2016 MDF
ANNUAL CONFERENCE

September 15-17 2016, Washington DC

MYOTONIC DYSTROPHY FOUNDATION

Care and a Cure

DM 101: GETTING A HANDLE ON THE BASICS

Jacinda Sampson MD PhD

Myotonic dystrophy: what's in a name?

- Myotonic = inability of muscles to relax after contracting them

MYOTONIC
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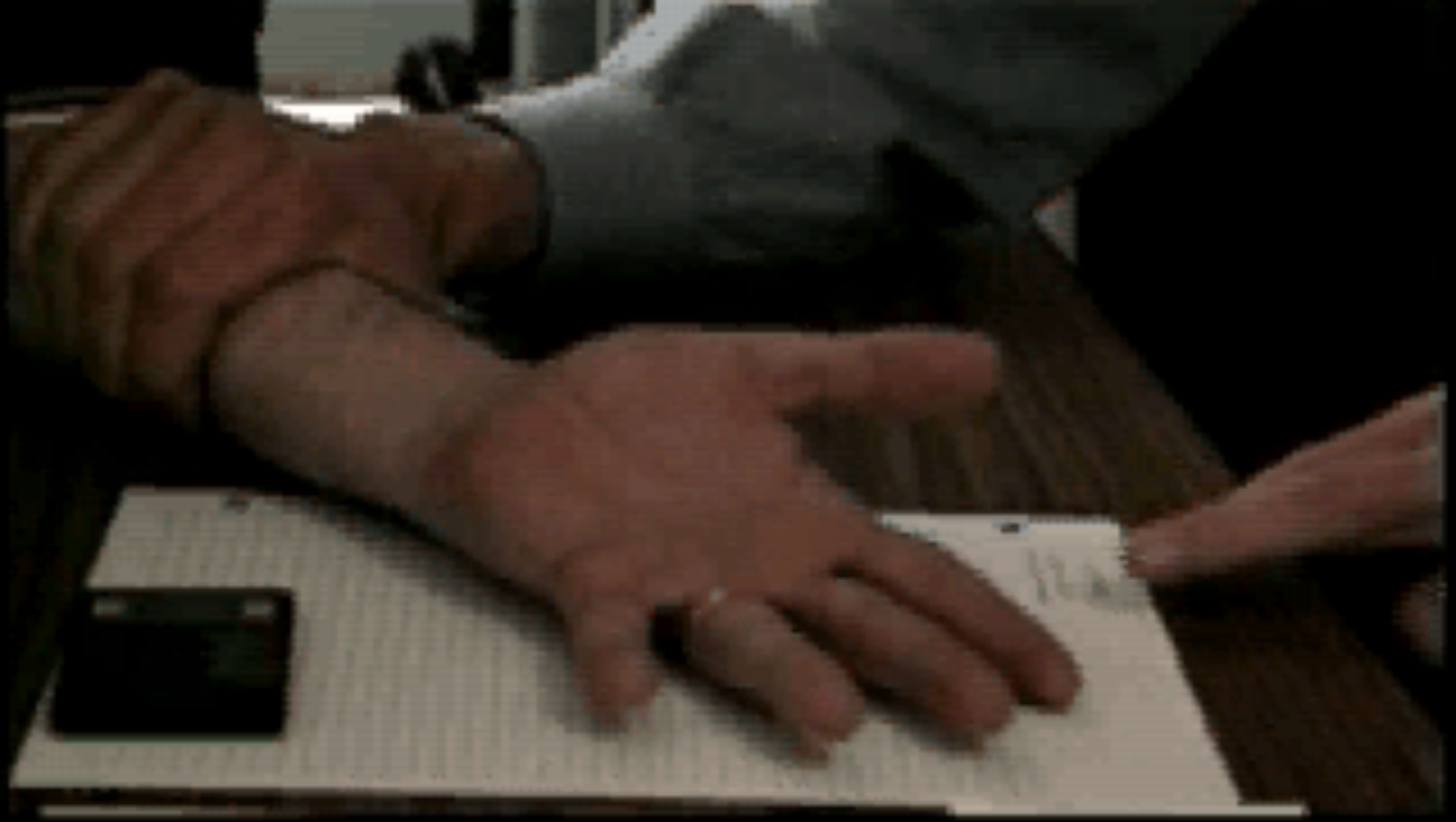
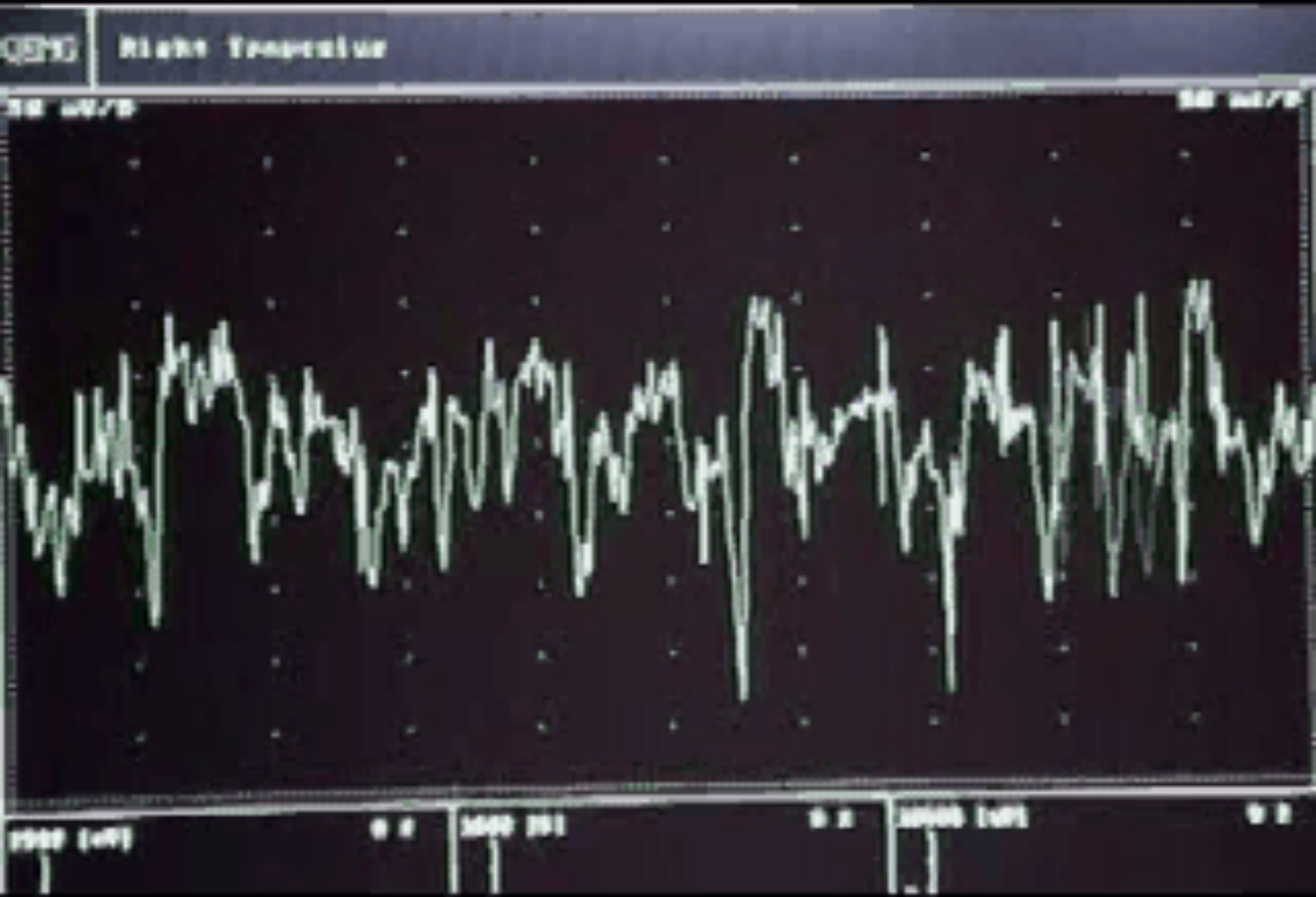
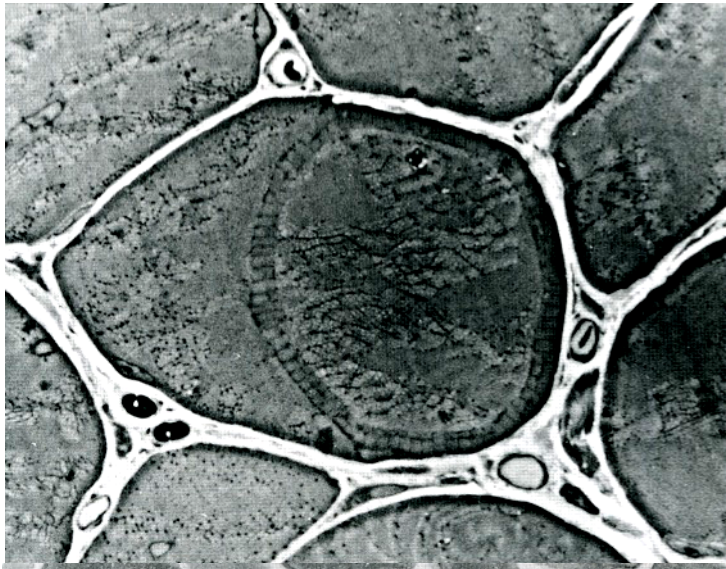
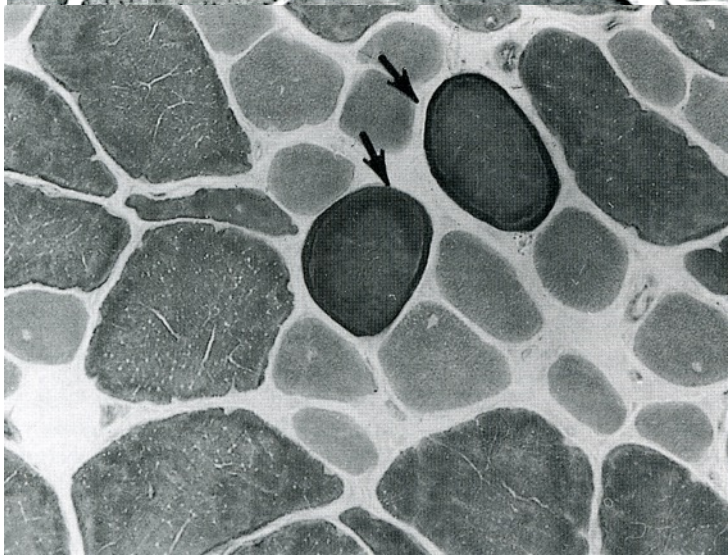



Right Temporal

Myotonic dystrophy: what's in a name?

- Dystrophy= degeneration of the muscle fibers
  - Causes progressive muscle weakness





Carpenter &Karpati, Pathology of Skeletal Muscle 2nd ed. 2001

How many types of DM are there?

- Myotonic dystrophy type 1 = Dystrophia myotonica type 1 (DM1)
  - Congenital myotonic dystrophy= DM1 with onset in infancy
- Myotonic dystrophy type 2 = Dystrophia myotonica type 2 (DM2) = Proximal Myotonic Myopathy (PROMM)
  - No identified infancy onset form

Are there other types of myotonia?

- Non-dystrophic myotonias include:
  - Myotonia congenita (not to be confused with congenital myotonic dystrophy) =
    - Becker myotonia
    - Thompson myotonia

Who discovered DM1?

- DM1
  - Described 1909 by Hans Steinert
  - Congenital form described 1970
  - Prevalence 13/100,000
  - Most common adult muscular dystrophy
- Male = female

Wagner &Steinberg, Hans Steinert. J Neurol. 2008: 1607

Who were the discoverers of DM2?

- Proximal Myotonic Myopathy (PROMM) was described by Richard Moxley
- DM2 may be as common as DM1, but underrecognized
- Mutation discovered only 15 yr ago!

Richard Moxley

John Day

Laura Ranum

Christina Liquori

What is a ___-nucleotide repeat?

- Poly = many
- tri = three
- Tetra = four
- Penta = five
- …etc

- In the DNA, these nucleotides get repeated over and over

What is a polynucleotide repeat?

- Non-coding repeat:
  - RNA regions that don't code ("spell") the amino acids that make the protein
  - DM1 and DM2 have non-coding repeats
- Coding repeat:
  - RNA regions do code ("spell") amino acids

Are there other polynucleotide repeat diseases?

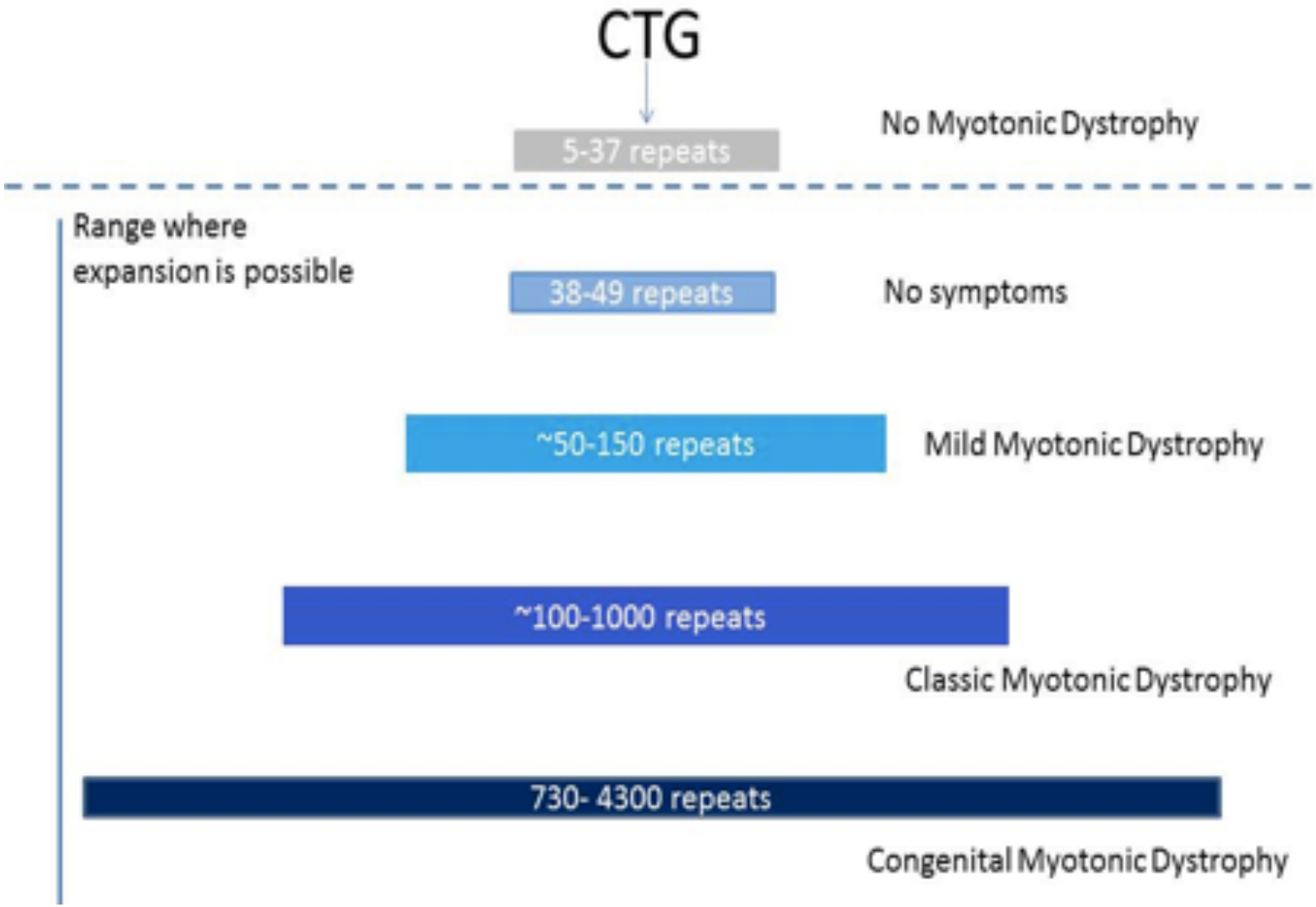
- Yes, there are several different disorders, including:
- Several Spinocerebellar ataxias
- Friedreich's ataxia
- Huntington's disease
- Certain forms of amyotrophic lateral sclerosis (Lou Gehrig's disease)
  - Caused by C9ORF72
  - Spinobulbar muscular atrophy (SBMA)
- Oculopharyngeal muscular dystrophy (OPMD)

What gene mutation causes DM1?

- DMPK (dystrophica myotonia protein kinase) gene
- Non-coding Trinucleotide repeat

…CTG CTG CTG CTG CTG…

Myotonic Dystrophy Type 1



What gene mutation cause DM2?

- Zinc finger 9 (ZNF9) gene = cellular retroviral nucleic acid binding protein 1 (CNBP)

- Non-coding Tetranucleotide repeat
- …CCTG CCTG CCTG CCTG …

Myotonic Dystrophy type 2

CCTG

11- 26 repeats — Normal repeat number

27-74 repeats — Borderline expansions

Range where expansion
Or contraction is possible

75-11,000 repeats

Myotonic dystrophy type 2

So to review:

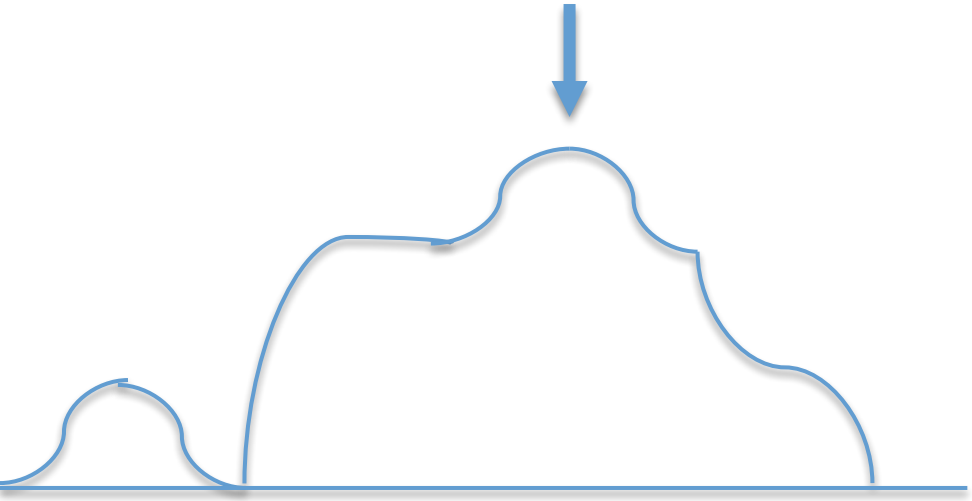
- Myotonic dystrophies-
  - Caused by polynucleotide repeat expansions
- Myotonic dystrophy type 1
  - CTG repeats in DMPK
- Myotonic dystrophy type 2
  - CCTG repeats in ZNF9 gene
- Non-dystrophic myotonias, or Myotonia congenita-
  - Caused by chloride or sodium channel mutations
- Thomson myotonia
- Becker myotonia

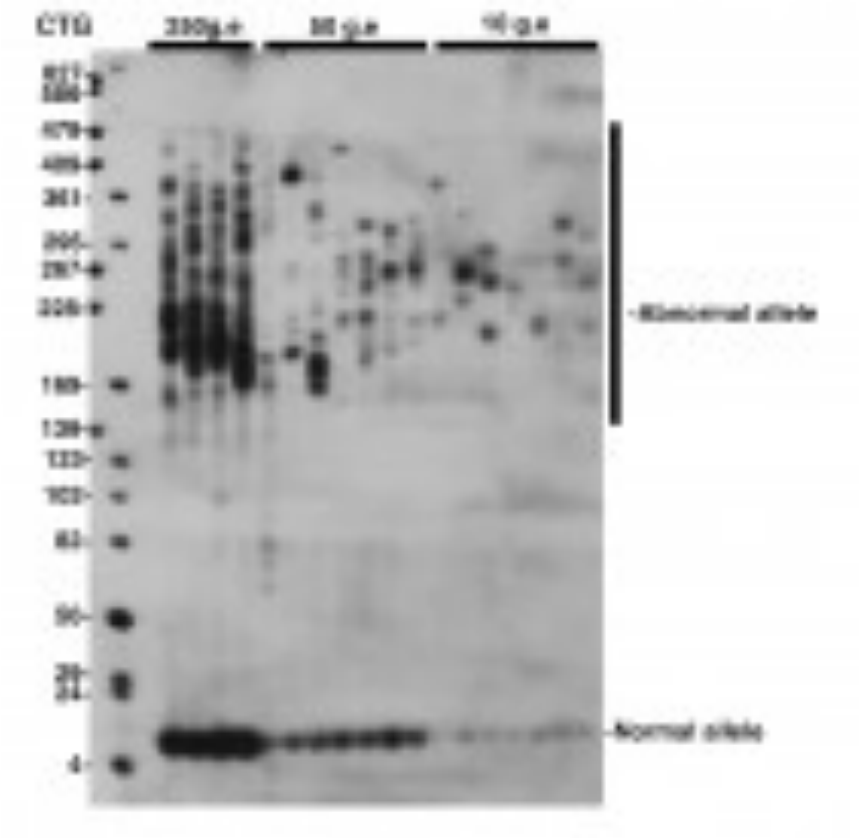
What is “mild” DM?

- used to describe the severity of symptoms
- Some doctors use it to describe DM1 with lower repeat size and later onset
- Some doctors use it to describe DM2 compared to DM1

- Either way, these people’s experience compared to unaffected people may not feel “mild”!

How do you test for DM?

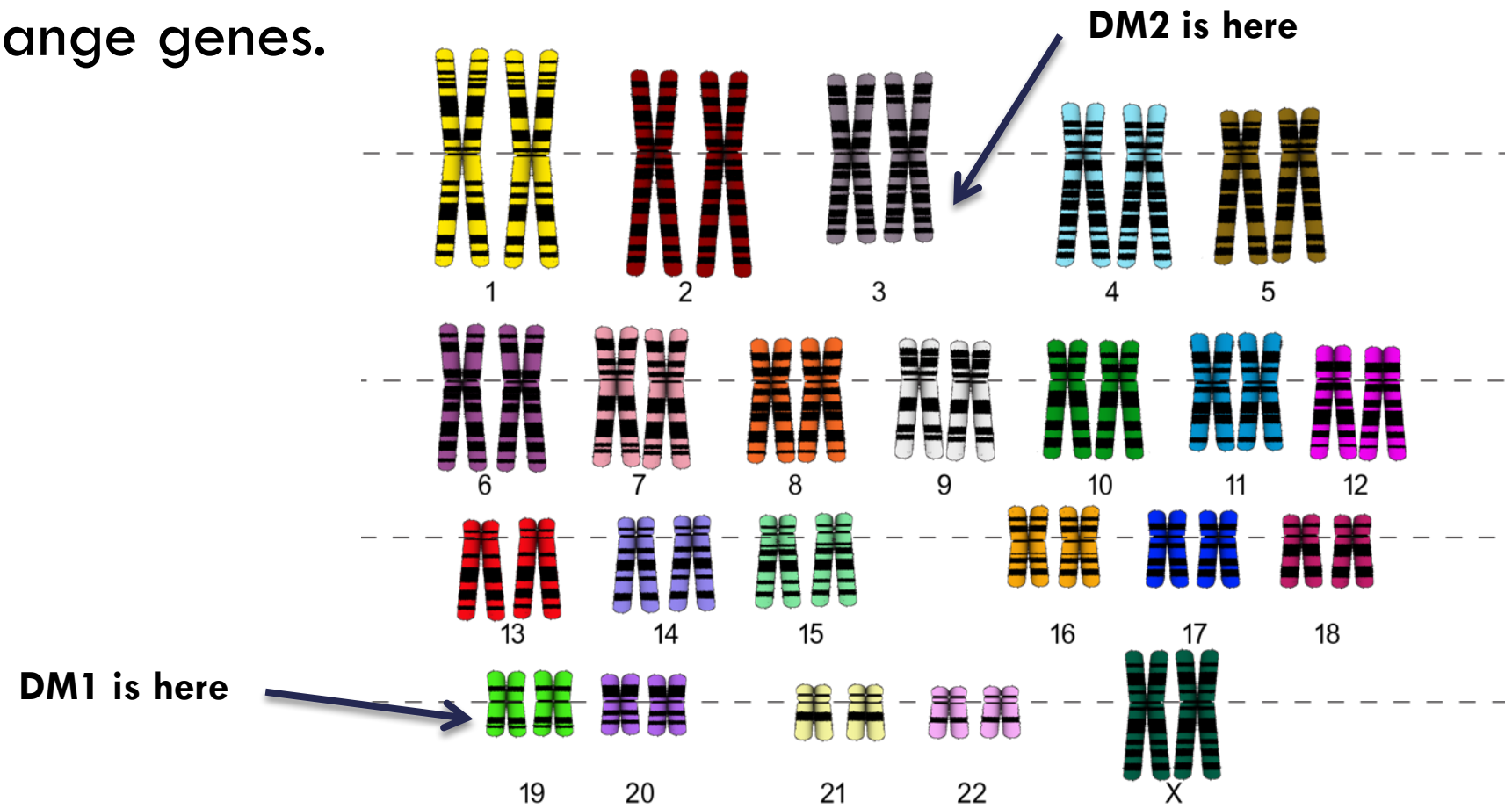




Tomé S. PLOS1. 2014 Mar 6

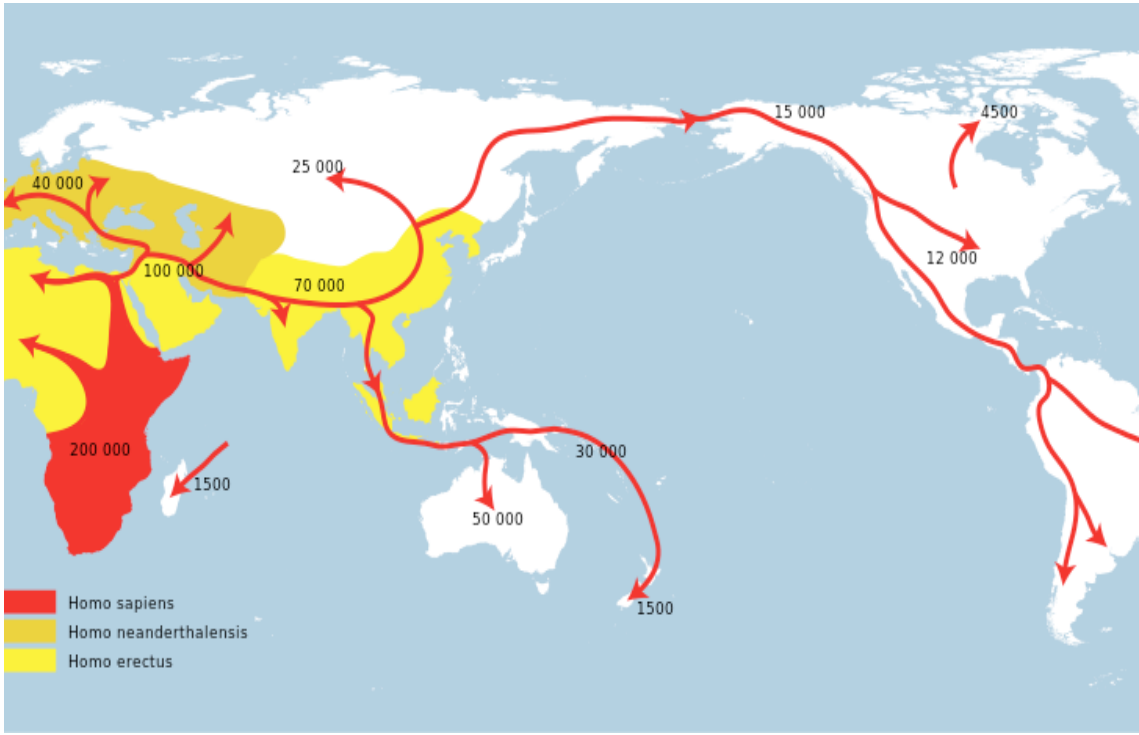
Can DM2 turn into DM1?

- Nope. The repeats can change length, but can't change genes.



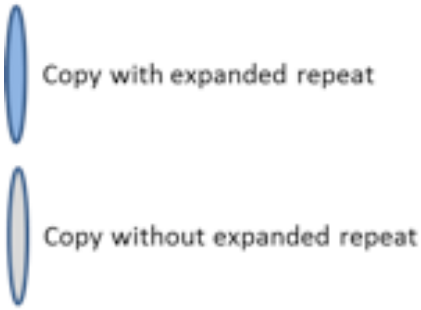
Where did DM come from?

- DM1
  - Out of Africa migration
- DM2
  - 1,000- 2,000 BC

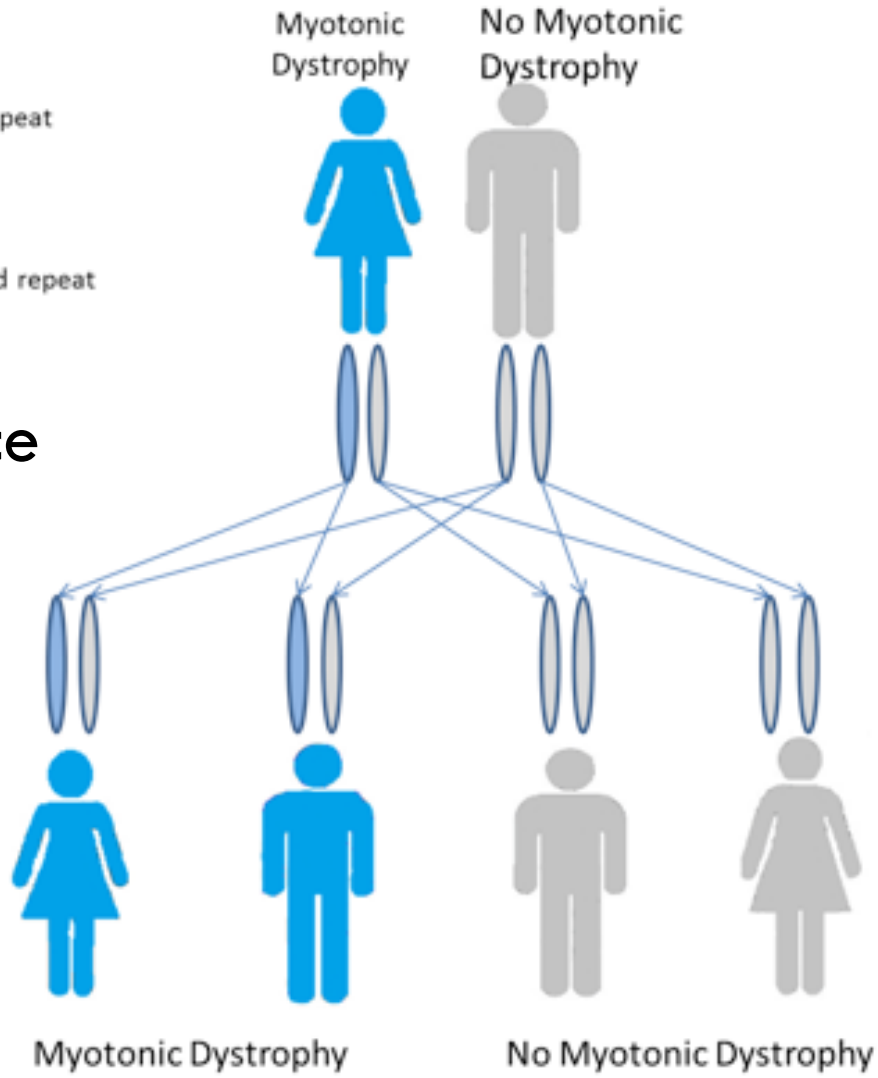


Wikipedia, early human migrations

How is it inherited?



Dominant inheritance



Dominant inheritance

- 50% chance of inheriting abnormal gene
- 50% chance at each pregnancy
- Does not alternate or "even out"

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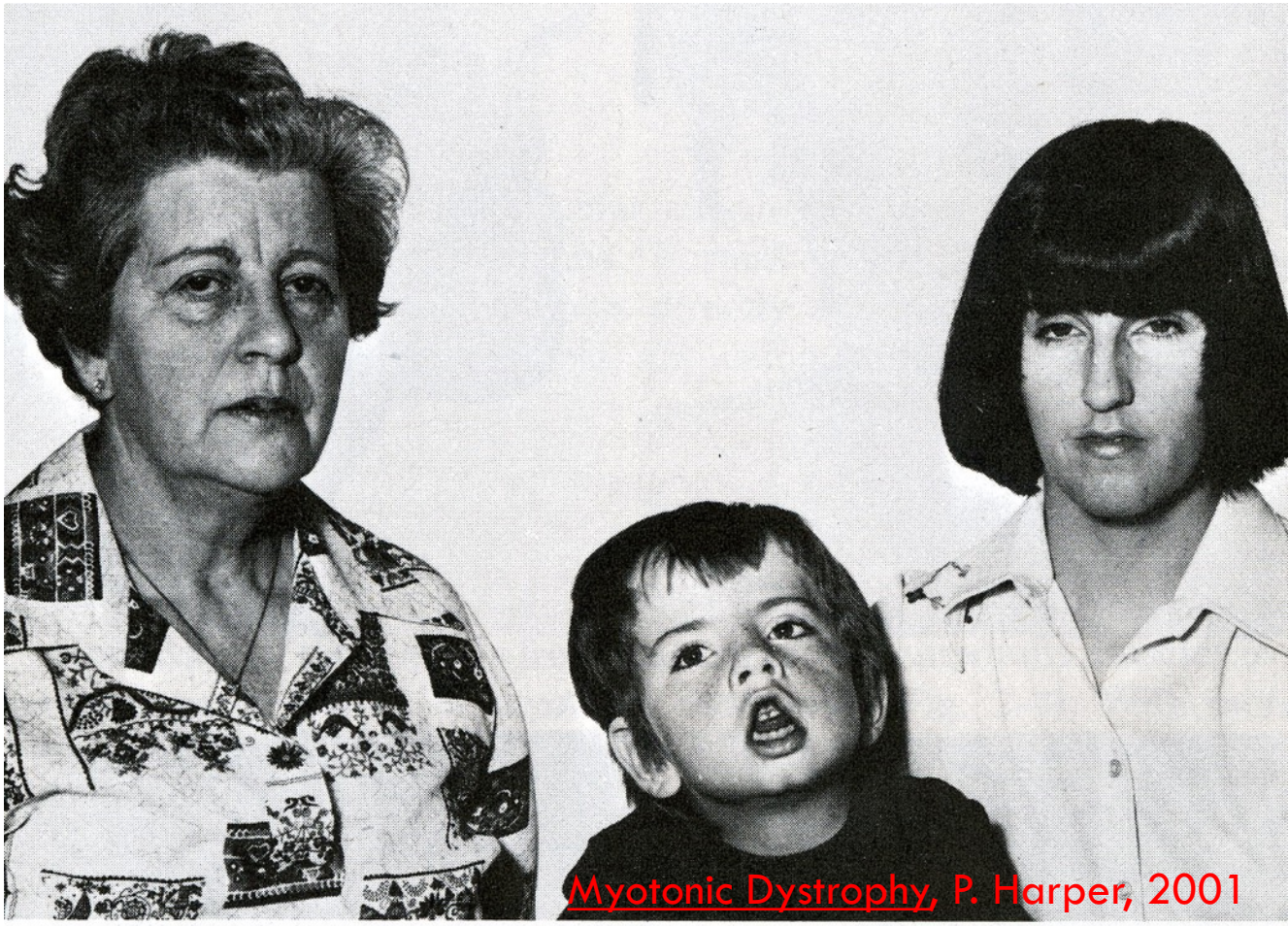
What is anticipation?

- Earlier onset of symptoms with successive generations

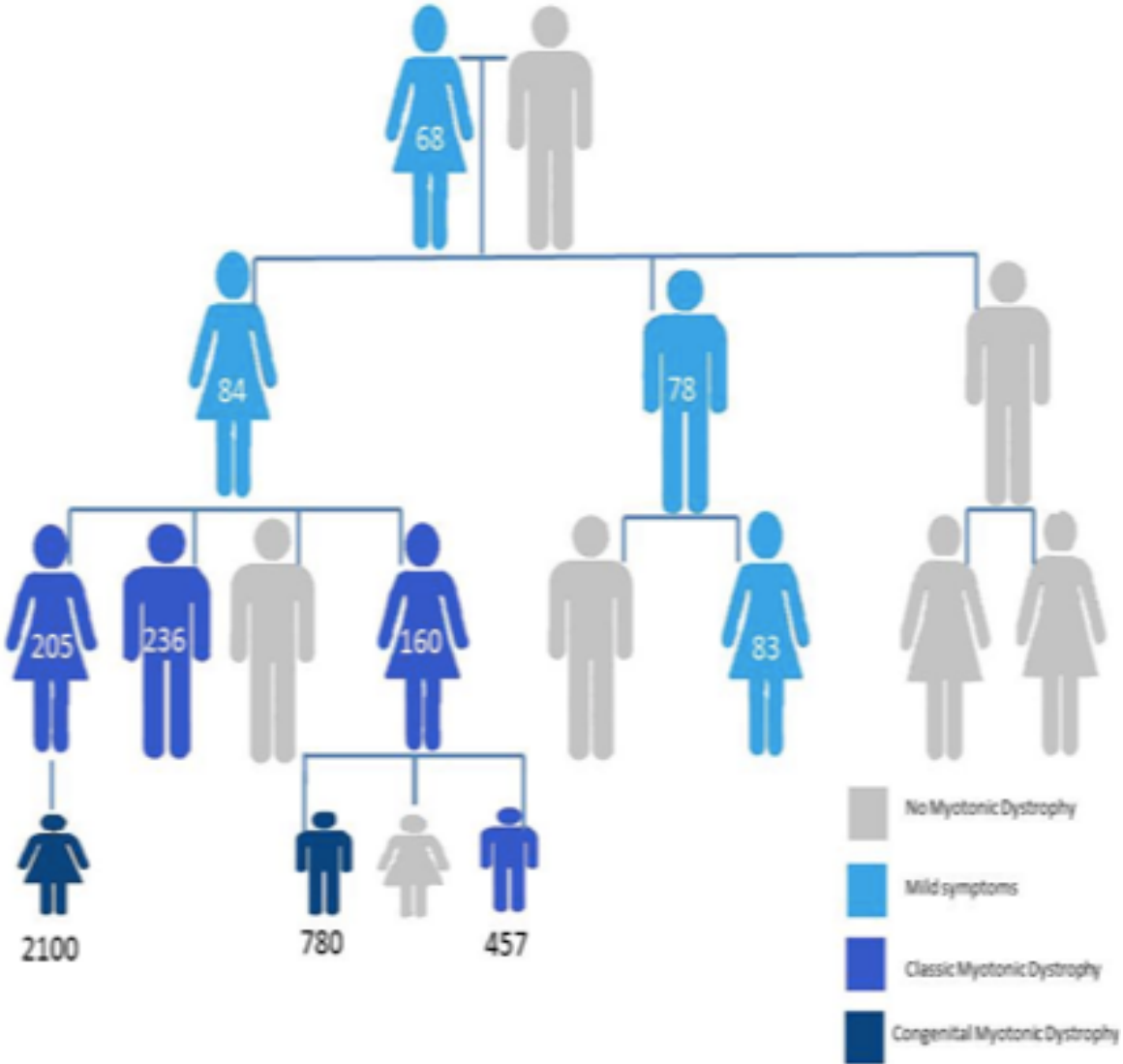


Myotonic Dystrophy, P. Harper, 2001

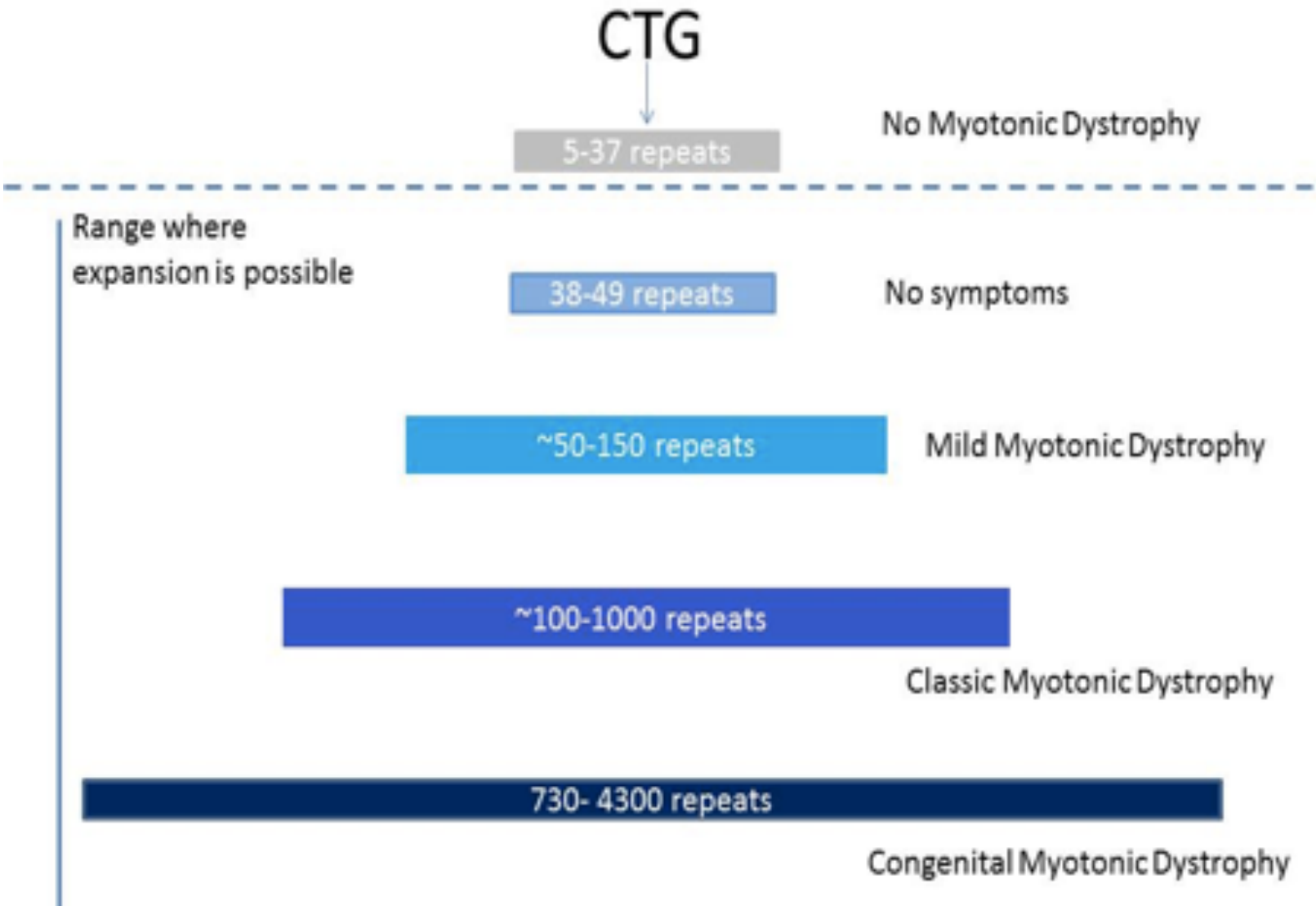
What is anticipation in DM1?

< 35 repeats	normal
<50 repeats	premutation
50-4,000 repeats	disease
~1000 (>730) repeats	congenital form

What is anticipation?

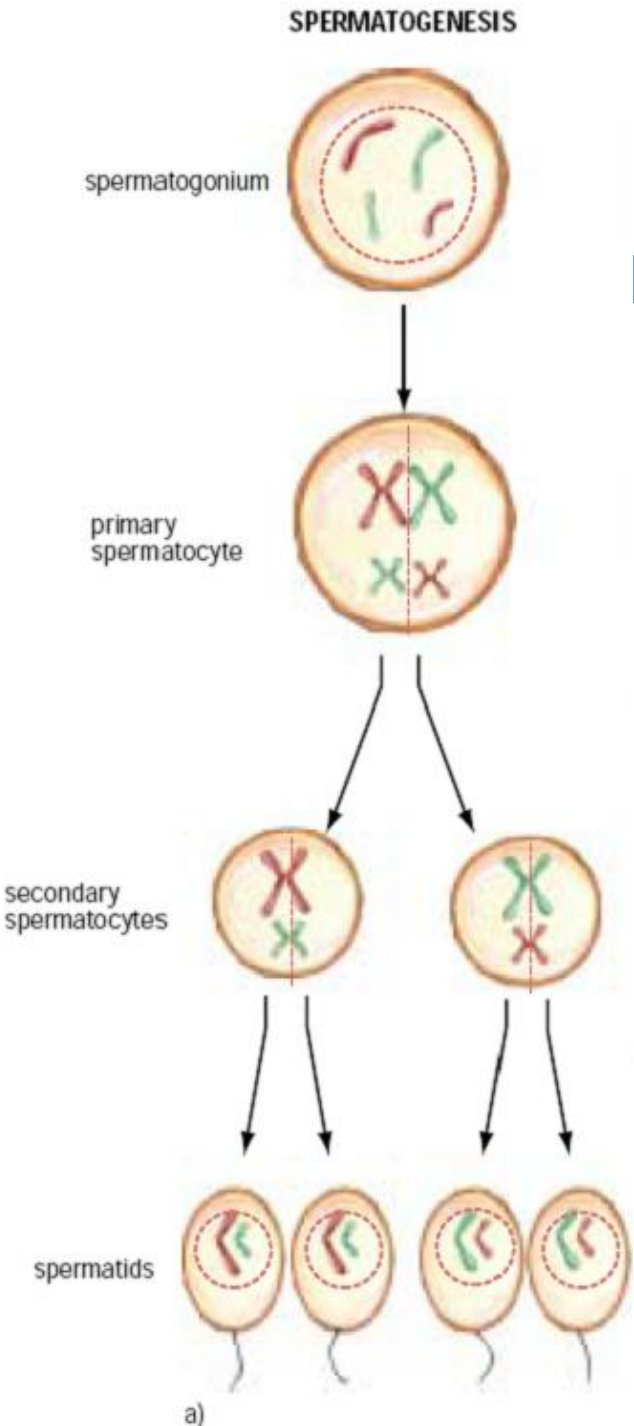


Myotonic Dystrophy Type 1



Sperm repeat expansion

- Repeat expansions <100 are more unstable when inherited from the father's side
- Even NORMAL repeat sizes show repeat number variation in sperm

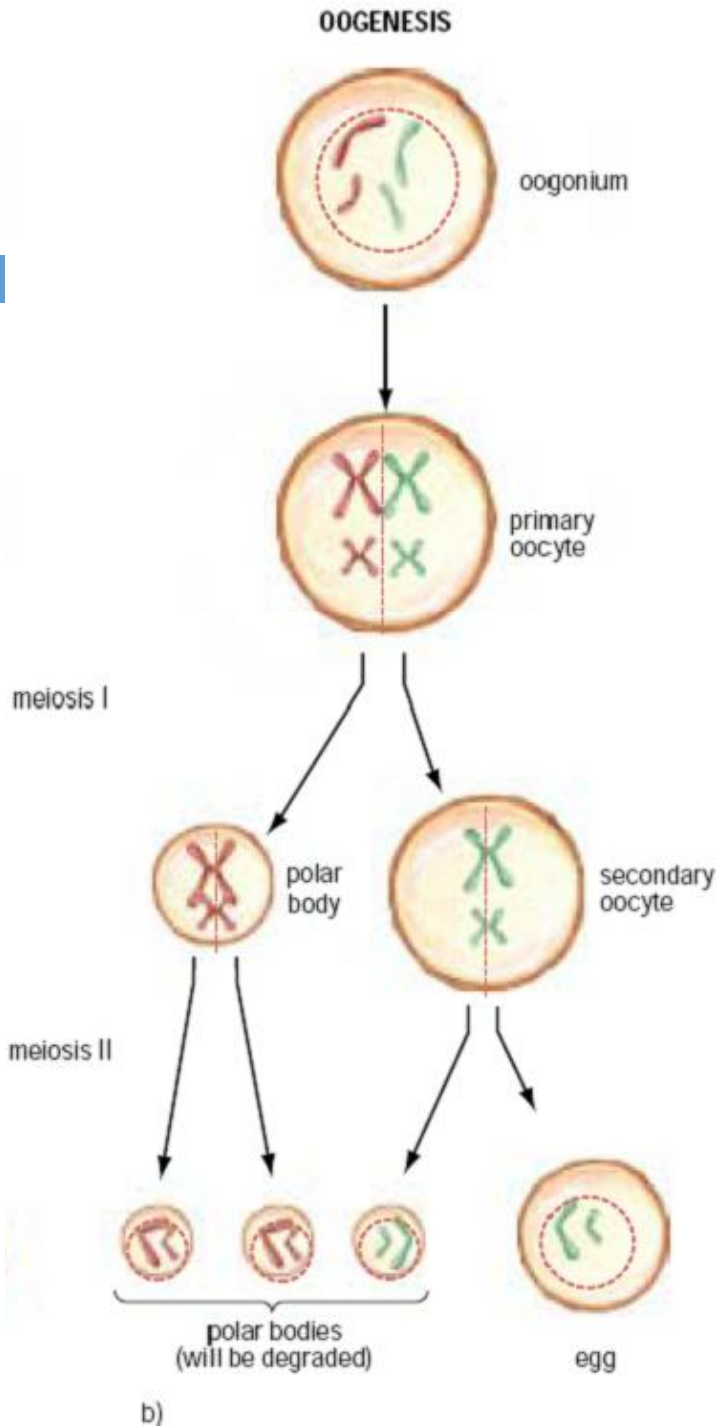


Dean et al. Fertil. Steril. 2006:86:98-105

http://oscss-biology.wikispaces.com/Images

Egg repeat expansion

- Occurred prior to fertilization
- Somatic mosaicism
  - Different tissues have different repeat sizes
  - Repeat size increases during development
  - Somatic expansion observed at 13-16 weeks

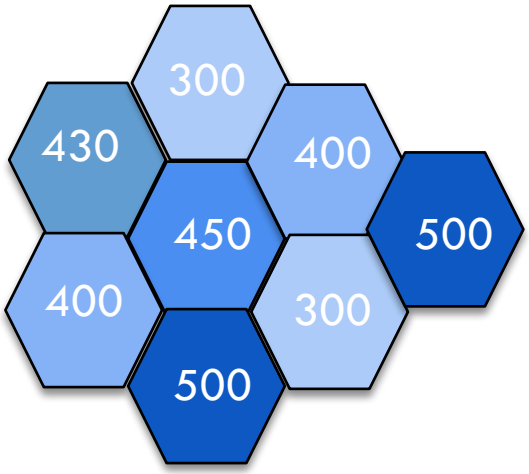


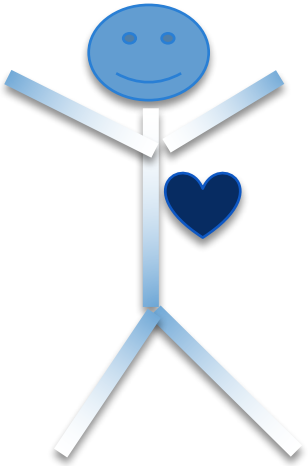
Dean et al. Fertil. Steril. 2006:86:98-105

http://oscss-biology.wikispaces.com/Images

What is somatic mosaicism?

- Repeat size can vary between:
  - Cells
  - Tissues
  - Organs

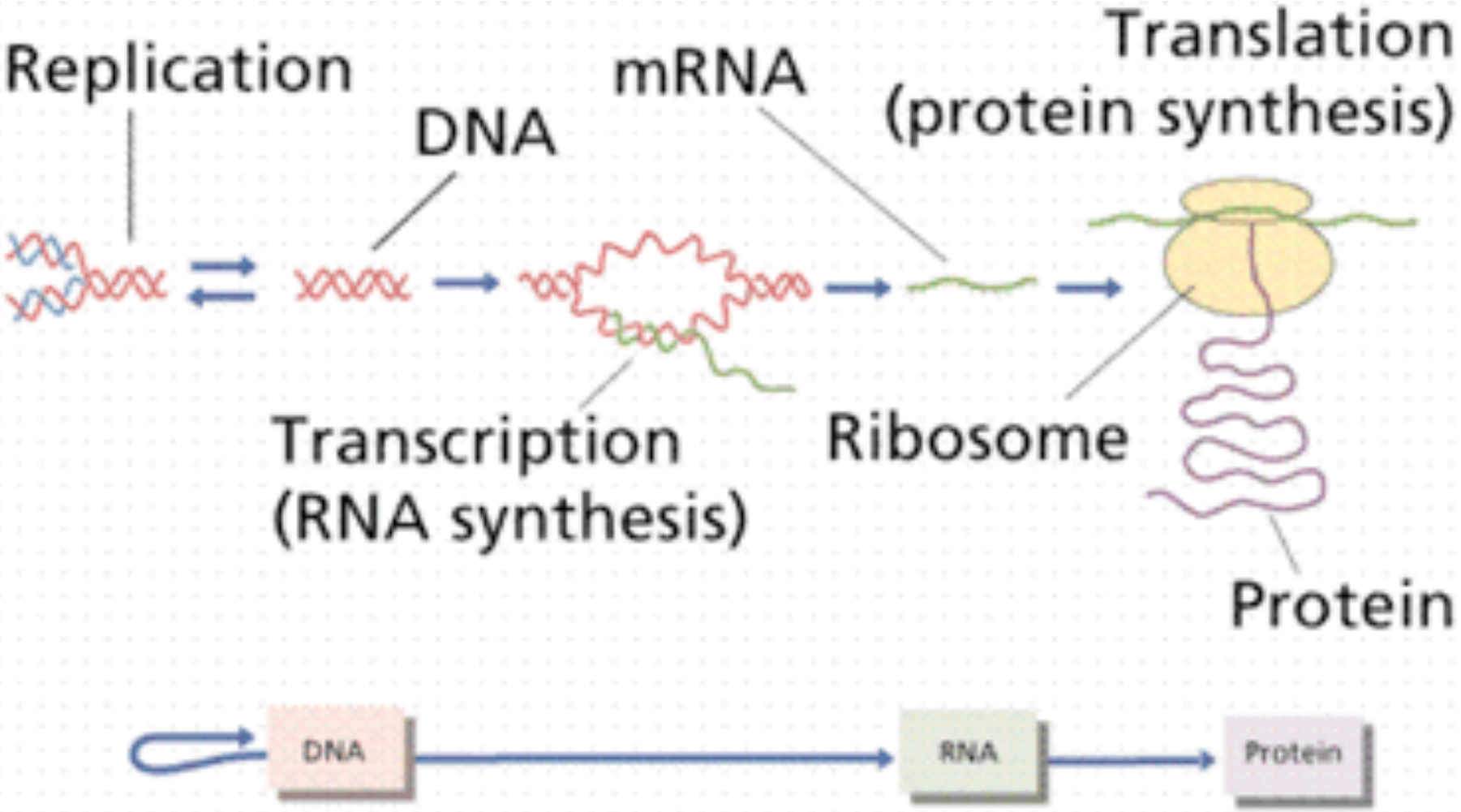




How does DM cause disease?

- There are several hypotheses…

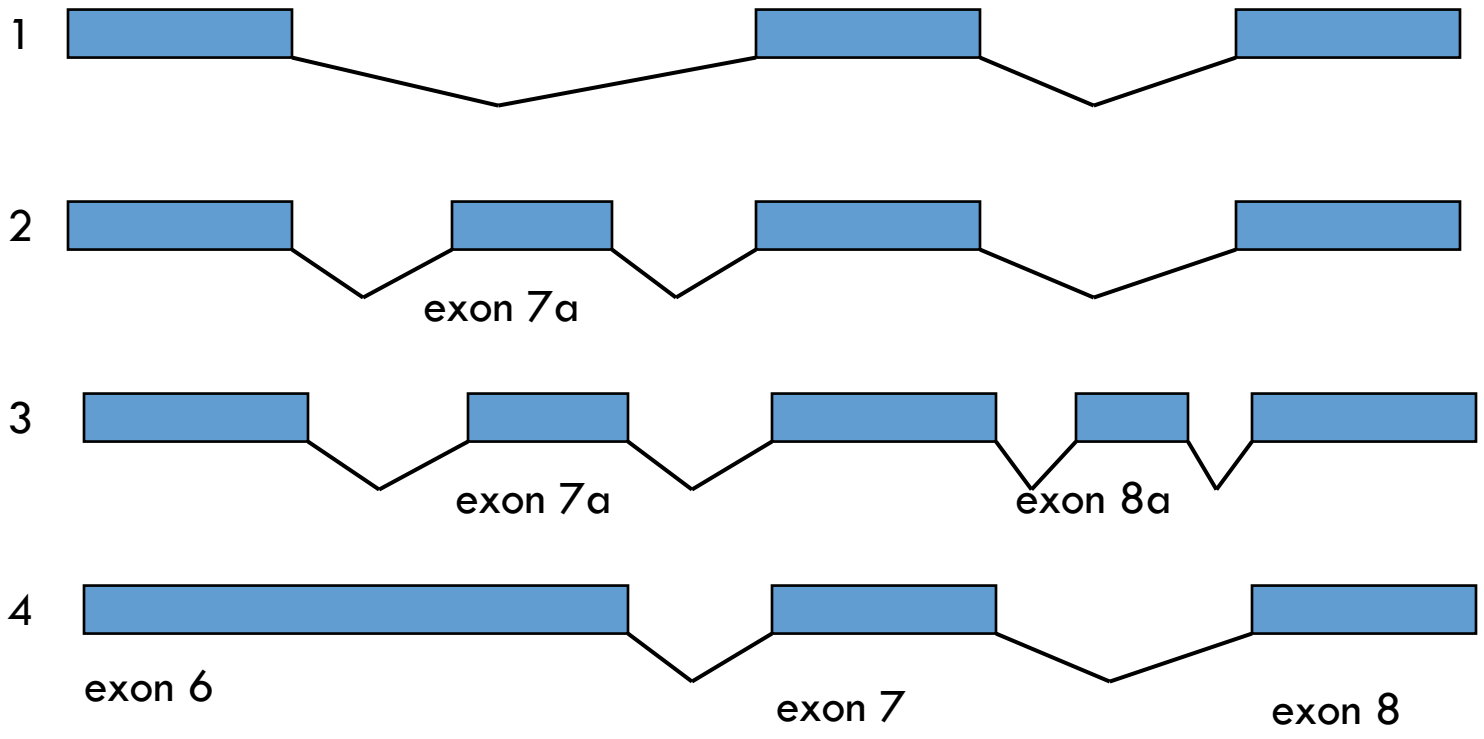
Review: DNA, RNA, and protein



http://rpdp.net/sciencetips_v2

What is a spliceopathy?

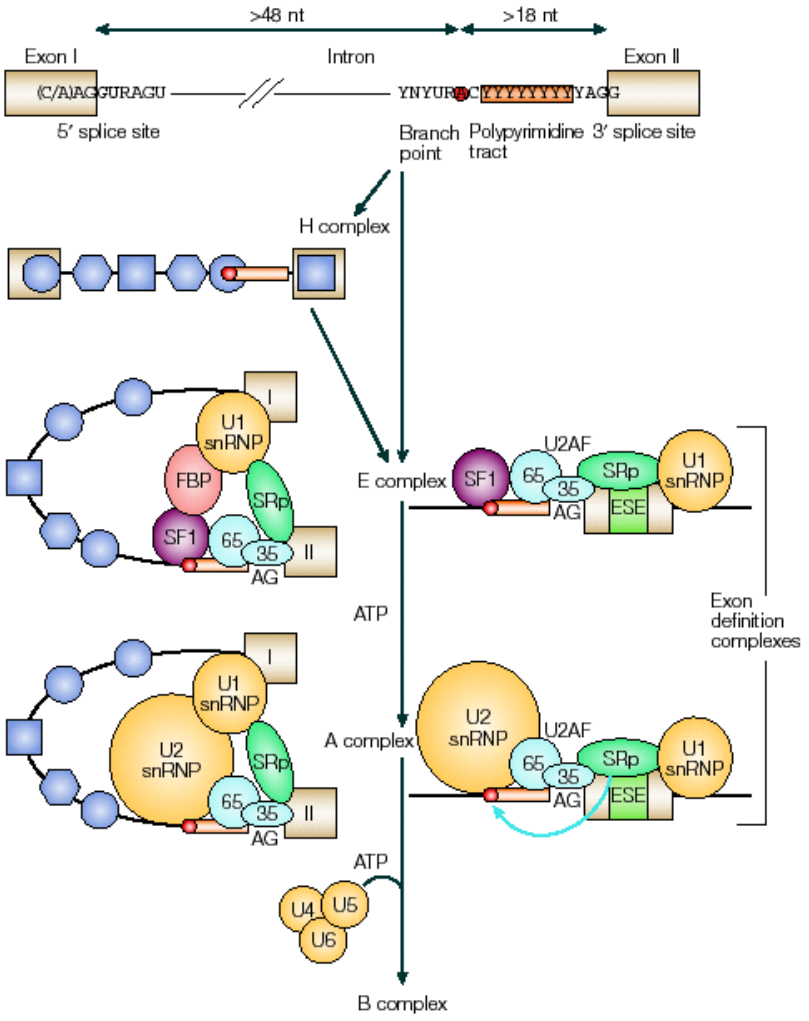
RNA must be cut and pasted (spliced) before it can be translated into a protein



Choosing different exons can vary the protein sequence

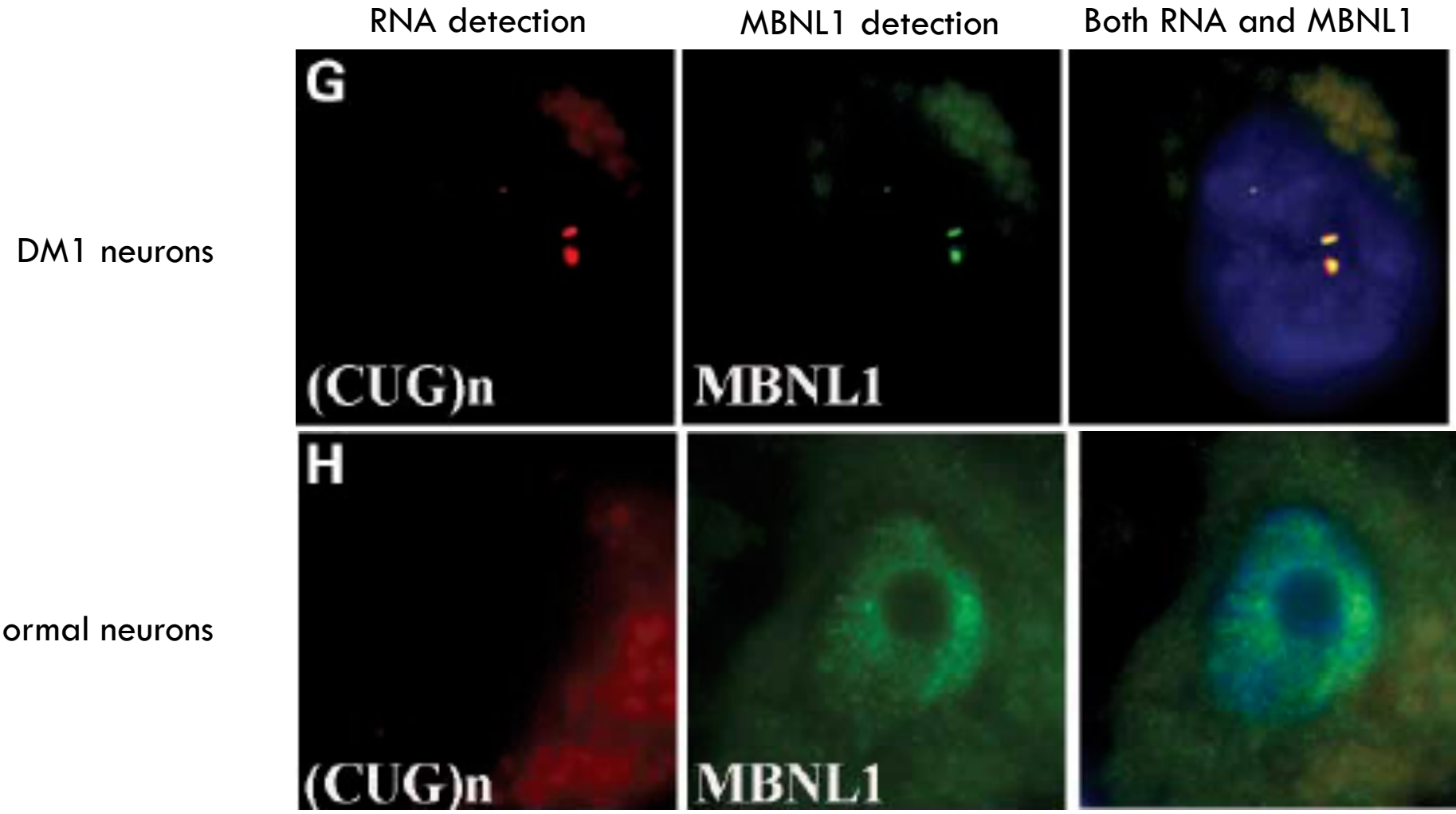
What is the toxic RNA hypothesis?

- Polynucleotide repeat bind up RNA splicing proteins
  - MBNL1 (Muscleblind 1)
  - CUGBP (CUG binding protein)
- Incorrect RNA splicing occurs
- Many RNAs, encoding many proteins for many tissues, are affected!



Matlin et al, Nature MolCellBiol. 2005 (6): 386-398

Splicing proteins get stuck in nucleus in "foci"



Jiang et al, Hum. Mol. Gen. 2004, 13(24):3079-3088

How is DM multisystemic?

- Muscle
- Brain
- Eyes
- Heart
- Lungs

How is DM multisystemic?

- Gastrointestinal tract
- Skin and hair
- Hormones
- Pregnancy
- Anesthesia

How does it affect the muscles?

- DM1– distal muscles
  - Hands, ankles, but also neck

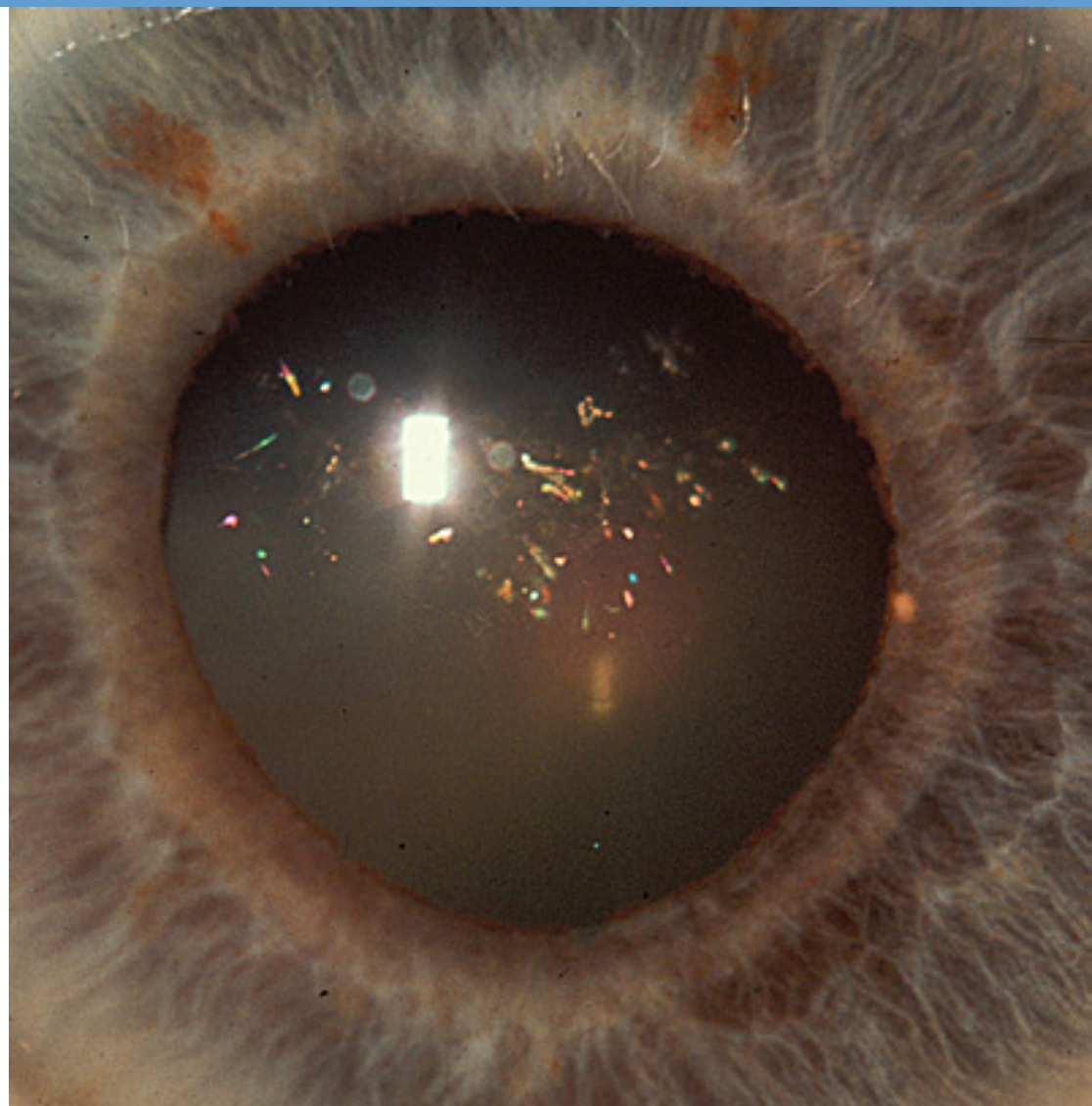
- DM2- proximal muscles
  - Hips and shoulders

Saturday 11 AM: Occupational Therapy:
Getting a Grip on Daily Activity Cynthia Gagnon, PhD

Saturday, 10 AM: DM & Exercise: A Panel Discussion
Katy Eichinger, DPT and community panelists

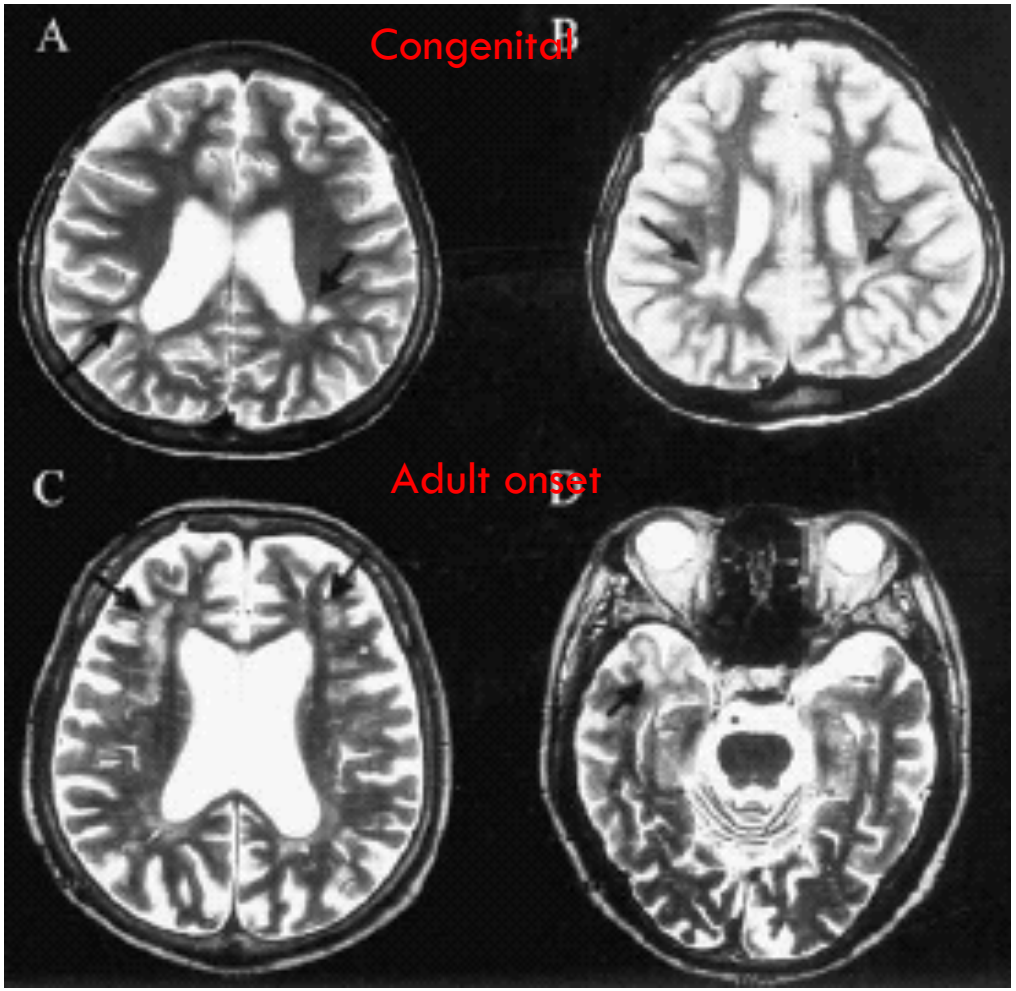
How does it affect the eyes?

- Cataracts
  - "Christmas tree"
  - tinsel effect



How does it affect the brain?

- Congenital DM1
  - Increased incidence of:
    - intellectual disability
    - Attention deficit disorder
- Adult onset DM1
  - Frontal and executive tasks



Saturday 2:30 – 3:15 PM: **DM & the Brain: Science & Symptoms**
John Day, PhD; David Moser, PhD; Giovanni Meola, MD, PhD

How does it affect the heart?

- Heart rhythm (arrhythmia)
  - Conduction block
  - Atrial flutter or fibrillation
  - Risk of sudden cardiac death
- Cardiomyopathy
  - Decreased strength of heart muscle

How does it affect the gastrointestinal tract?

- Swallowing difficulties (dysphagia)
  - Can lead to choking, aspiration

- Constipation
- Pseudo-obstruction
- Diarrhea
- Irritable bowel syndrome (IBS)- like symptoms

Saturday 11AM, 1 PM: DM & the GI Tract: Overview & Symptom Management
Linda Nguyen, MD

How does it affect the lungs?

- The muscles of breathing
  - Diaphragm
  - Intercostal muscles (muscles between the ribs)
- Brain control of breathing in sleep
  - Sleep apnea
- Aspiration pneumonia

How does it affect the hormones?

- irregular or absent menstrual periods
- Testicular atrophy
- Growth hormone
- Parathyroid hormone imbalance
- Thyroid hormone imbalance

How does it affect sleep?

- Increased sleep requirement (hypersomnolence)
- Daytime sleepiness
- Sleep apnea and snoring
  - Obstructive
    - weak tongue and throat muscles collapse during sleep
  - Central
    - brain directing breathing rhythm
- fatigue

What are the anesthesia effects of DM?

- Different types of anesthesia have different risks:
  - Weaken breathing, coughing, swallowing
  - Confusion/delerium
  - Constipation
  - Cause all-over myotonia
- See myotonic.org website for anesthesia reccommendations

What can I do about it?

- Learn about it!
  - Which is what you are doing!
- Establish a medical care team
- Do your preventative care
- Support groups- support each other
- Consider research – see what is right for you
  - Registries
  - surveys
  - Observational studies
  - Treatment studies

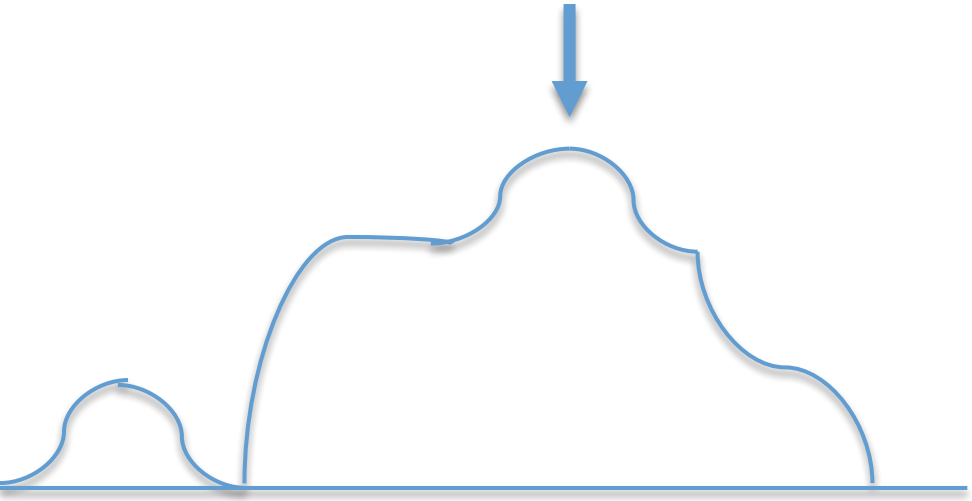
What research is being done?

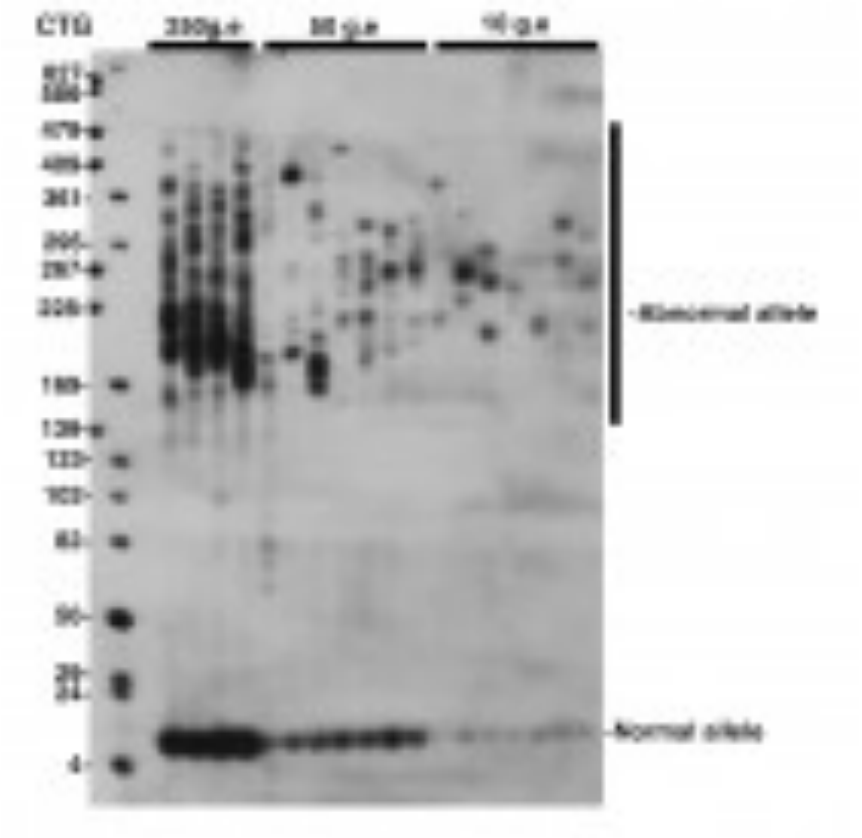
Saturday, 3:15: Early Stage DM Therapy Development Update
Matt Disney, PhD; Roberto Guerciolini, MD; Lauren Wood, PhD

Saturday 4:00: DM Clinical Trial Updates
Ionis Pharmaceuticals, Laury Mignon, PhD; AMO Pharma, Joseph Horrigan, MD

The end-Questions?

How do you test for DM?





Tomé S. PLOS1. 2014 Mar 6