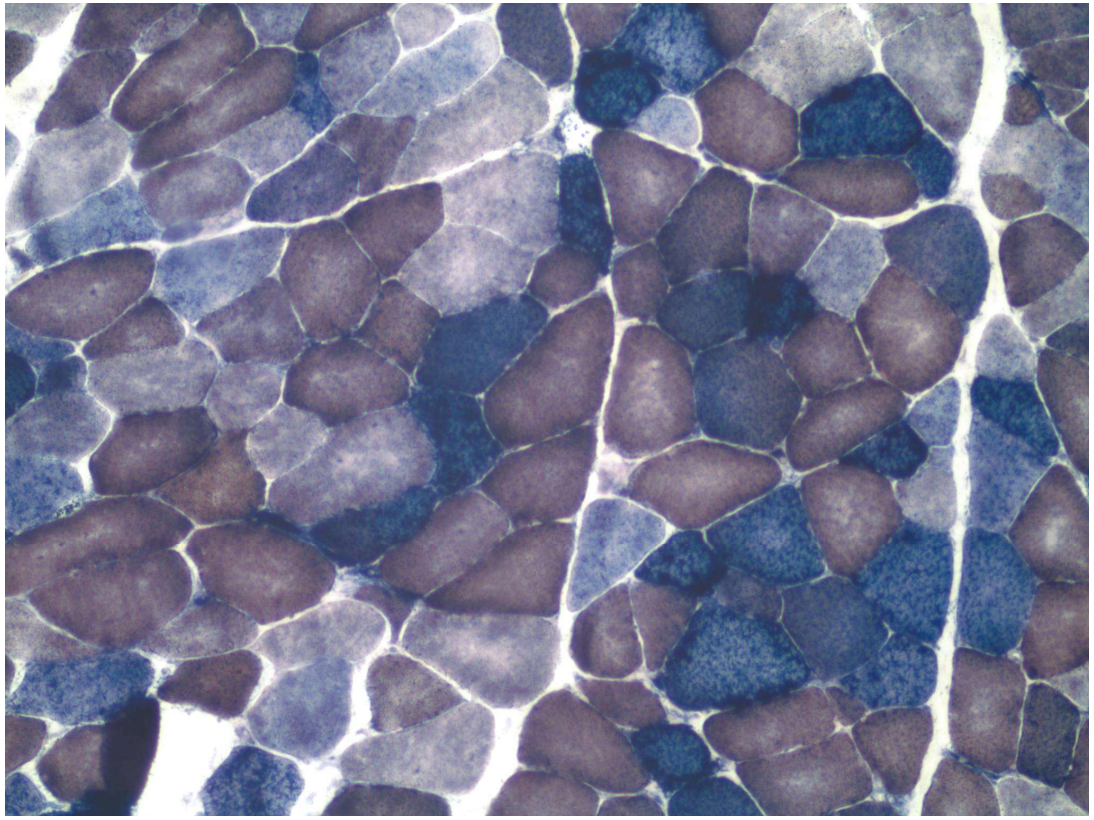


Muscle Biopsy

- COX counterstained by SDH.
- Many COX negative fibers that stained positive with SDH (blue fibers).



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Any thoughts on differential?

What next diagnostic test you would like?

Mitochondrial genome plus Mito Nuclear gene panel

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- Mitochondrial genome sequencing and deletion analysis of muscle sample:

  3 large deletions of mitochondrial genome: 10.7kb, 12.6 and 9.6 kb.

  The sum total of heteroplasmy of these deletions was estimated to be less than 15 percent.

- Next generation sequencing and deletion/duplication analysis of 319 nuclear genes using blood sample:

  Deoxyguanosine (DGUOK) kinase gene mutations

  1) c.195 G>A in exon 2 and
  2) c.462T>A in exon 4.

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Diagnosis

DGUOK related autosomal recessive multiple mitochondrial deletion syndrome producing proximal muscle weakness and progressive external ophthalmoplegia.

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Mitochondrial Myopathy

- Mitochondrial myopathy is a disease of skeletal muscles, with or without central nervous system involvement, caused by defective mitochondrial metabolism.

- It is caused by defects in nuclear or mitochondrial DNA.

- Nuclear genes responsible for maintenance of mtDNA:

  POLG*, *POLG2*, *C10ORF2*, *TYMP*, SUCLA2, SUCLG1, *TK2*, *RR2MB* and *DGUOK

  Defects in these genes affect **mtDNA content** (number of copies) or cause **mtDNA deletions**.

Deoxyguanosine Kinase (DGUOK)

- The enzyme DGUOK is encoded by the nuclear DNA and transported into the mitochondria.

- It is responsible for phosphorylation of purinedeoxyribonucleosides in the mitochondrial matrix.
- Loss of function mutations in *DGUOK* are associated with autosomal recessive inheritance of three main phenotypes:

    - MtDNA depletion syndrome-3
    - Noncirrhotic portal hypertension
    - Autosomal recessive progressive external ophthalmoplegia (PEO) with mtDNA deletions.

DGUOK gene related myopathy

- Mutations in *DGUOK* have largely been described in mtDNA depletion syndromes.
- Very few cases of myopathy have been observed.
- Of those reported, most cases had adult-onset of symptoms.
- However, our case had symptom-onset in childhood with no liver or cardiac disease.

c.195 G>A (W65X)

- The c.195 G>A mutation is predicted to produce a p.Trp65Ter nonsense pathogenic variant.
- This pathogenic variant is predicted to cause loss of normal protein function either through protein truncation or mRNA decay.
- It has been reported in association with mitochondrial DNA depletion syndrome producing neonatal hepatocerebral disease in trans to another truncating mutation.

c.462 T>A (N154K)

- The second variant, c.462 T>A, is predicted to result in the Asn154Lys substitution.
- It has been reported in cases of adult-onset PEO and mitochondrial myopathy in *trans* with other pathogenic variants.
- The affected cases described previously had evidence of DNA depletion and decreased enzyme activity in muscle biopsies.

Primary sequence of DGUOK

- The position of asparagine (N) in different species including humans (Hs), mouse (Mm), zebrafish (Dr) & *Drosophila* (Dm).

Diagram courtesy:

Paolo Moretti, MD

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Hs	Y	I	F	A	K	N	L	F	E	N	G	159
Mm	Y	I	F	A	K	N	L	F	E	N	G	159
Dr	Y	I	F	A	L	N	M	F	A	L	G	151
Dm	Y	C	F	V	E	N	M	R	R	N	G	122

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Take Home Point

- Our case expands the phenotypic spectrum of *DGUOK* mutations and highlights the importance of NGS in children and adults to timely diagnose mitochondrial myopathy.
- The markedly slow progression of symptoms like in our case, sometimes result in delay in diagnosis.
- Longitudinal studies are needed to further investigate the course and predict the outcomes in patients harboring *DGUOK* mutations.

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Questions?