RYR1 Myopathies

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RYR1 Family Conference
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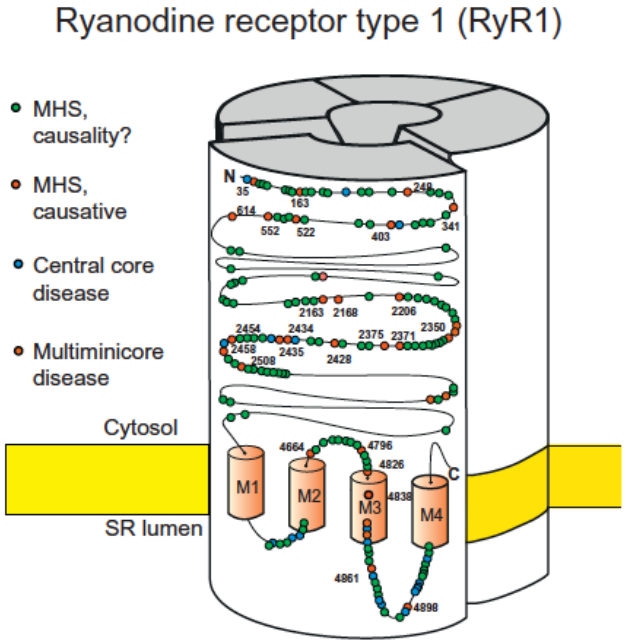
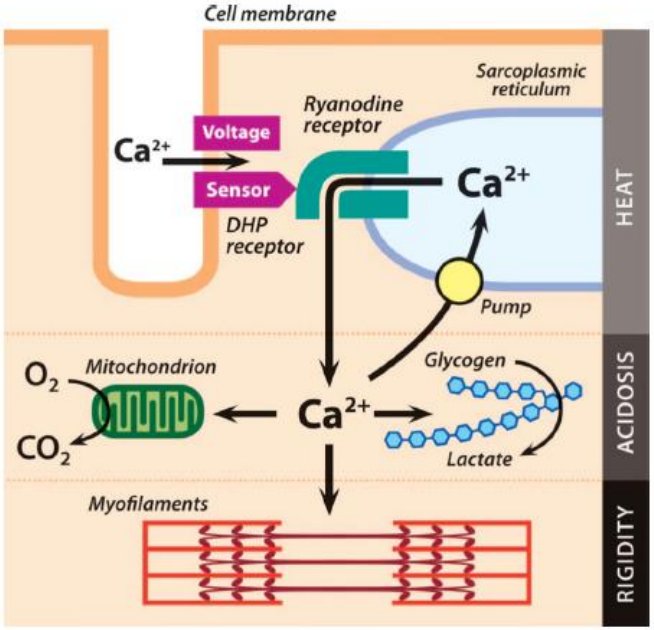
What are RYR1 related myopathies?

- RYR1 = ryanodine receptor type I
  - Large gene on chromosome 19
  - Encodes the RyR1 protein
  - Intracellular (inside the cell) calcium channel
  - Required for converting nerve impulses into muscle contractions (excitation contraction coupling)
  - Reviewed by Dr. Bob Dirisksen at 10:30am today





What are RYR1 myopathies?

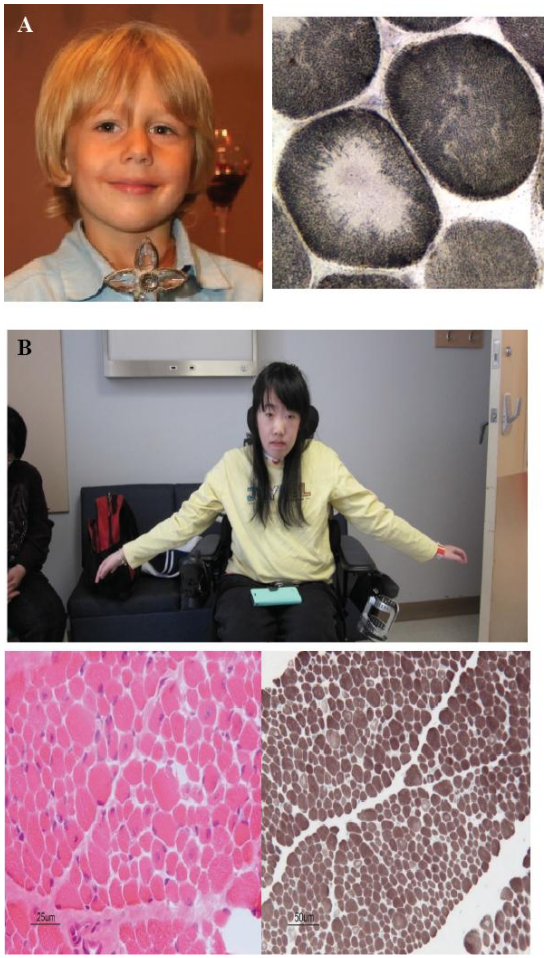
- Myopathies are any conditions that result in muscle impairment as a result of muscle dysfunction
  - "static"
    - Weakness, motor delay, difficulties walking, scoliosis, facial weakness, ophthalmoparesis, inability to climb stairs
  - "dynamic"
    - Malignant hyperthermia, exercise induced rhabdomyolysis, myalgias, muscle cramps, fatigue
  - Myopathies will be reviewed further by Dr. Carsten Bonnemann at 10:00am today

What is a mutation?

- How do we define mutation?
  - A change in a gene that alters the function of that gene product and causes symptoms
- Mutations can be missense, nonsense, splice site changing, intronic, deletions, duplications
  - These different types of changes may have different consequences on how the RYR1 gene is processed and expression, and what the resulting RyR1 protein looks like
- RYR1 Mutations can be inherited as dominant, recessive, or be “new” (de novo) in an individual
- Livija Medne will review mutations and other genetic concepts at 9:00am today

Who has an RYR1 myopathy?

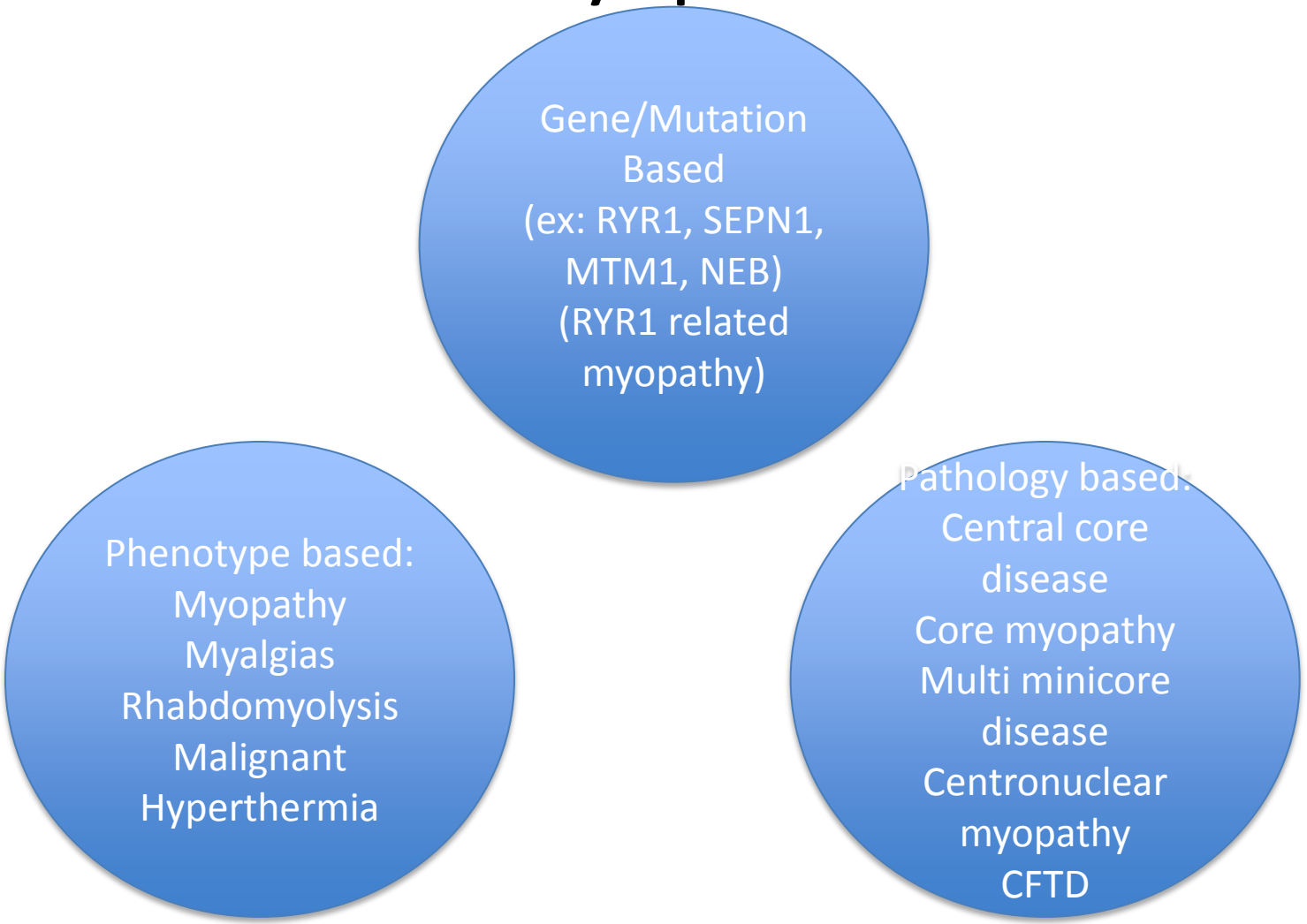
- Anyone with:
  - (a) myopathy
  - (b) mutation in *RYR1*



A brief history of RYR1 mutations and human muscle disease

- 1991: Mutation found in RYR1 in porcine MH
  - (Fujii et al., Science)
- 1991: Mutation found in RYR1 in Canadian individuals with MHS
  - (Gillard et al., Genomics)
- 1993: First RYR1 gene mutation discovered in human central core disease (CCD)
  - Zhang et al. and Quane et al., Nature Genetics
- 2002: First recessive RYR1 mutation patient reported (mulit-minicore myopathy)
  - Jungbluth et al.,Neurology and Ferreiro et al., Annals of Neurology
- 2005: Recessive RYR1 mutations in small cohort of patients with minicore myopathy and ophthalmoplegia
  - Jungbluth et al., Neurology
- 2010: RYR1 mutations associated with centronuclear myopathy
  - Wilmshurst et al., Annals of Neurology
- 2010- present: RYR1 mutations found in CFTD, core-rod myopathy, and nemaline myopathy
- 2010- present: RYR1 mutations found in “non-classical” myopathy settings (exertional rhabdomyolysis, isolated ophthalmoparesis, etc)
- 2013: RYR1 mutations associated with dystrophic pathology
  - Bharucha-Goebel et al., Neurology

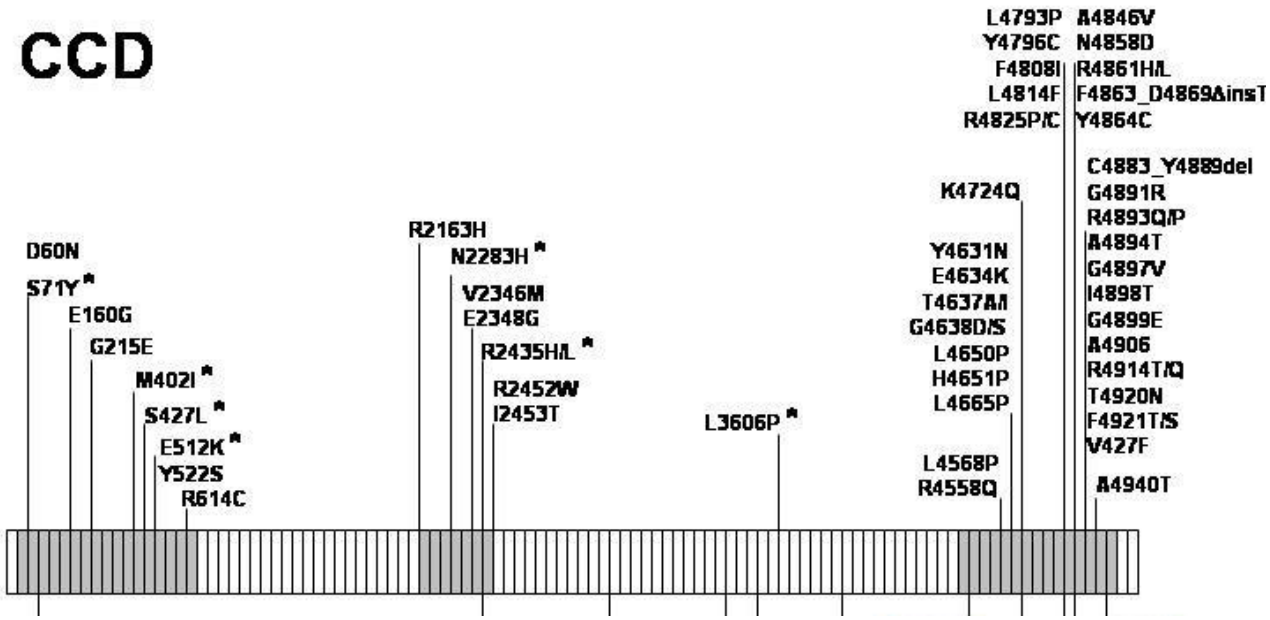
How do we describe and/or define RYR1 myopathies?



Gene/mutation based definition: A few key points to consider

- There are many many different mutations in RYR1
  - Different mutations can have different clinical consequences
  - Some individuals may have more than one mutation
  - Individuals with the same mutation may have different clinical presentations
  - There are still “undiscovered” mutations in RYR1, including those outside of the coding sequence

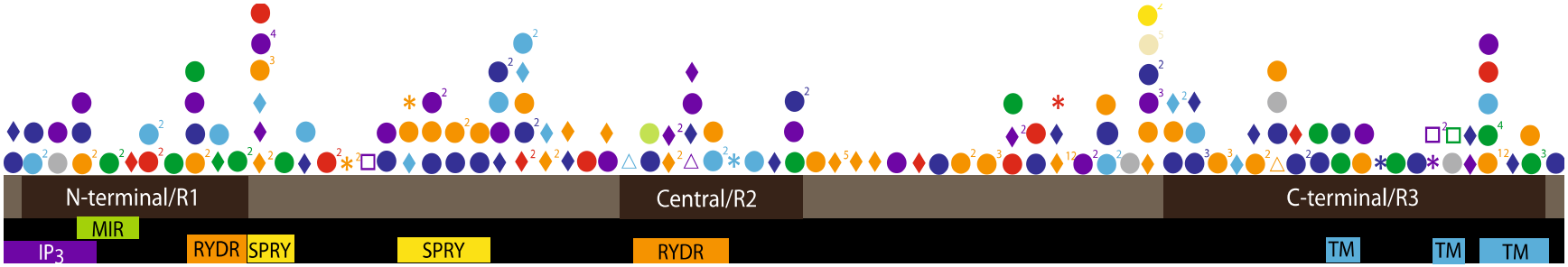
RYR1 mutations in central core disease



Jungbluth 2007

Mutations generally cluster in 3 “hot spots”

Recessive mutations are spread throughout the gene…



Domain KEY

N-terminal/Region I: Exons 2-17
Central/Region II: Exons 39-46
C-terminal/Region III: Exons 85-103

●Missense
♦Nonsense
□Deletion
■Insertion
△Duplication
*Splice Site

MmD
CCD
Core Myopathy
CNM/CNM-like
CFTD
RRM
KDS
Congenital Myopathy/MH
AR MD
Core/Rod Disease

Does my specific mutation matter?

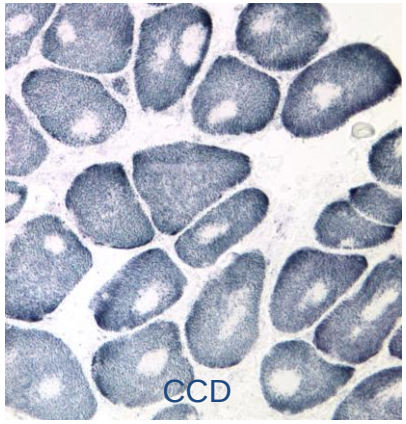
- Initial evidence suggests that having two or more mutations, with one reducing the ability of the RyR1 protein to be made, is associated with a more severe phenotype than missense changes alone
- Some mutations may be associated with specific phenotypes
  - Evidence for this with malignant hyperthermia
  - Do certain mutations predispose to other symptoms, like rhabdomyolysis, or other clinical features, like ophthalmoparesis?
  - This is a subject of ongoing research

Pathologic heterogeneity

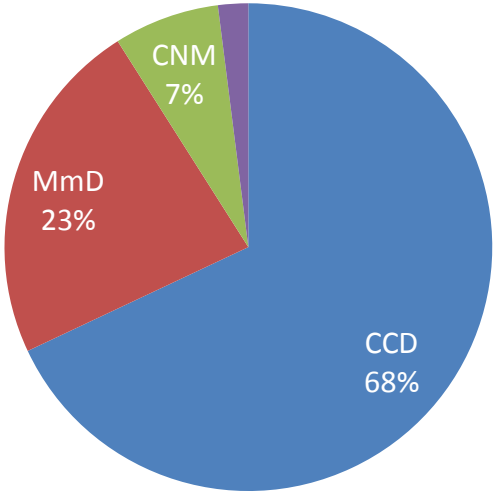
- RYR1 mutations associated with a range of different muscle biopsy findings, including:
  - Central core disease
  - Minicore myopathy
  - Centronuclear myopathy
  - Congenital fiber type disproportion
  - Core rod myopathy (or rod myopathy only)
  - Non specific myopathy
  - Muscular dystrophy
- There is some association between type and location of mutation and histopathology
- The association between histopathology and clinical presentation is not clear
- Note: mutations in other genes can cause the same histopathologic findings
  - So someone with central core disease may not have an RYR1 related myopathy
- Muscle biopsy patterns and their relation to RYR1 myopathy will be reviewed by Kim Amburgey at 9:30

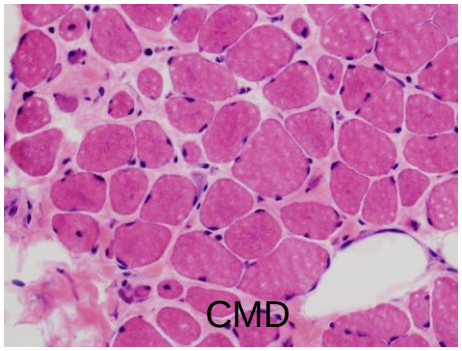
The changing picture of RYR1 mutations

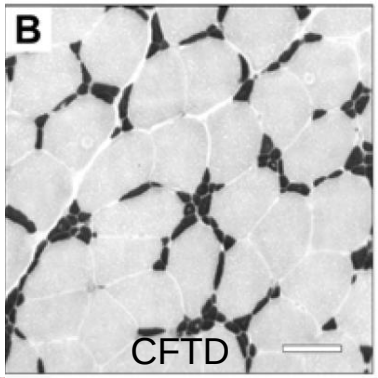
Pre-2003

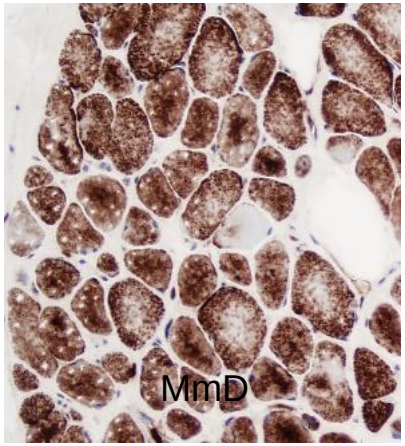


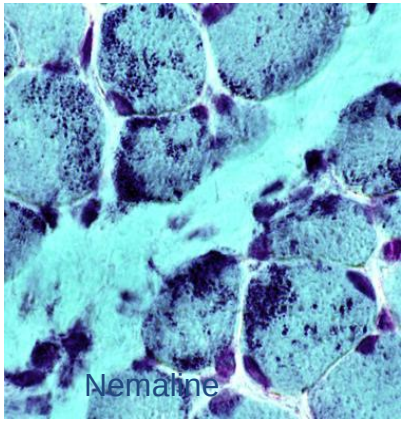
Circa 2013

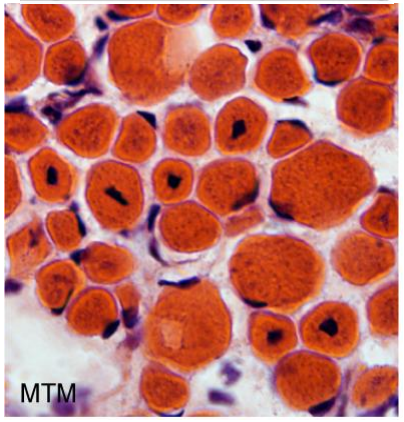




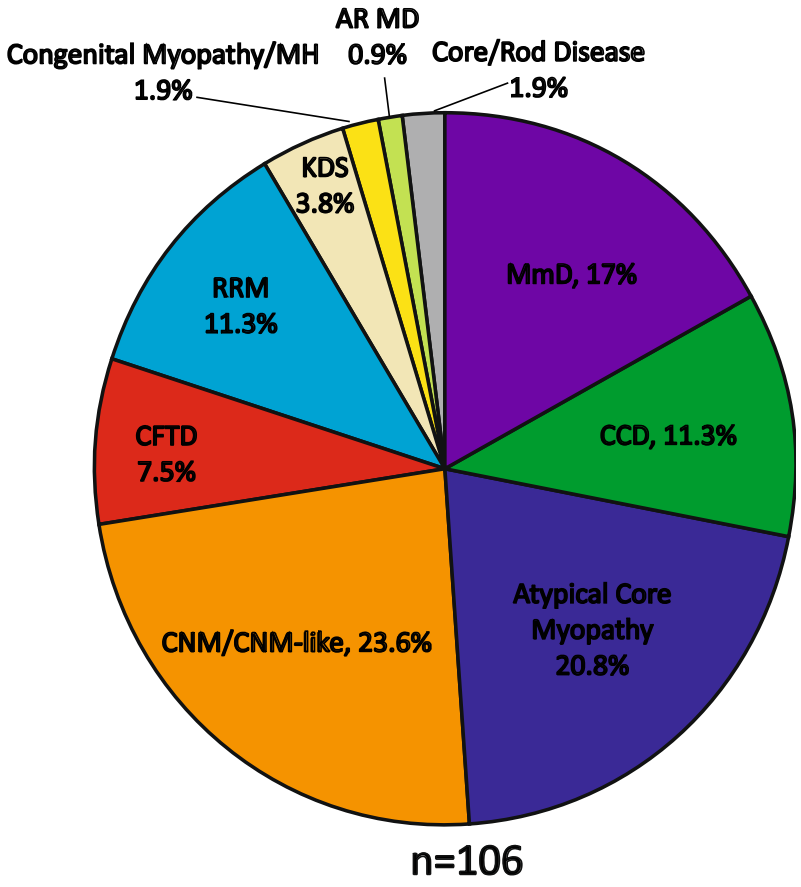








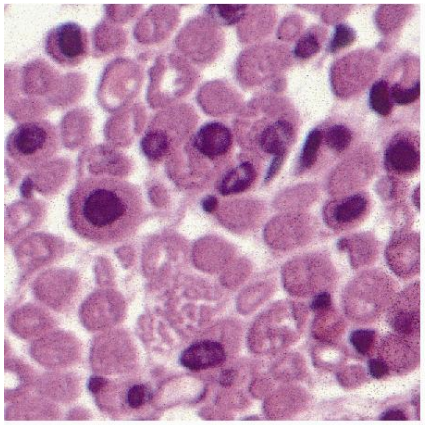
Non-core myopathies comprise a larger than expected percentage of all recessive RYR1 related myopathies



I have an RYR1 mutation, does it matter what my biopsy looks like?

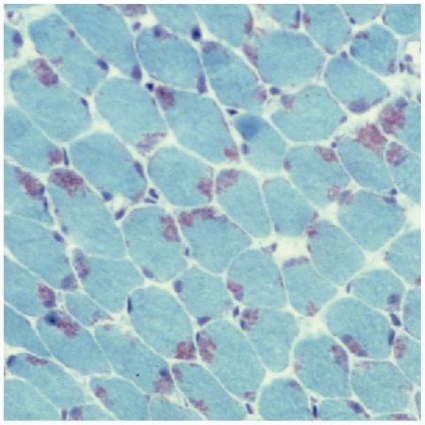
- In general, muscle biopsies are used for diagnosis and not for prognosis or management
- The reason(s) why patients with RYR1 mutations have different muscle biopsy findings are poorly understood
- At present, the relationship between biopsy pattern and clinical severity and/or prognosis is not clear
- The significance of the different changes is also not well understood?
  - In other words, does it matter if I have CCD or minicore myopathy or centronuclear myopathy?

Genetic heterogeneity and CM histopathologic subtypes



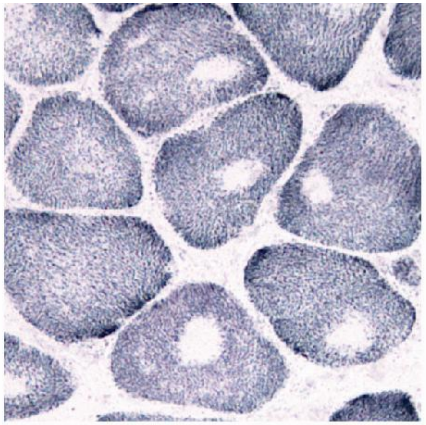
Centronuclear Myopathy

MTM1, DNM2, RYR1
SPEG, BIN1, SPEG



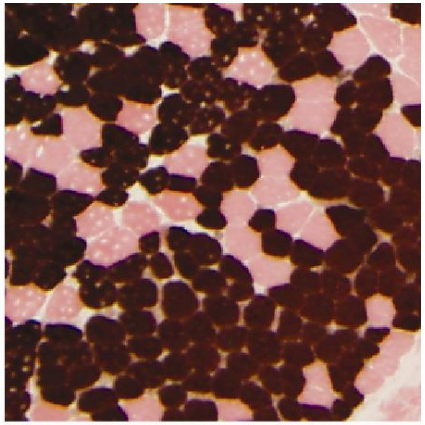
Nemaline Myopathy

ACTA1, NEB, TPM2, CFL2
TPM3, TNNT1, LMOD3,
KLHL40, KLHL41, KBTBD13



Core Myopathy

CCD: RYR1, MYH7
MmD/other: RYR1, SEPN1,
ACTA1, TTN, MYH7
CCDC78, MEGF10



Congenital Fiber Type Disproportion

ACTA1, TPM3, RYR1
SEPN1, TPM2

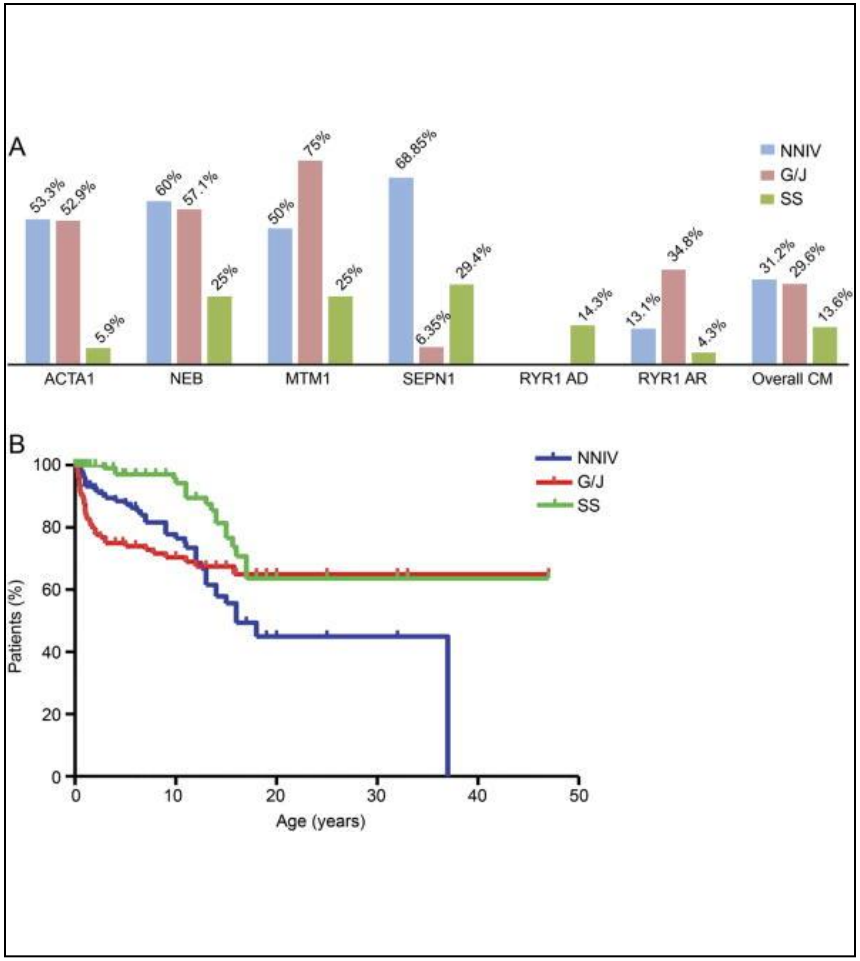
I have central core disease, doesn't that mean I have RYR1 myopathy?

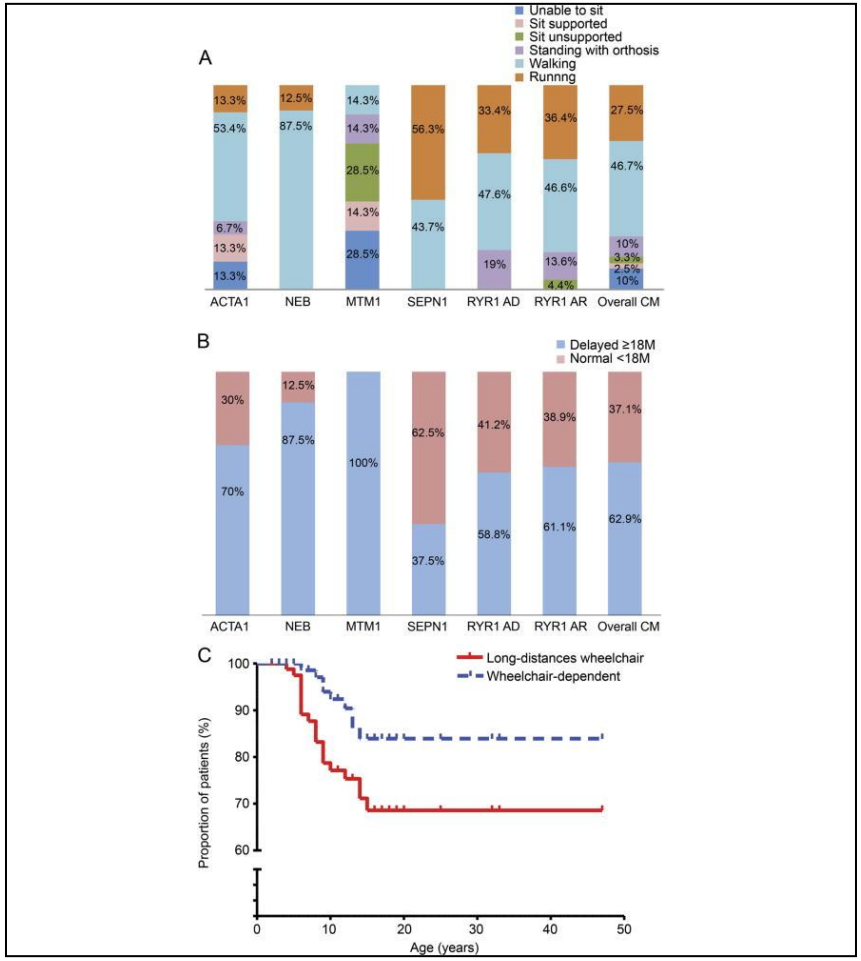
- 90% of all CCD caused by mutations in RYR1
- If you have CCD but have not had genetic testing, you likely have an RYR1 mutation
- However, there are other genetic causes of CCD
  - MYH7, TTN, etc
- It is therefore important to have genetic testing even if your muscle biopsy is highly suggestive of RYR1 mutation

Clinical heterogeneity

- There are many many different clinical presentations associated with RYR1 mutations
- These include:
  - Weakness and disability from birth (i.e. congenital muscle disease)
    - This can range in severity
  - Weakness starting in childhood
  - Weakness presenting in adulthood
  - Dynamic presentations
    - Exertional rhabdomyolysis
    - Exercise related myalgias
    - Heat intolerance and heat stroke
    - Malignant hyperthermia
    - Patients can have both static and dynamic symptoms

Having recessive RYR1 myopathy is associated with a increased clinical severity





Congenital myopathies: Natural history of a large pediatric cohort.
Colombo, Irene; Scoto, Mariacristina; Manzur, Adnan; Robb, Stephanie; Maggi, Lorenzo; Gowda, Vasantha; Cullup, Thomas; Yau, Michael; Phadke, Rahul; Sewry, Caroline; PhD, FRCPath; Jungbluth, Heinz; MD, PhD; Muntoni, Francesco
Neurology. 84(1):28-35, January 6, 2015. DOI: 10.1212/WNL.0000000000001110

Should I get genetic testing?

- Many reasons to pursue genetic testing and an confirmed genetic diagnosis
  - End of the diagnostic odyssey, aids with prognosis and care management, helps with family planning
  - May influence availability to future gene specific or mutation based therapies
- Remember, by definition, to have an RYR1 myopathy you need to have an RYR1 mutation

My doctors have looked every way possible, but not found a mutation. What should I do?

- Consult (can be virtually) with a congenital myopathy diagnostic expert
  - This is to ensure that all avenues have been pursued
- Consider participation in research studies looking into causes of “unsolved” muscle diseases (ex: Alan Beggs, Carsten Bonnemann, and myself)

I have a RYR1 variant of unknown significance, what does that mean???

- Variants of unknown significance are changes in the DNA sequence where the consequence of the change is not well understood
- Variants of unknown significance may, in fact, be the mutation that causes diseases
- Variants of unknown significance may instead have little or no association to the muscle condition
- Additional methods are needed to evaluate such variants to prove that they are either true mutations or else benign (ie non disease associated)

So I (or my family member) has an RYR1 myopathy, what can I/we do?

Standards of care for congenital myopathies

Special Article

Journal of Child Neurology
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Consensus Statement on Standard of Care for Congenital Myopathies

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A few clinical points

- Scoliosis and skeletal complications (joint contractures, hip dysplasia) are common
- Heart involvement is rare
- Need to look out for breathing problems, and these can manifest only at night
  - Noctural hypoventilation and sleep apnea are relatively common, particularly in recessive RYR1
  - Sleep studies are important for diagnosing these problems
  - Respiratory issues in RYR1 will be reviewed tomorrow by Dr. Hank Mayer
- Pain and fatigue are often under-recognized aspects of the condition

I have an RYR1 mutation, am I definitely at risk for malignant hyperthermia?

- It is estimated that 30% of patients with *RYR1* myopathy are at risk for MH
  - This has not been rigorously determined
  - Conversely >70% of individuals who have had an MH reaction or are MHS have an *RYR1* mutation
- Some *RYR1* mutations are proven to be associated with MH
- No mutations have been definitively proven to NOT be associated with MH
- Some patients with primary MH or MH susceptibility also can have other muscle symptoms
- Note: MH and related dynamic symptoms will be discussed further tomorrow by Dr. Jerry Parness and Dr. Ron Litman

What about treatment considerations?

- "Secondary" management strategies are very important
  - Physiotherapy, good pulmonary care, orthopedic intervention when necessary
- No approved drug therapies at this time
- Dantrolene is the standard of care for MH reactions
  - It may also help with myalgias and other dynamic symptoms in individuals with certain RYR1 mutations
  - However, it may worsen muscle strength in individuals with certain other RYR1 mutations
- Oral salbutamol has been looked at in a pilot study of core myopathy
  - Improved muscle strength in a small group of patients
  - Awaits more widespread testing and study
- Mestinon has been tried in RYR1 myopathy patients with features of myasthenia
  - How applicable this therapy may be to other RYR1 patients has not been tested

What about research to identify develop new therapies?

- New treatment approaches are being actively developed
  - Dr. Alan Beggs will review research strategies and RYR1 at 11:30am
- N-acetylcysteine is the “furthest alone”, as it is being tested in clinical trial
  - Dr Katy Meilleur will talk about NAC at 1:00 today
- Other approaches, such as RyCal treatment, are showing promising pre-clinical data
  - Dr Andy Marks will talk about RyCals at 11:00am

Thanks!