MYOTONIC DYSTROPHY FOUNDATION

Care and a Cure

2018

MDF ANNUAL CONFERENCE

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DM 101: GETTING A HANDLE ON THE BASICS

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VCU Health

Overview

- Myotonic Dystrophy genetics
- Myotonic Dystrophy type 1 diagnosis
- Myotonic dystrophy type 1 symptoms
- Myotonic dystrophy type 2 diagnosis
- Myotonic dystrophy type 2 symptoms

Myotonic dystrophy (Dystrophia myotonica

- Two disorders: type 1 and type 2
- Both disorders are caused by repeat expansion
- Repeat expansion impairs RNA splicing
- Different symptoms/overlapping symptoms

Why is DM described as "the most variable human disease?"

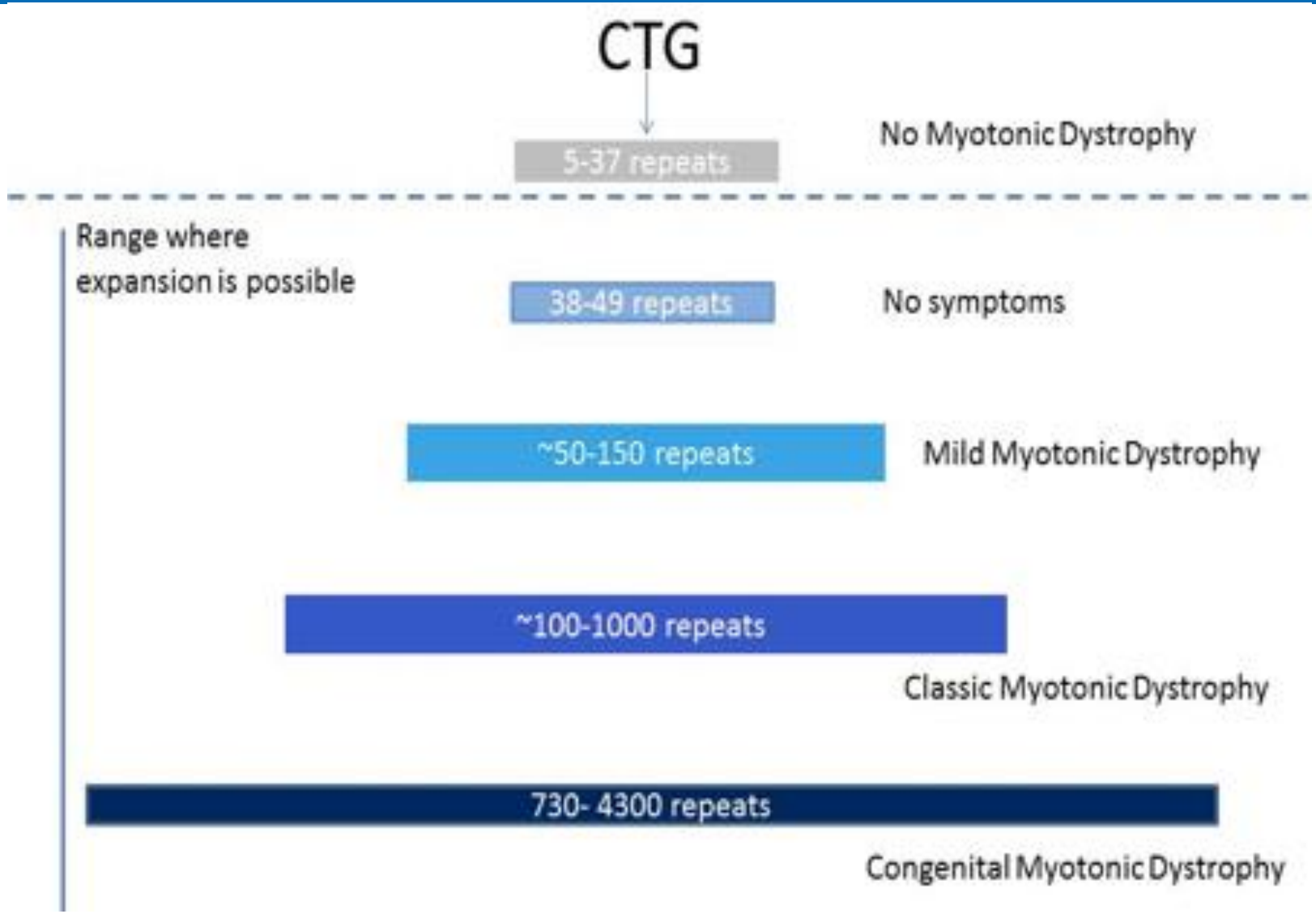
- Most genetic disorders are due to a single missing protein or too much of a single protein (all or none)
- DM genetics are influenced by:
  - Repeat length
  - Somatic mosaicism/repeat instability

What gene mutation causes DM1?

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

…CTG CTG CTG CTG CTG…

Myotonic Dystrophy Type 1



Sub definitions of DM1

- Congenital onset (symptoms start at birth)
- Childhood onset (symptoms before age 10)
- Adult onset (symptoms after 10)
- Mild/late onset/oligosymptomatic

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

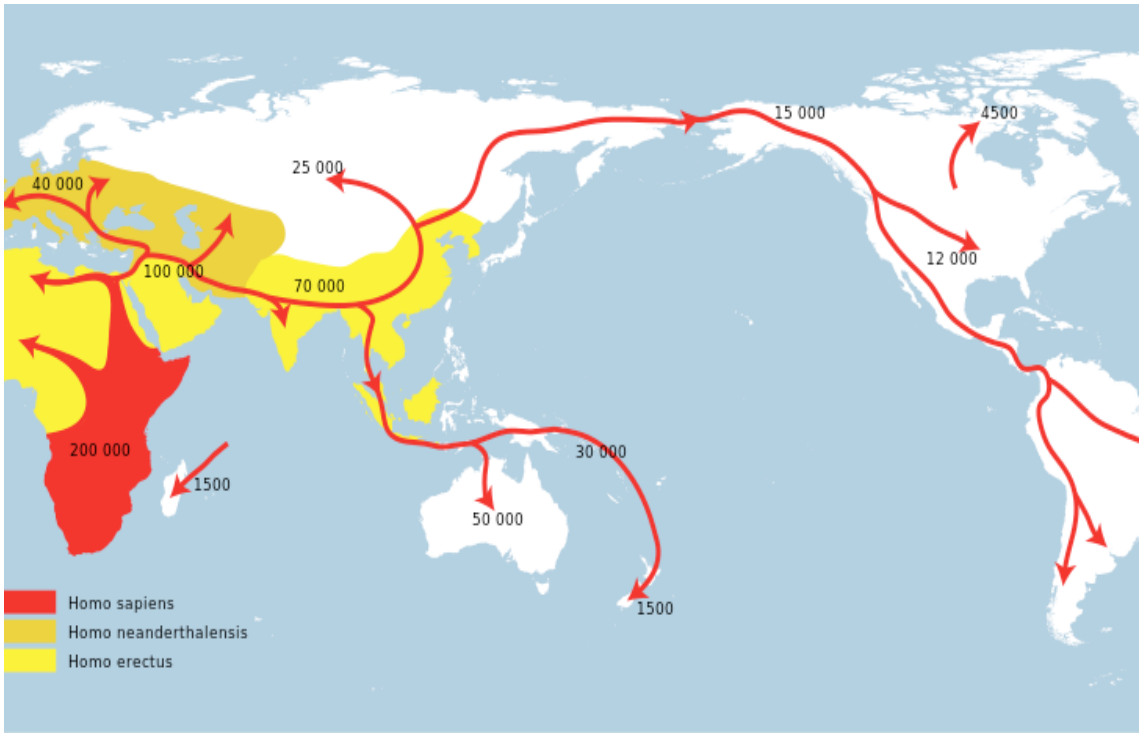
Range where expansion
Or contraction is possible

75-11,000 repeats

Myotonic dystrophy type 2

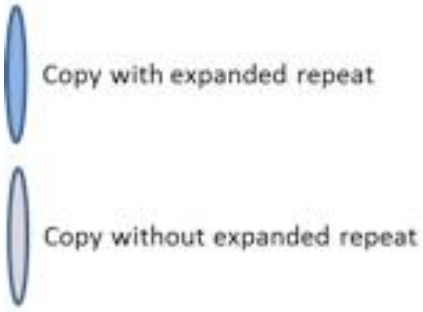
Where did DM come from?

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

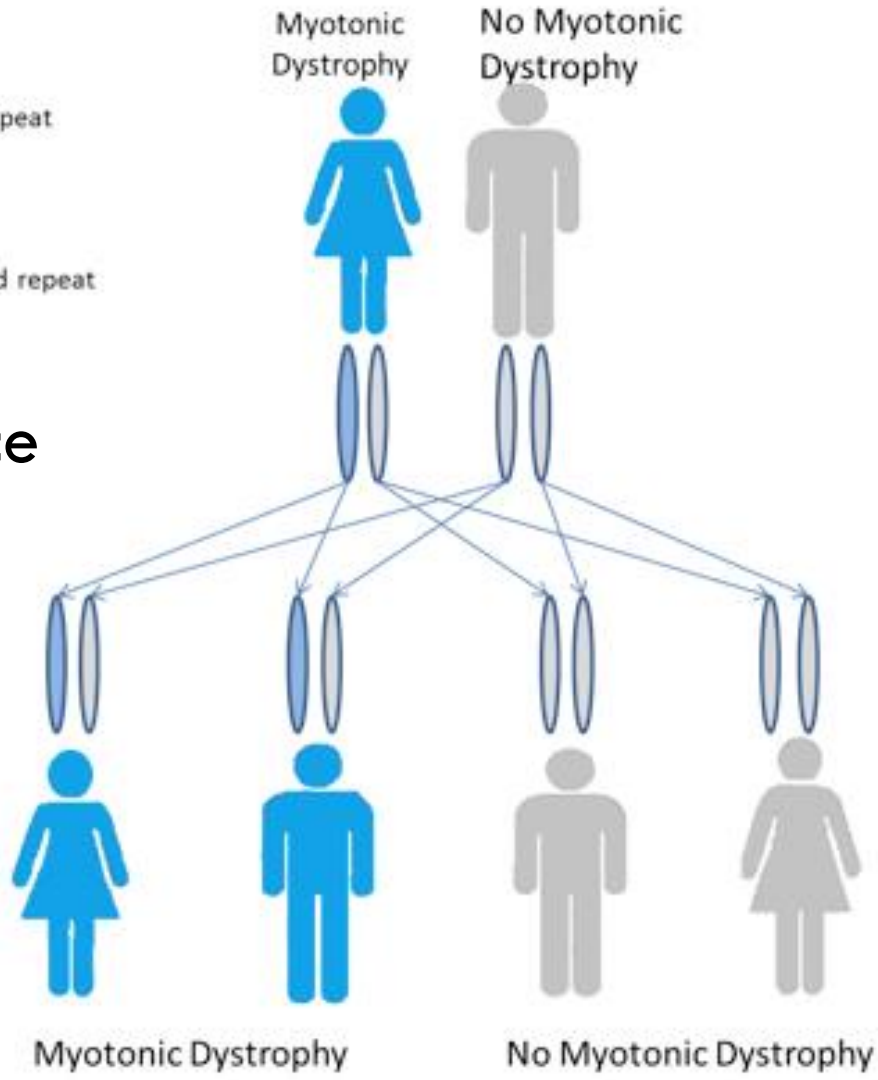


Wikipedia, early human migrations

How is it inherited?



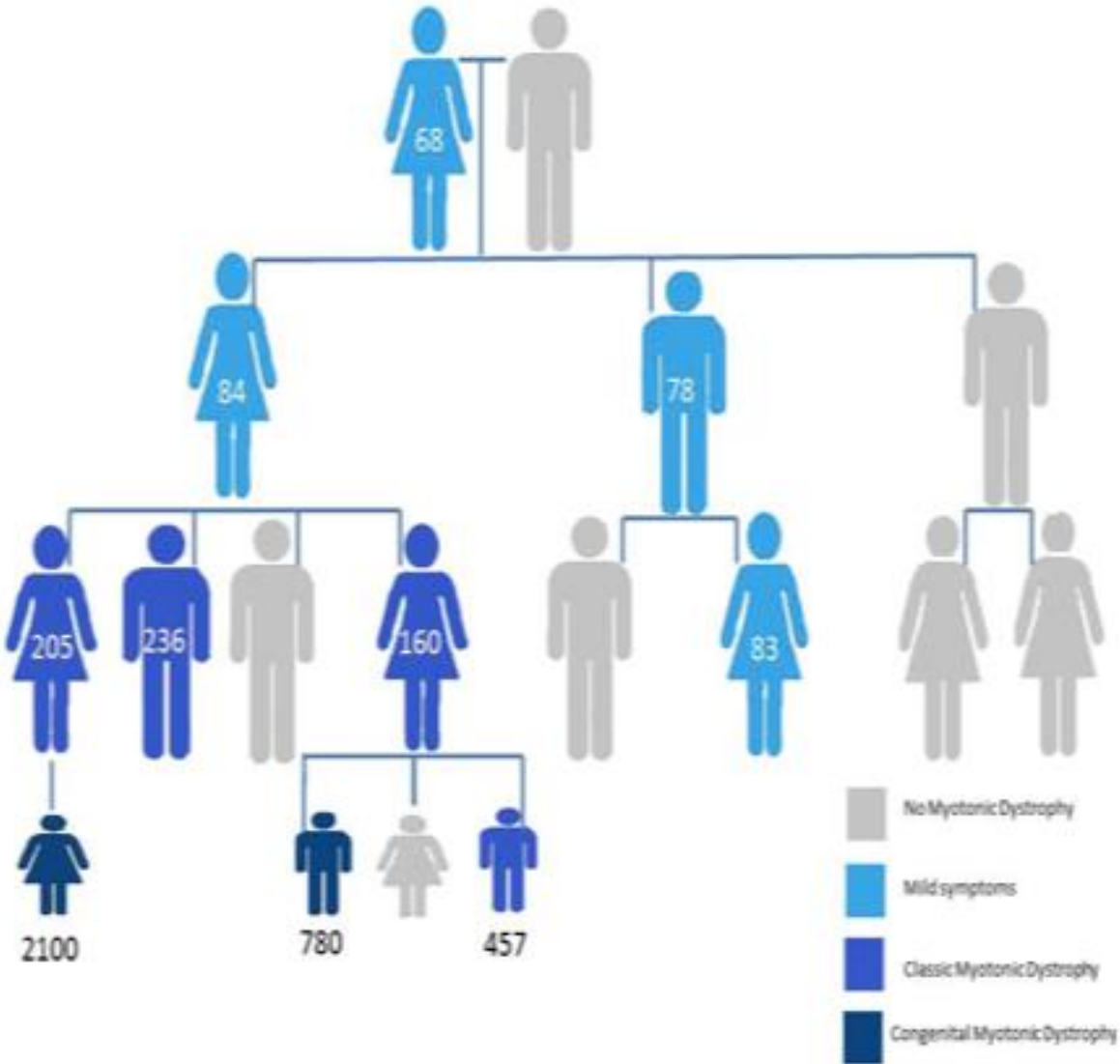
Dominant inheritance



Dominant inheritance

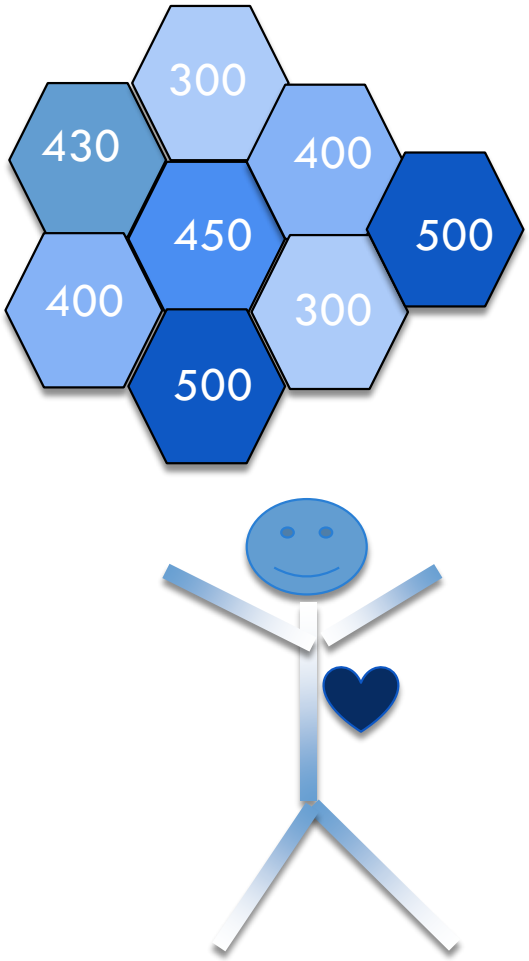
- 50% chance of inheriting abnormal gene
- 50% chance at <u>each</u> pregnancy
- Does not alternate or “even out”

What is anticipation?

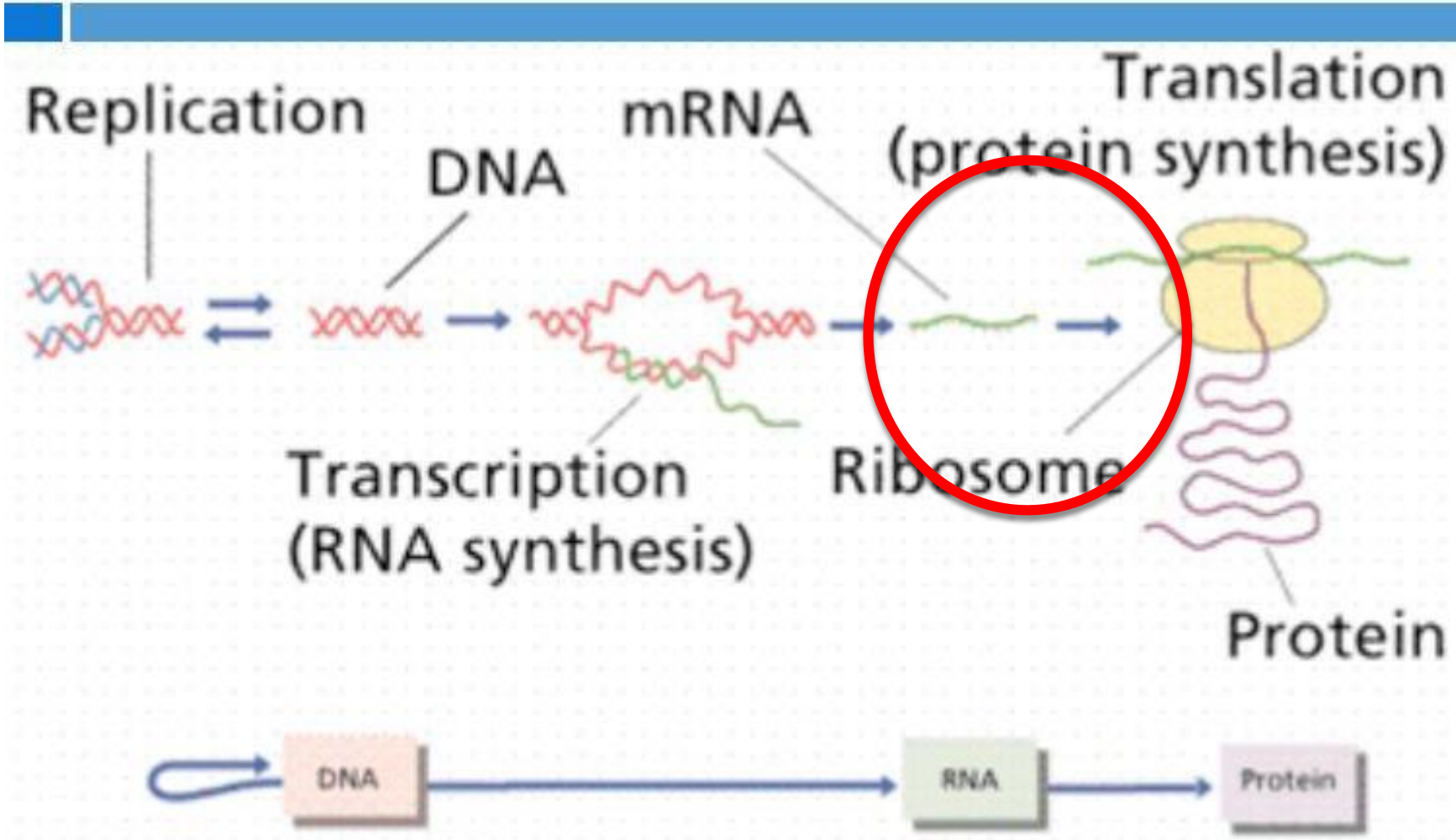


What is somatic mosaicism?

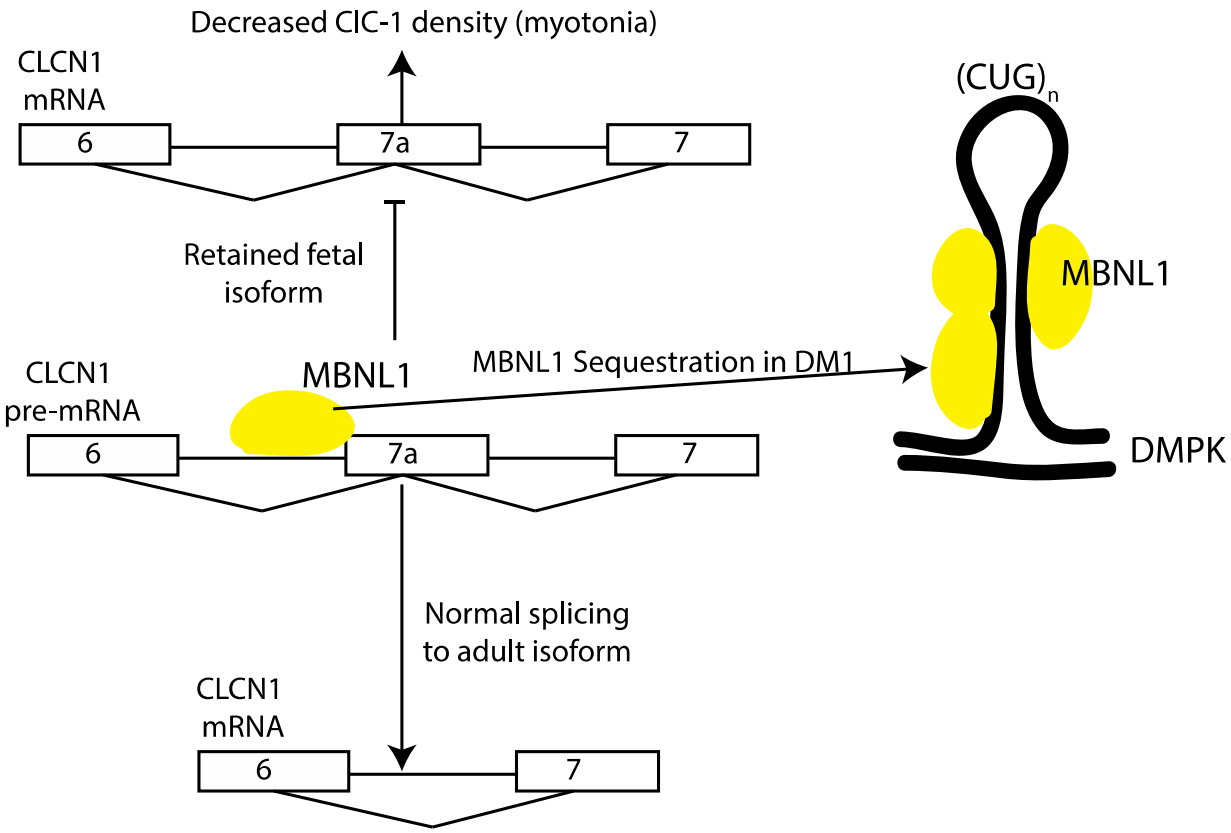
- Repeat size can vary between:
  - Cells
  - Tissues
  - Organs



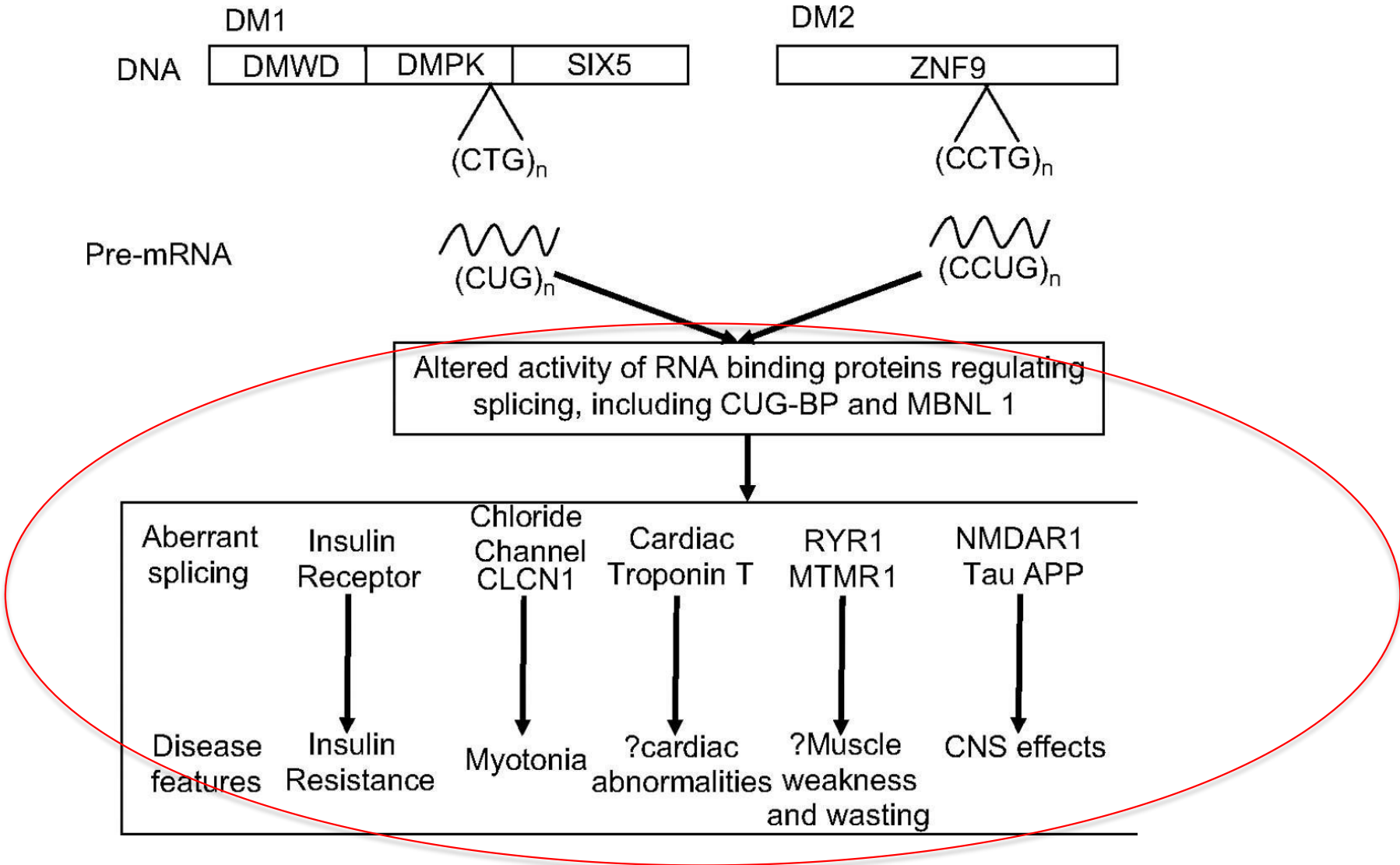
Review: DNA, RNA, and protein



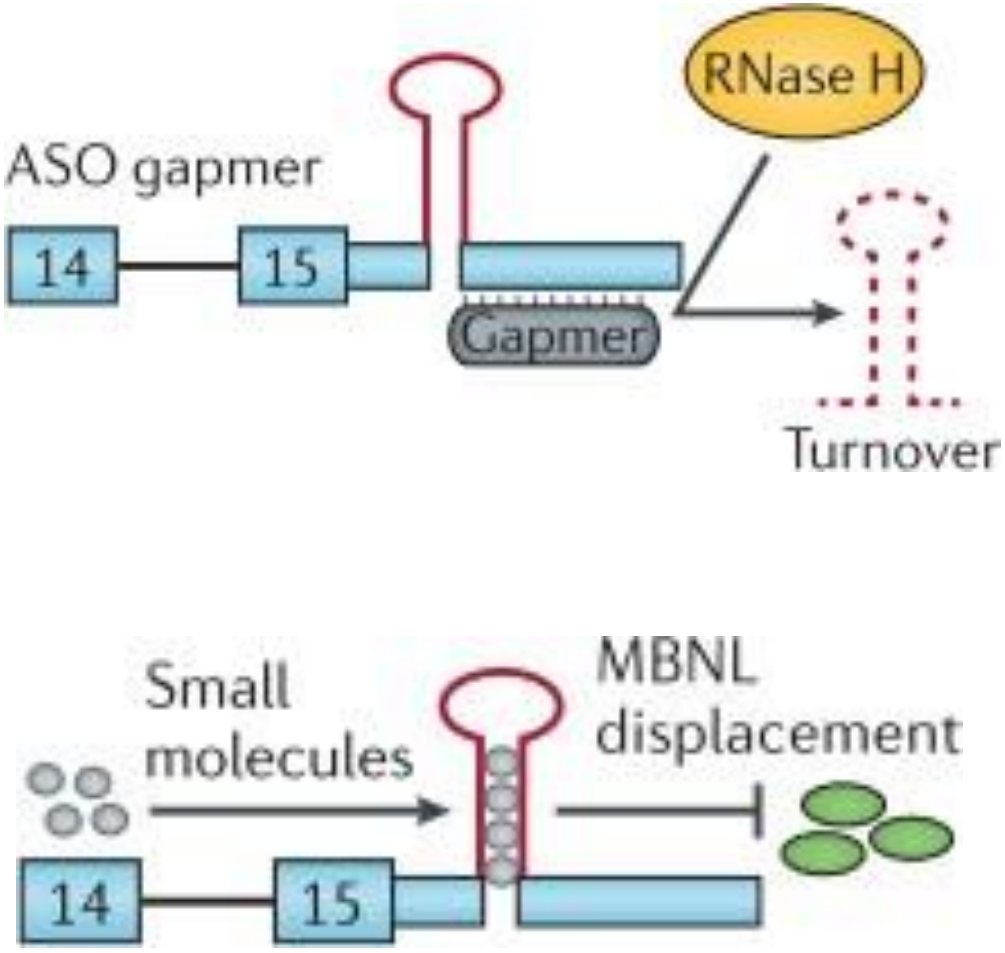
RNA splicing is disrupted in DM



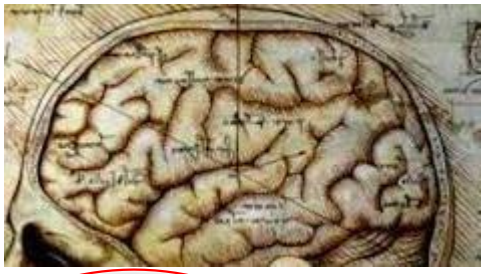
Splicopathy

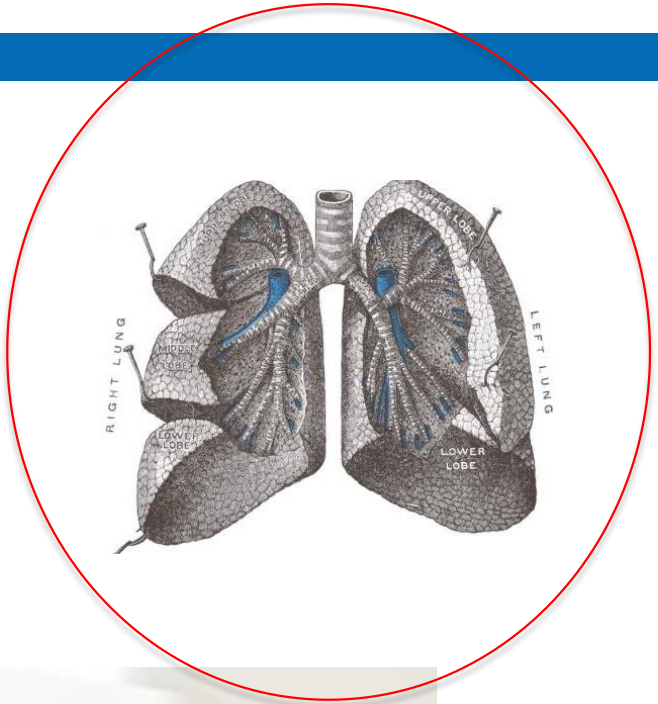


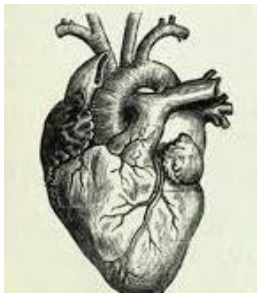
Treatment Targets

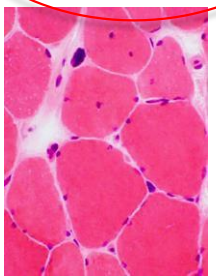


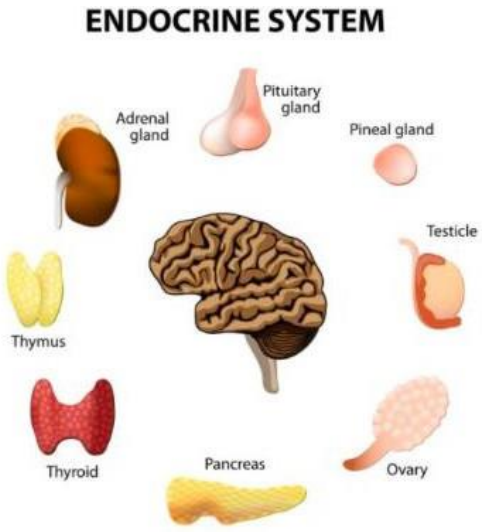
Multi-systemic Disease

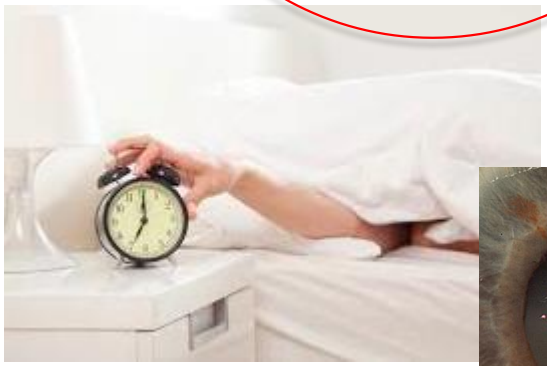


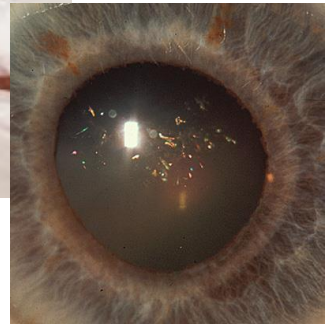










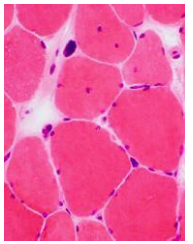


DM 1		DM2
common	Facial weakness	rare
common	Difficulty swallowing, speaking	rare
common	Difficulty breathing	rare
common	Heart problems	variable
rare	Pain	common
common	Difficulty thinking, memory	uncommon
yes	Congenital form	No

How does it affect the muscles?

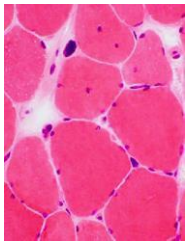
- DM1– distal muscles
  - Hands, ankles, but also neck
- DM2- proximal muscles
  - Hips and shoulders

MUSCLE



- Myotonia (“muscle stiffness”) – delayed muscle relaxation

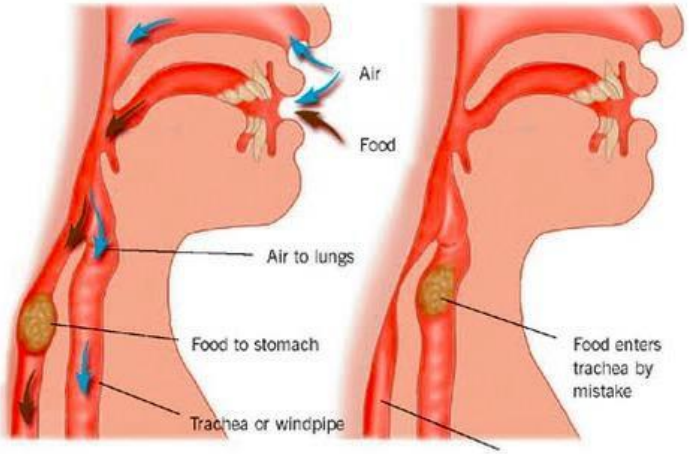
MUSCLE



- Myotonia ("muscle stiffness") – delayed muscle relaxation

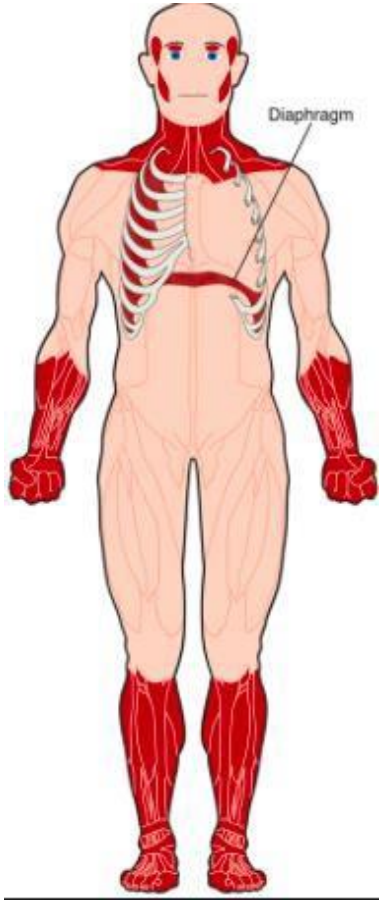
- Dystrophy – progressive weakness and loss of muscle mass

- Swallowing – difficulty swallowing with risk of aspiration and slurred



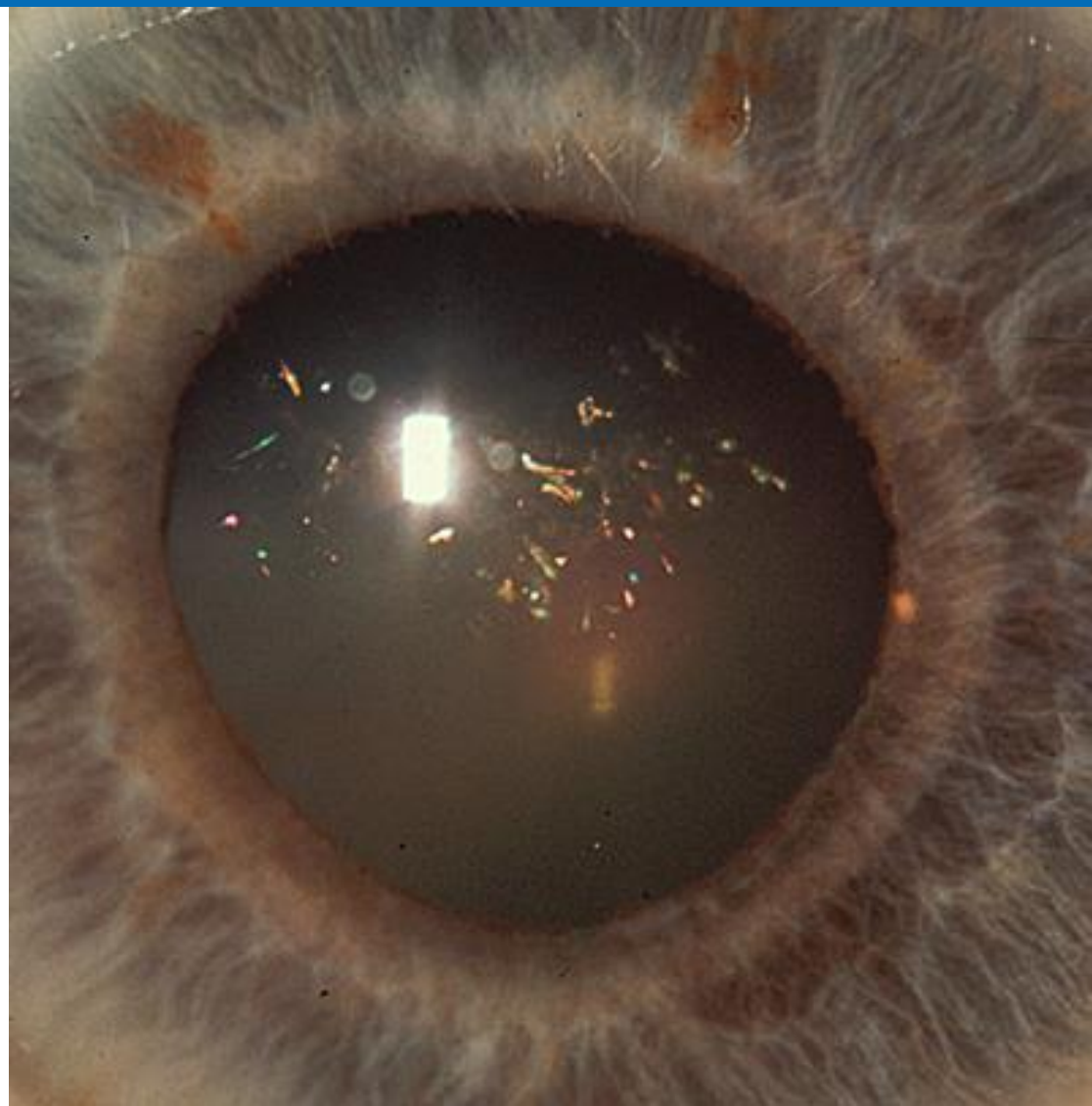
DM 1

DM2



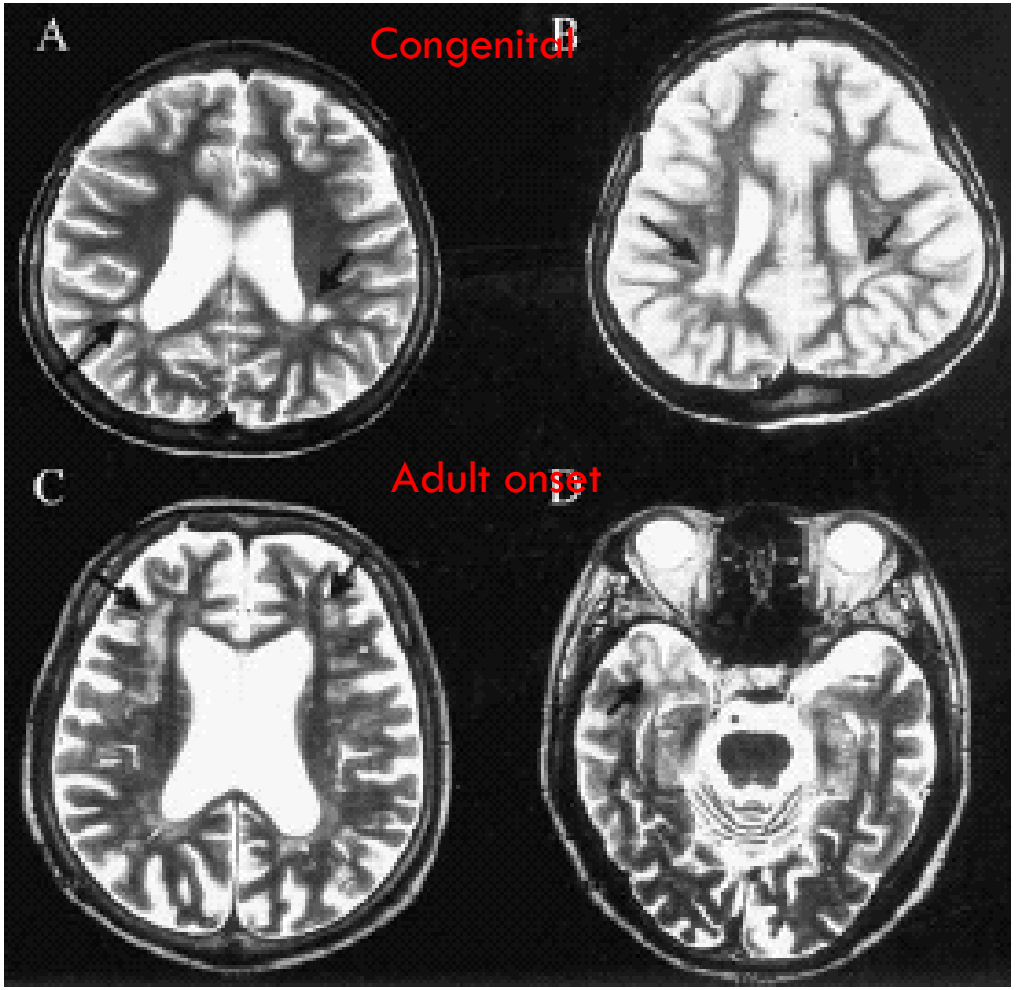
How does it affect the eyes?

- Cataracts
  - "Christmas tree"
  - tinsel effect



How does it affect the brain?

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



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

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?

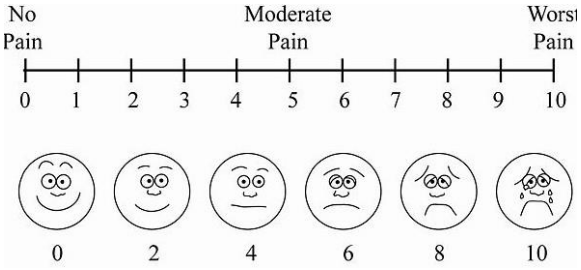
- irregular or absent menstrual periods
- Testicular atrophy
- Growth hormone
- Parathyroid hormone imbalance
- Thyroid hormone imbalance

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**

Others

- **Pain:** DM2 > DM1



- **Cancer:** Increased risk of cancer → up to date with cancer screening

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 you do?

- Learn about it and inform your family
- Establish an interdisciplinary medical care team
- Preventative care (cancer screening, diabetes)
- Support groups - support each other
- Consider research – see what is right for you
  www.clinicaltrials.gov
  - Registries
  - Surveys
  - Observational studies
  - Treatment studies