A Tale of Two Brothers and Some Others

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Case 1: WT

History of Present Illness

- 11 year-old boy who presented to the CMC Neuromuscular clinic at age 6 for muscle weakness and abnormal gait
- Difficulty with walking and poor balance with frequent falls
- Trouble climbing stairs and getting in/out of a vehicle

Birth History

- No pregnancy complications
- 40 weeks gestation via SVD
- Delivery complicated when the umbilical cord was cut before clamping
- BW 3.6 kg
- One week NICU stay
  - Sacral lipoma noted, which led to discovery of a tethered cord

Past Medical & Surgical

- Motor developmental delay
- Neurogenic bladder & bowel
- Scoliosis
- Anosmia
- Feeding difficulties and malabsorption
- Surgical release of tethered cord at 6 months
- Gastrostomy tube placement

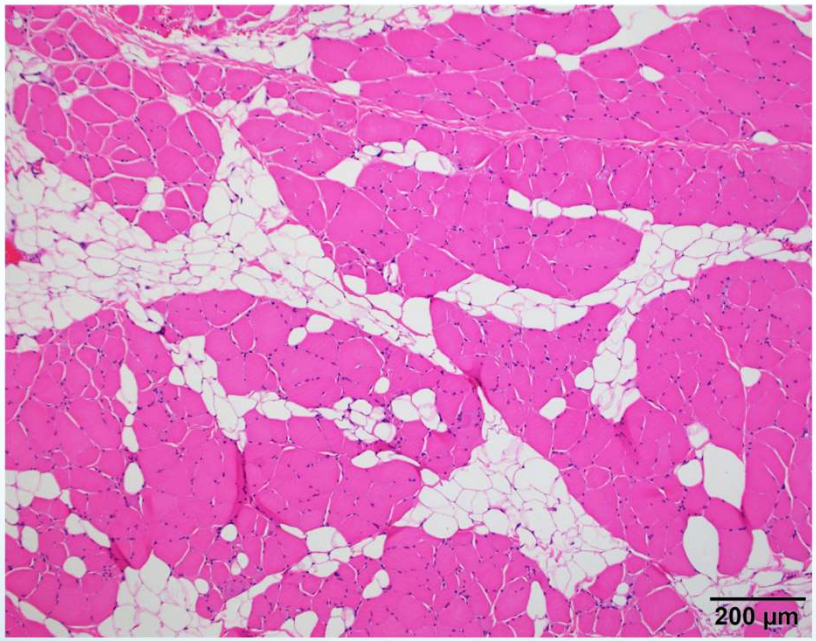
Developmental History

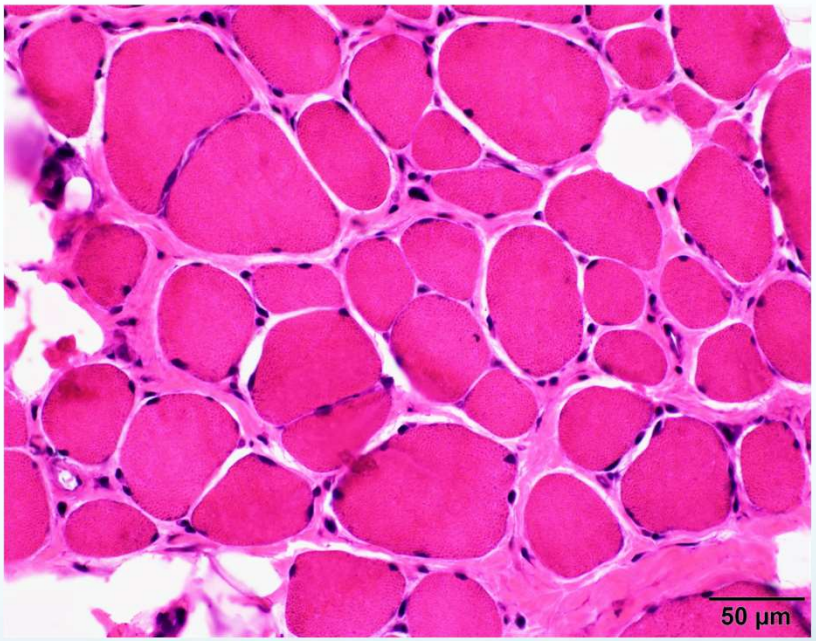
- Gross Motor
  - Rolled and Sat at 7 months
  - Crawled at 11 months
  - Walked at 22 months
- Fine Motor- delayed
- Speech/Language- normal
- Social- appropriate

Diagnostic Studies

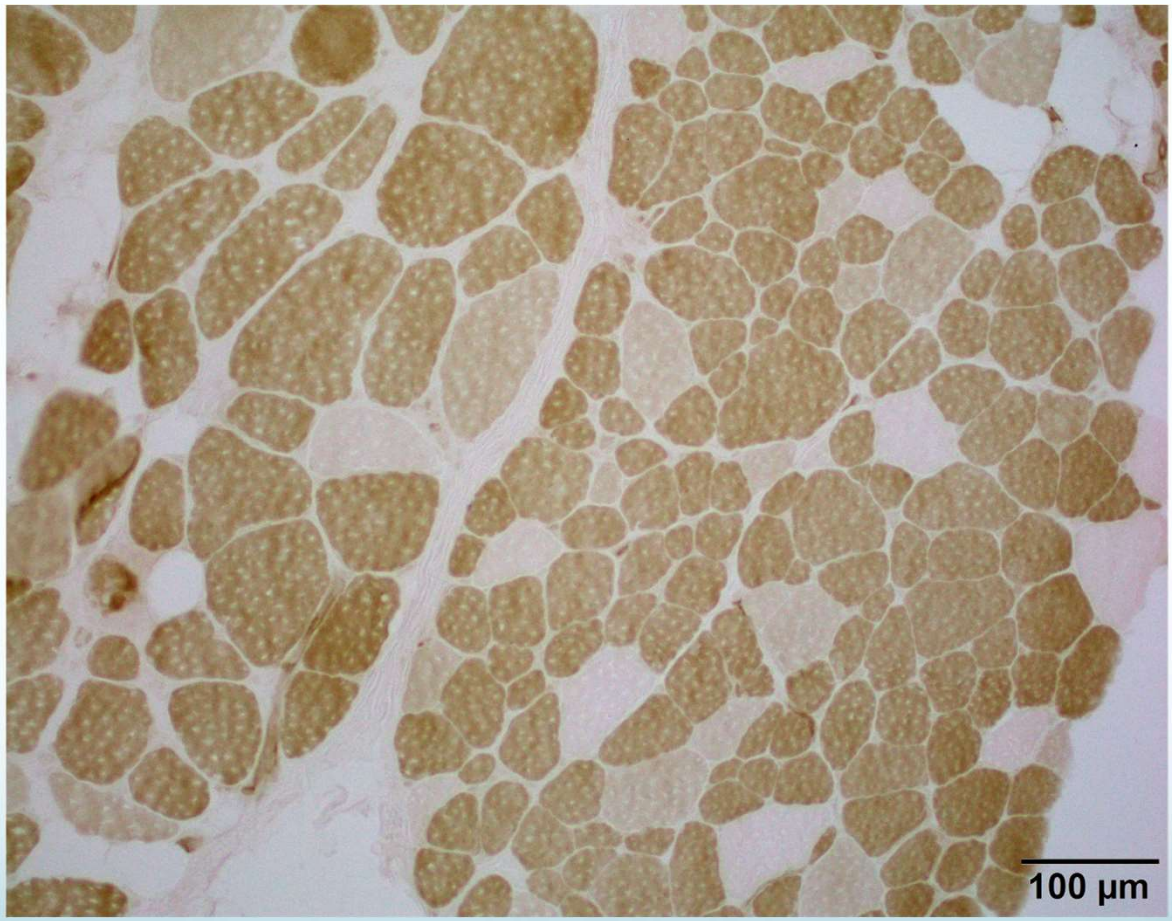
- CK level: reportedly normal
- Muscle Biopsy
  - Type I myofiber predominance with chronic myopathic alterations
  - Rare denervated fibers

H&E

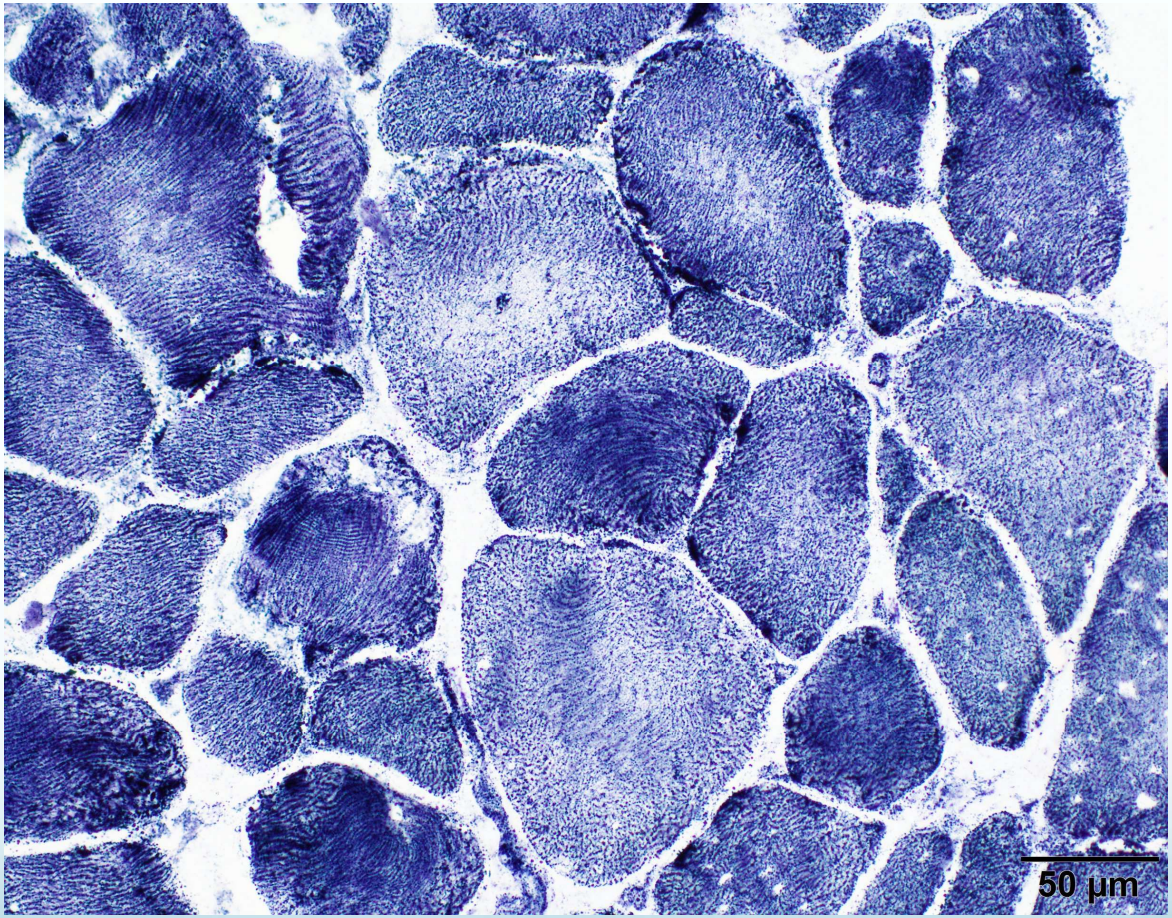




ATPase



NADH-TR



Case 2: HT

History of Present Illness

- 7 year-old boy who was referred to the CMC Neuromuscular clinic at age 2 for muscle weakness
- Daily falls
- Fatigues easily following short periods of activity

Birth History

- 41 weeks gestation via SVD at home
- No pregnancy or delivery complications
- BW 2.95 kg
- Congenital heart defects (ASD & VSD), micropenis, and facial hemangioma
  - Genetics evaluation- diagnosis of partial trisomy 6

Past Medical & Surgical

- Gross motor developmental delay
- GERD
- Failure to thrive with feeding difficulties
- Seizures
- Gastrostomy tube placement
- Orchiopexy

Developmental History

- Gross Motor
  - Rolled at 12 months
  - Sat at 13 months
  - Crawled at 15 months
  - Walked at 19 months
- Fine Motor- normal
- Speech/Language- normal
- Social- appropriate

Diagnostic Studies

- CK level: 83
- EMG/NCS
  - Nerve conduction study was normal
  - EMG showed many low amplitude and short duration motor units in the right upper and lower extremities consistent with diffuse myopathy

Physical Examination

Genetic Changes in WT & HT

- **RYR1**
  - exon 33, c.4711A>G heterozygous, p.Ile1571Val (paternal)
  - exon 67, c.10097G>A heterozygous, p.Arg3366His (paternal)
  - exon 86, c.11798A>G heterozygous, p.Tyr3933Cys (paternal)
  - exon 102, c.14731G>A heterozygous, p.Glu4911Lys (maternal)

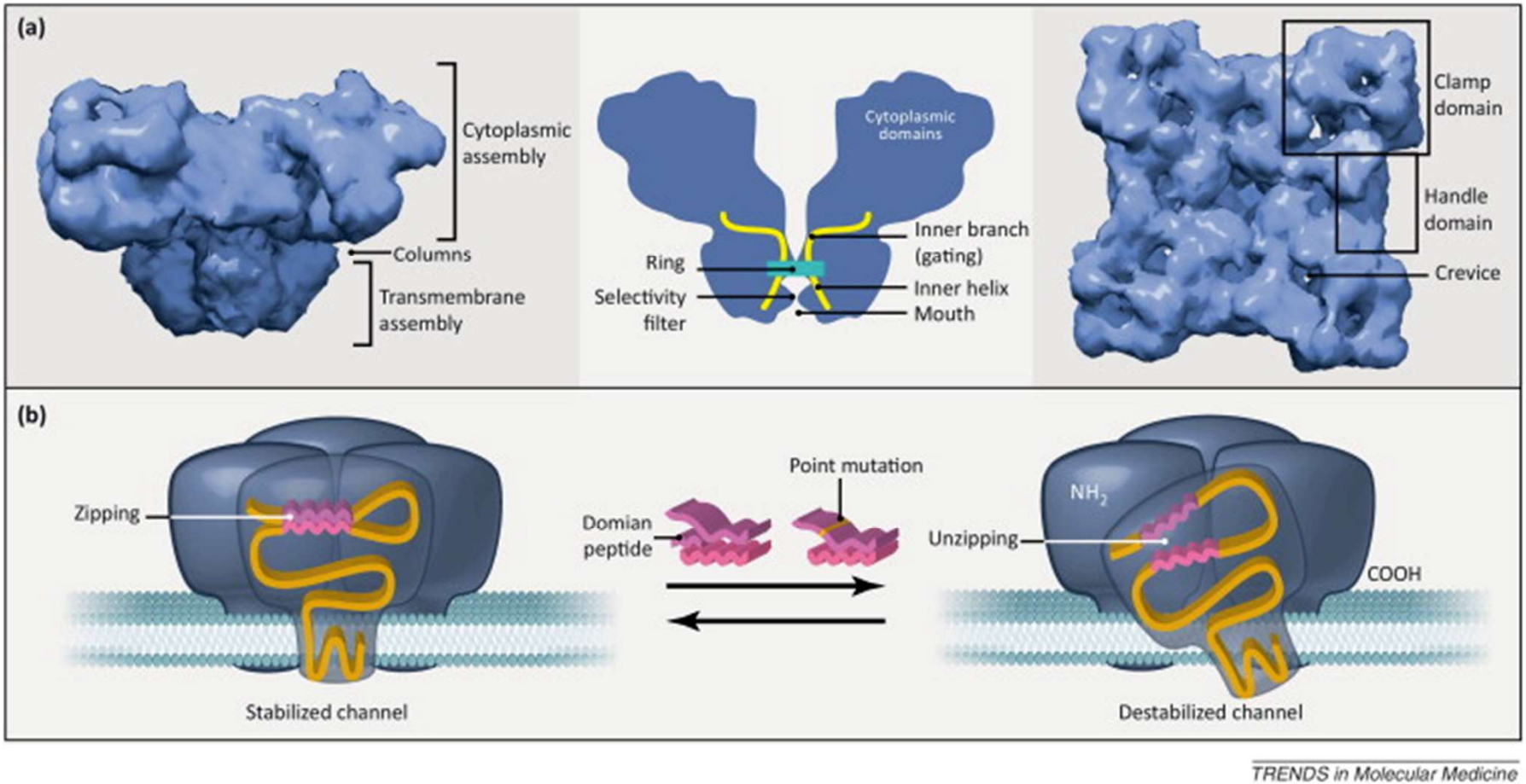
Ryanodine Receptor 1 (RYR1)

- AKA: sarcoplasmic reticulum calcium release channel
- 19q13.1
- 106 exon gene encoding skeletal muscle ryanodine receptor
  - Intracellular calcium-release channel essential for excitation-contraction coupling
- Mutations leading to neuromuscular disease
  - Dysregulation of calcium homeostasis

Ryanodine Receptor 1 (RYR1)

- Genetic Testing
  - Single Gene
  - Congenital Myopathy Panel
  - Neuromuscular Panel
  - Whole Exome Sequencing
- Malignant Hyperthermia Risk

RYR1


(a)
Cytoplasmic assembly
Columns
Transmembrane assembly
Cytoplasmic domains
Ring
Selectivity filter
Inner branch (gating)
Inner helix
Mouth
Clamp domain
Handle domain
Crevice
(b)
Zipping
Stabilized channel
Domian peptide
Point mutation
NH2
Unzipping
COOH
Destabilized channel
TRENDS in Molecular Medicine

Background

- Pathogenic mutations in the ryanodine receptor type 1 (RYR1) gene have been well documented as a cause of congenital myopathies. The clinical presentation, genetic changes, and histopathology among this group have been demonstrated to be very heterogenic.

Objective

- To review a group of patients with congenital RYR1-related myopathies in order to aid in future diagnosis.

Methods

- A group of patients in the Neuromuscular Clinic at a tertiary pediatric center with documented RYR1 variants were selected, and their charts were retrospectively reviewed.
- History, physical examinations, laboratory studies, and other diagnostic investigations were accessed.

Results

- 12 patients with RYR1 variants, which were felt likely to be pathogenic or were documented as causative for their disease
- Female = 7, Male = 5 were male
- Age range at the time of review: 3-22 years
- 9 of 10 with permanent weakness had symptoms at birth
  - Remaining patient presented with symptoms at 2 years
- Two other patients had induced weakness secondary to malignant hyperthermia due to anesthesia
  - Both presented at 7 years of age

PATIENT NUMBER	CURRENT AGE (years)	AGE AT ONSET	GENDER F = Female M = Male
1	3	Birth	F
2	6	Birth	F
3	6	Birth	M
4	7	Birth	M
5	7	Birth	M
6	10	7 years	F
7	11	Birth	M
8	11	7 years	F
9	14	Birth	F
10	15	2 years	F
11	15	Birth	F
12	22	Birth	M

Results

- Notable clinical findings in those with permanent weakness
  - Respiratory weakness, ptosis, and ophthalmoparesis
- 7 novel variants were seen in 5 of the total patients
- Biopsies were performed in 9 of the 10 patients with the congenital myopathy clinical presentation
  - 8 showed definite myopathic changes, including 3 with central nuclei and 2 with central cores.

PATIENT NUMBER	CARDIAC DYSFUNCTION	RESPIRATORY WEAKNESS	PTOSIS	OPHTHALMOPARESIS	OTHER FACIAL WEAKNESS	EXTREMITY WEAKNESS
1	Unknown, did not follow-up	Yes	Yes	Yes	Yes	Yes
2	No	Yes	Yes	Yes	Yes	Yes
3	No	No	No	No	Yes	Yes
4	No	Yes	No	No	No	Yes
5	Yes, but secondary to other genetic congenital heart defect	No	Yes	No	Yes	Yes
6	No	No	No	No	No	No
7	No, per parent's report, not seen at CMC	No	Yes, not at rest but fatigable	No	Yes	Yes
8	No	No	No	No	No	No
9	No (evaluated at outside facility)	Yes	No	No	Yes	Yes
10	No	No	No	No	No	Yes
11	No	Yes	Yes	No	Yes	Yes
12	No	No	Yes	Yes	Yes	Yes

PATIENT NUMBER	CK LEVEL	EMG/NCS	PATHOLOGY	GENETIC CHANGE
1	226 4/18/14	Non-irritative myopathic process affecting upper and lower extremities	Neonatal myopathyic process associated with central nuclei and marked myofiber atrophy	***1. exon 33, c.4816C>A heterozygous, p.Arg1606Ser ***2. exon 91, c.12978delC heterozygous, p.Glu4327Argfs*14 (Both variants undocumented as of test report 6/17/14.) *** undocumented variant
2	84 5/25/17	Non-irritative myopathic process affecting upper and lower extremities	Congenital myopathy with centrally-located nuclei and focal myofibrillar disarray	1. exon 41, c.6721C>T heterozygous, p.Arg2241* ***2. junction of exon 91 & intron 91, c.13437+1G>A heterozygous, (abnormal exon splicing)
3	107 4/6/11	Non-irritative myopathic process affecting upper and lower extremities	Moderate fiber size variability, type I myofiber predominance, and mild chronic myopathic changes	1. c.2122G>A heterozygous, p.D708N 2. c.14818G>A heterozygous, p.A4940T
4	834-1321 3/25-27/17	Not done	Non-specific morphologic and ultrastructural changes: Morphologic features include moderate fiber size variability, several esterase-positive denervated fibers, central sarcoplasmic pallor in several fibers on oxidative stains, and several fibers with blushy acid phosphatase reactivity; Ultrastructural exam with several atrophic fibers with slightly expanded Z-lines in continuity with usual sarcomeric architecture; Central pallor and Z-line expansion may represent early core and nemaline rod expansion respectively	exon 47, c.7523G>A heterozygous, p.Arg2508His
5	83 11/26/12	Diffuse myopathy affecting upper and lower extremities	Not done	1. exon 33, c.4711A>G heterozygous, p.Ile1571Val (paternal) 2. exon 67, c.10097G>A heterozygous, p.Arg3366His (paternal) 3. exon 86, c.11798A>G heterozygous, p.Tyr3933Cys (paternal) 4. exon 102, c.14731G>A heterozygous, p.Glu4911Lys (maternal)
6	247-567 5/11-13/15 *during admission	Not done	Not done	***1. c.7755delC heterozygous, p.Val2586Cysfs*160 (expected to be pathogenic) ***2. c.6726C>G heterozygous, p.Ile224Met (VUS)

PATIENT NUMBER	CK LEVEL	EMG/NCS	PATHOLOGY	GENETIC CHANGE
7	?, reportedly normal	Not done	Type I myofiber predominance with chronic myopathic alterations; rare denervated fibers--> nonspecific but likely congenital myopathy	1. exon 33, c.4711A>G heterozygous, p.Ile1571Val (paternal) 2. exon 67, c.10097G>A heterozygous, p.Arg3366His (paternal) 3. exon 86, c.11798A>G heterozygous, p.Tyr3933Cys (paternal) 4. exon 102, c.14731G>A heterozygous, p.Glu4911Lys (maternal)
8	4426-98,570 3/8-12/13 *during admission	Not done	Not done	exon 28, c.4071C>T homozygous, p.Pro1357Pro (VUS)
9	?	Not done	Central cores (performed at outside facility; could not find report)	exon 101, c.14581C>T heterozygous, p.Arg4861Cys
10	72 2/6/15	Normal	Slight myopathic changes with early multi-minicore formation	exon 29, c.4178A>G heterozygous, p.Lys1393Arg
11	147 6/27/17	Normal	Myopathy with central core formation	1. exon 45, c.7300G>A heterozygous, p.Gly2434Arg ***2. exon 101, c.14623A>G heterozygous, p.Met4875Val
12	44 2002 or earlier	Not done	Centronuclear myopathy	***exon 91, c.13324G>T heterozygous, p.Asp4442Tyr (This VUS had not been reported as of test report 1/27/14 but in region where other variants have been documented as pathogenic.)

Limitations

- Patients must be manually placed on the specific disease/disorder list in the EMR
- Additional patients with RYR1 variants who also have variants in other genes which can cause congenital myopathies, namely titin (TTN)
- Lack of centralized genomic database to know if undocumented variants are truly novel

Conclusions

- This study adds to the body of growing information regarding congenital RYR1-related myopathies.
- In those with ophthalmoparesis on exam, all had central nuclei documented on muscle biopsy.
- Genetic heterogeneity was seen in keeping with previously reported series, including 7 undocumented variants.

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