THE 2ND DECADE

MYOTONIC DYSTROPHY FOUNDATION

2017 MDF Annual Conference

Sept. 8–9, 2017 San Francisco

MYOTONIC DYSTROPHY FOUNDATION

Care and a Cure

DM 101: UNDERSTANDING THE BASICS

Johanna Hamel MD

UNIVERSITY of ROCHESTER MEDICAL CENTER

Myotonic dystrophy (Dystrophia Myotonica)

1. DM1 and DM2: 2 types of diseases

2. Inherited diseases caused by a genetic abnormality

3. Multi-systemic diseases: not only the muscle is affected but multiple other organ systems

DM1: 1909

DM2: 1994

Clinical Description

Hans Steinert

1909

"Über das klinische und anatomische Bild des Muskelschwunds der Myotoniker." in Dtsch Z Nervenheilkd

Richard Moxley

1994

"Proximal myotonic myopathy: a new dominant disorder with myotonia, muscle weakness, and cataracts." in Neurology

2001

"Myotonic Dystrophy Type 2 Caused by a CCTG Expansion in Intron 1 of ZNF9" in Science

Discovery of the Genetic Defect

J. David Brook

1992

"Molecular Basis of Myotonic Dystrophy: Expansion of a Trinucleotide (CTG) Repeat at the 3' End of a Transcript Encoding a Protein Kinase Family Member." in Cell

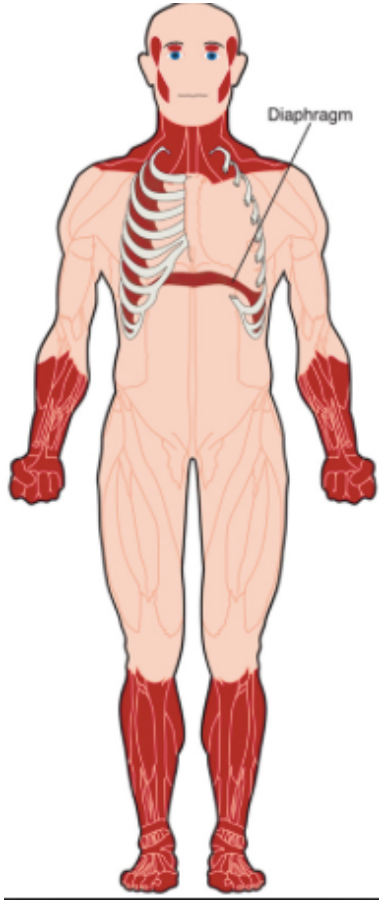
Christina Liquori

Laura Ranum

John Day

DM 1

DM2



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

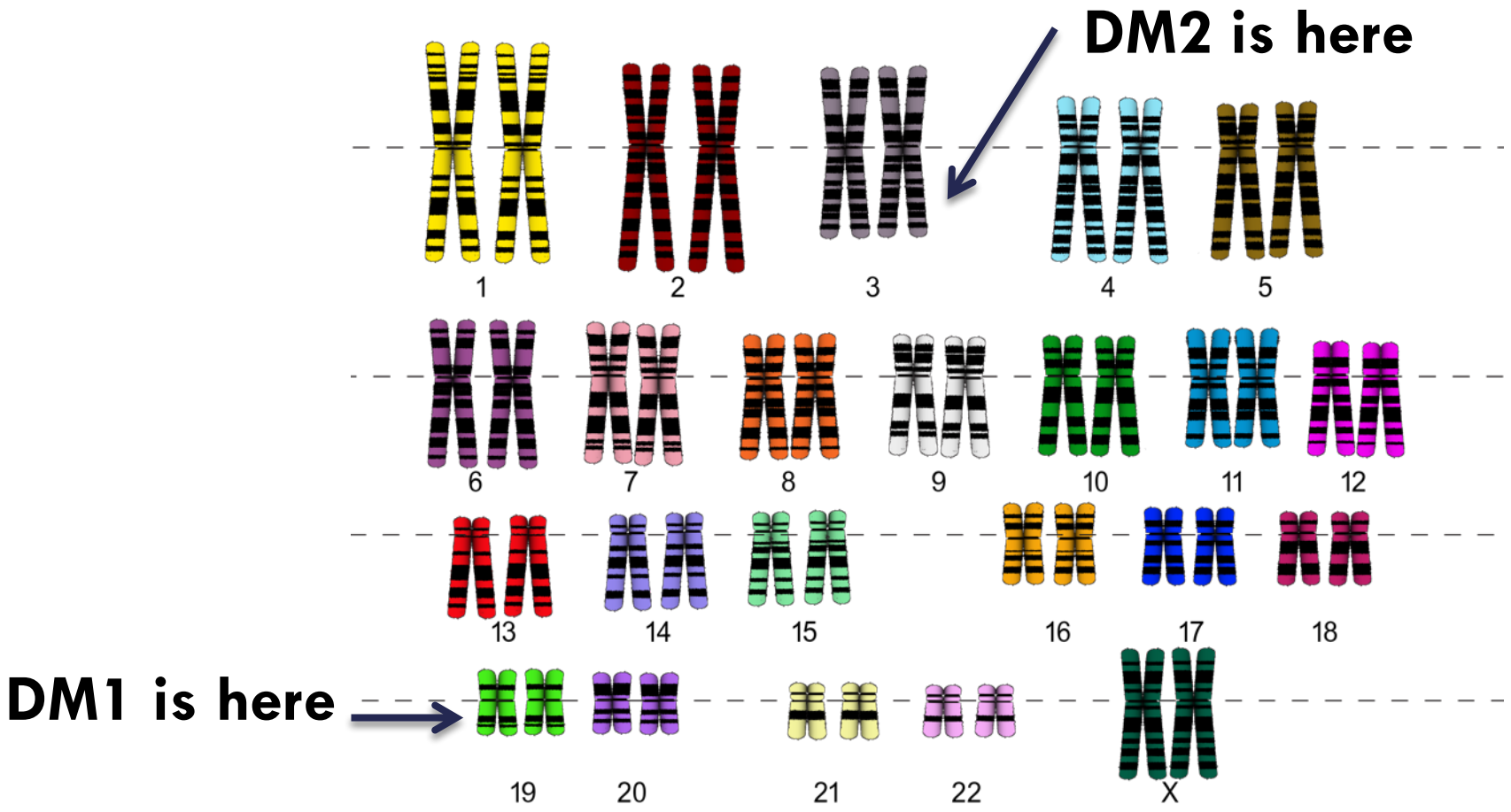
Myotonic dystrophy (Dystrophia Myotonica)

1. DM1 and DM2: 2 types of diseases

2. Inherited diseases caused by a genetic abnormality

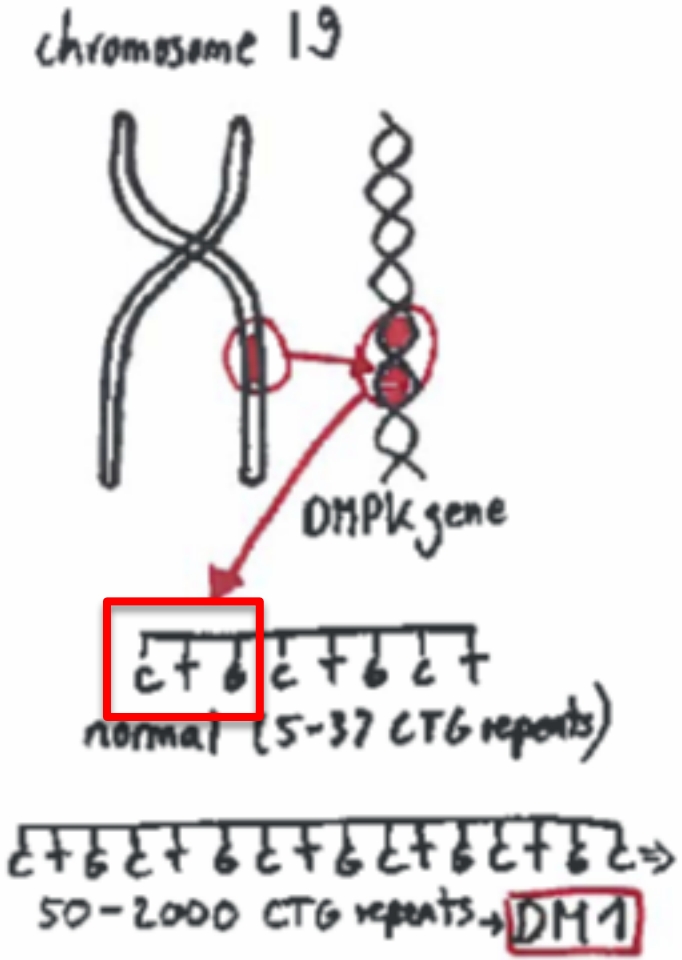
3. Multi-systemic diseases: not only the muscle is affected but multiple other organ systems

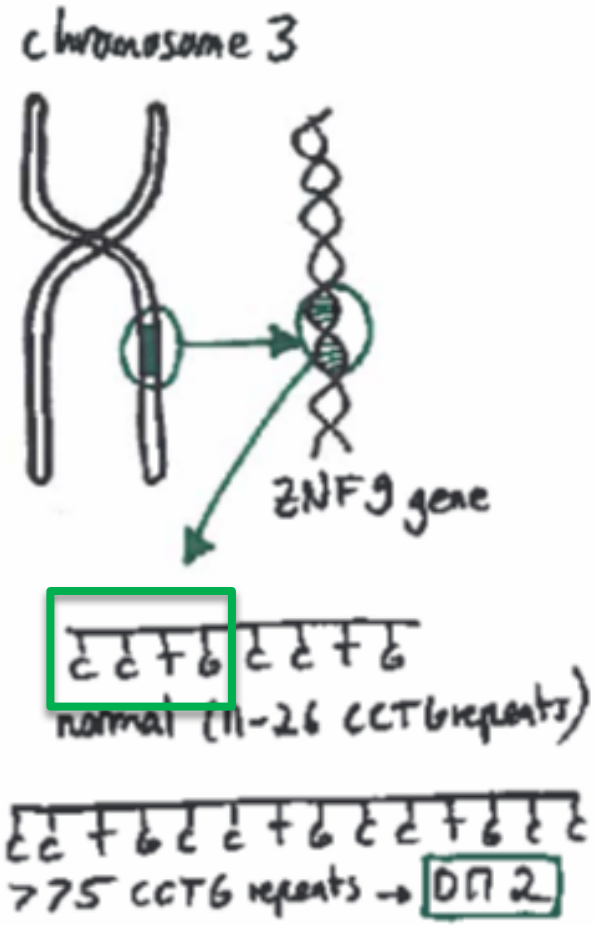
2 different chromosomes
2 different genes



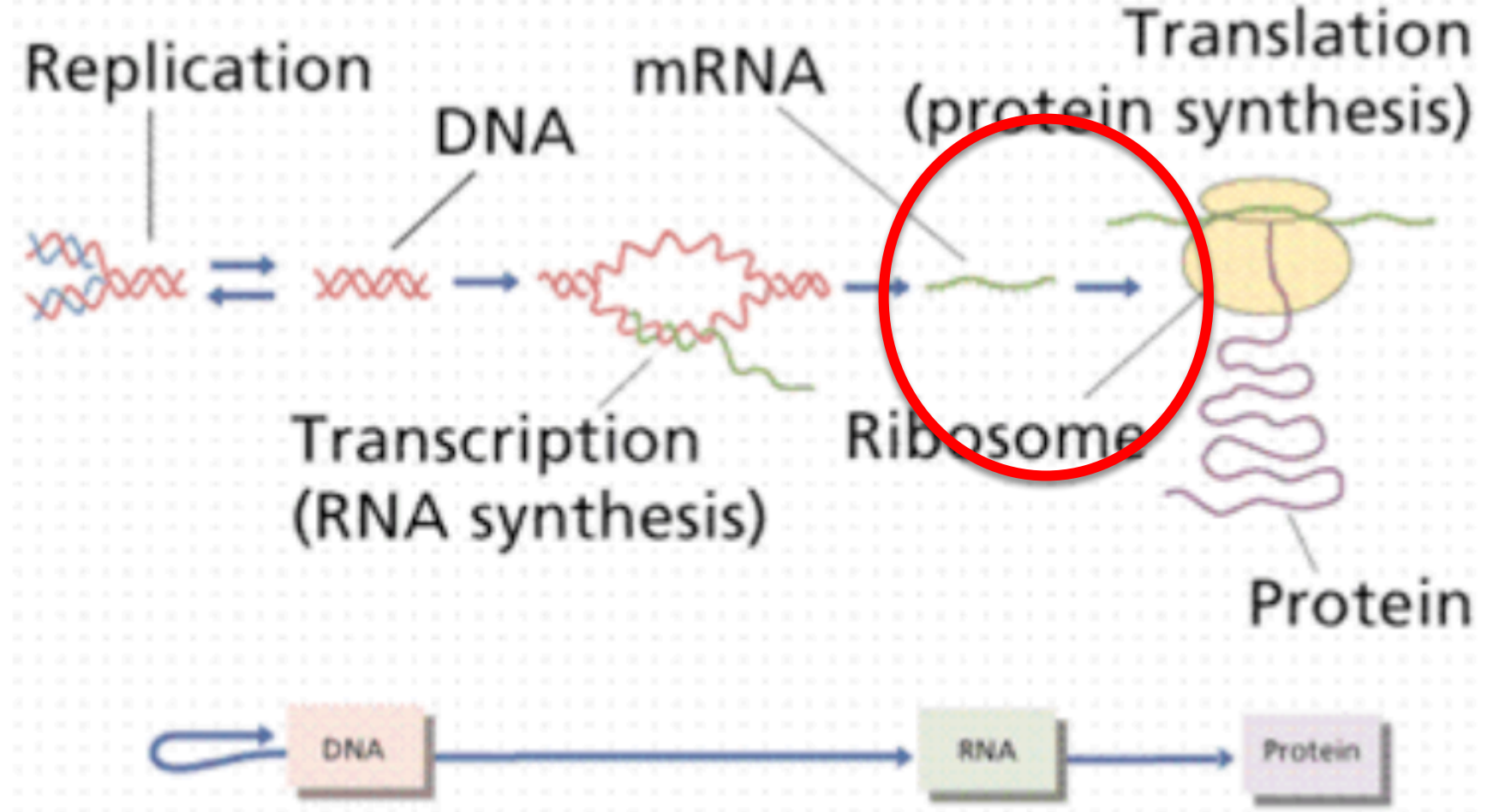
DM 1
CTG repeat expansion

DM2
CCTG repeat expansion

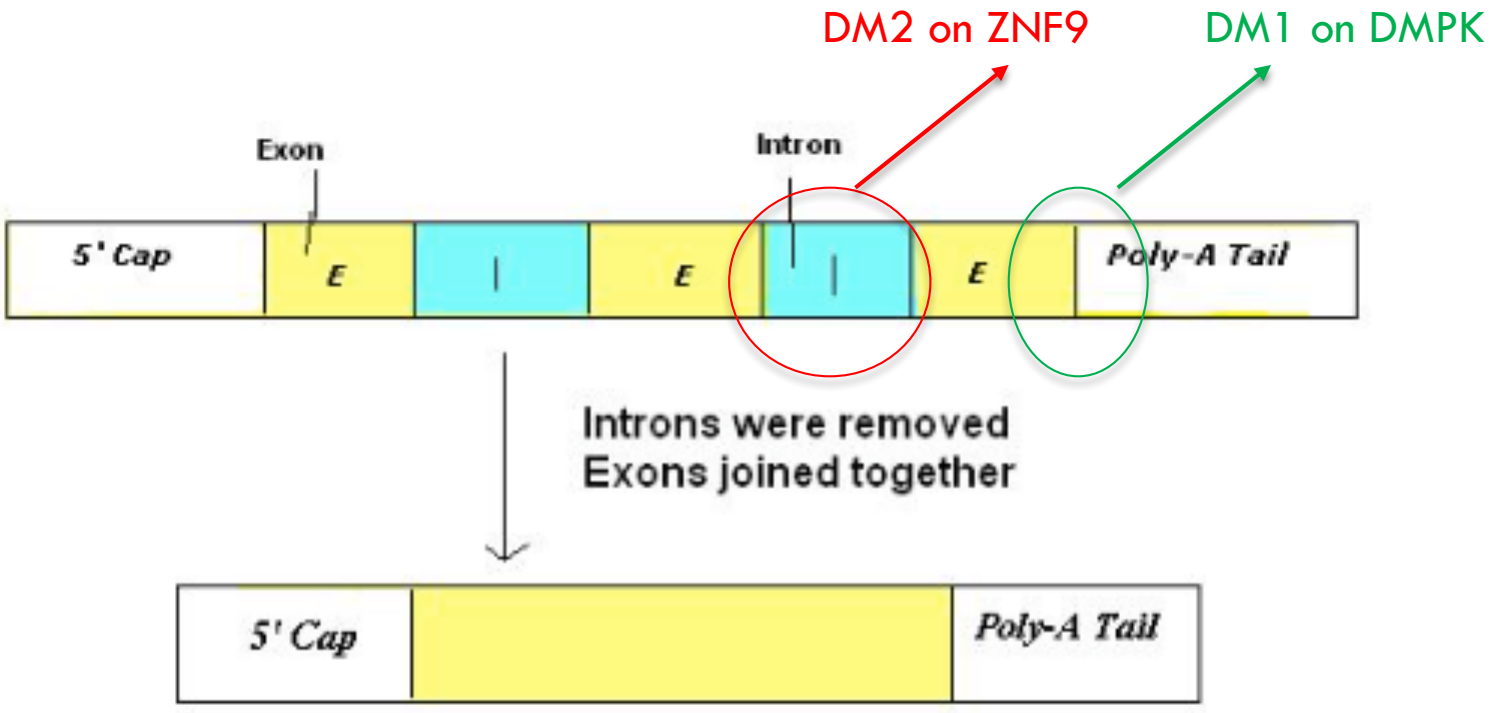




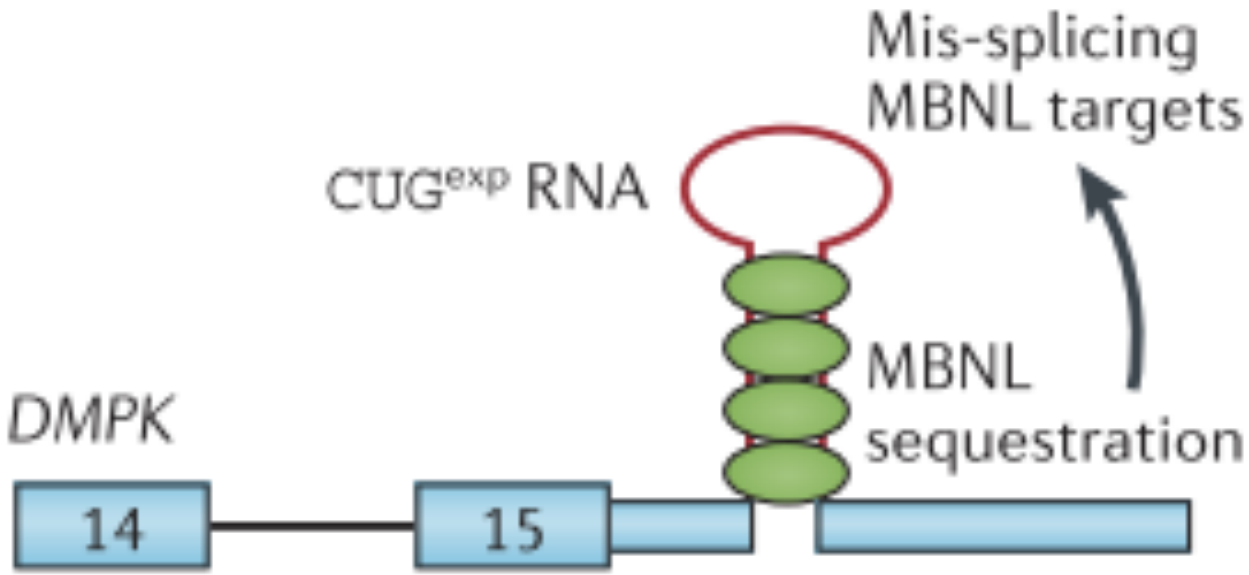
Review: DNA, RNA, and protein



Review: RNA Splicing

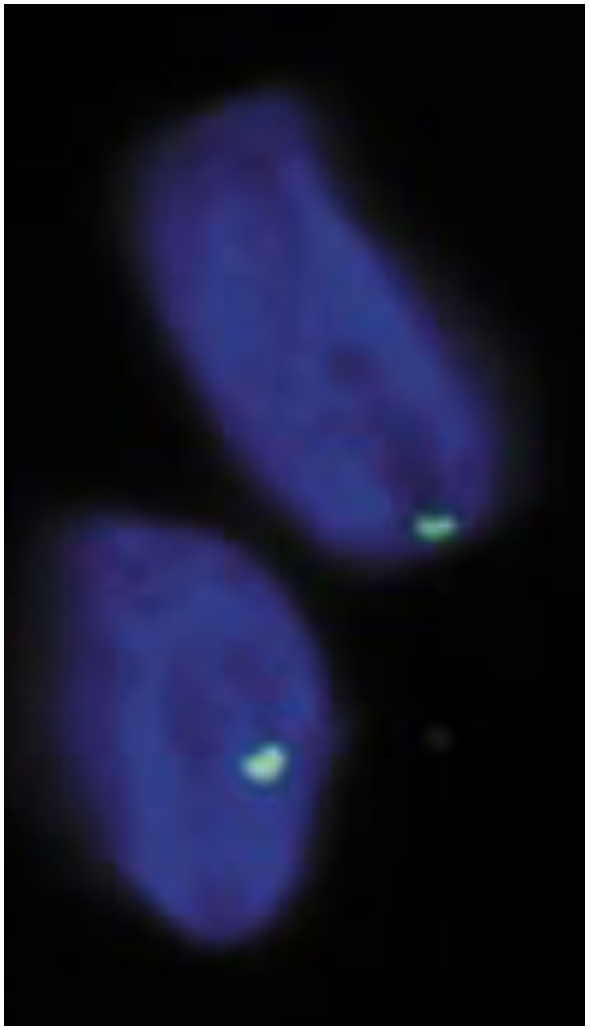


How does the repeat expansion cause a problem?



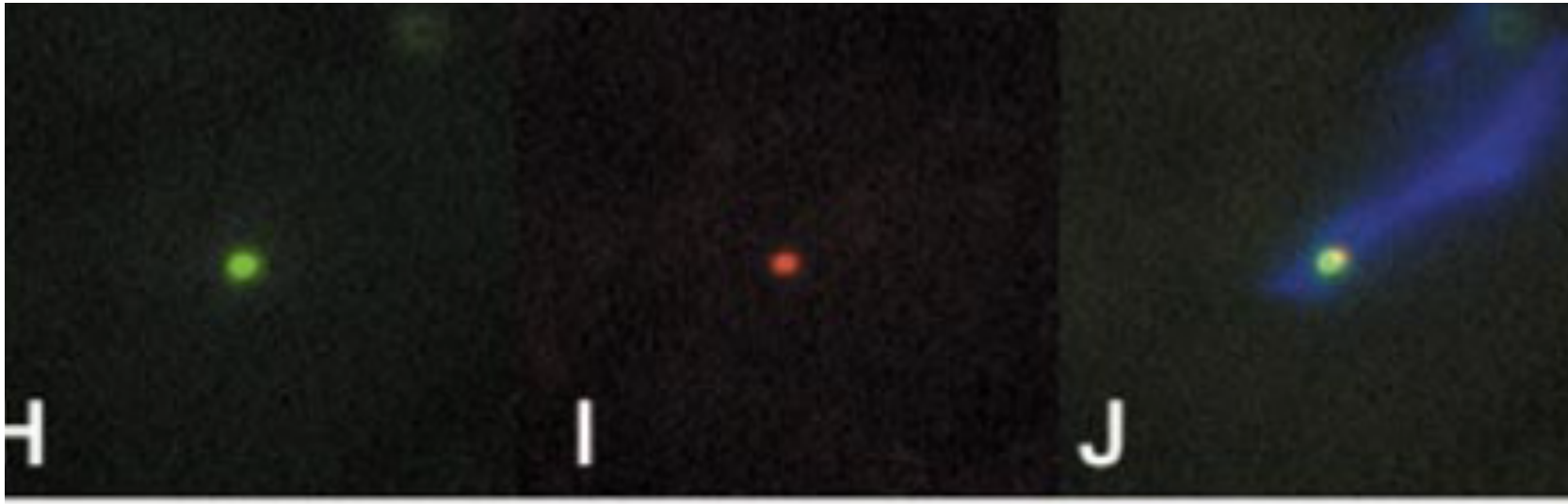
How does the repeat expansion cause a problem?

RNA toxicity

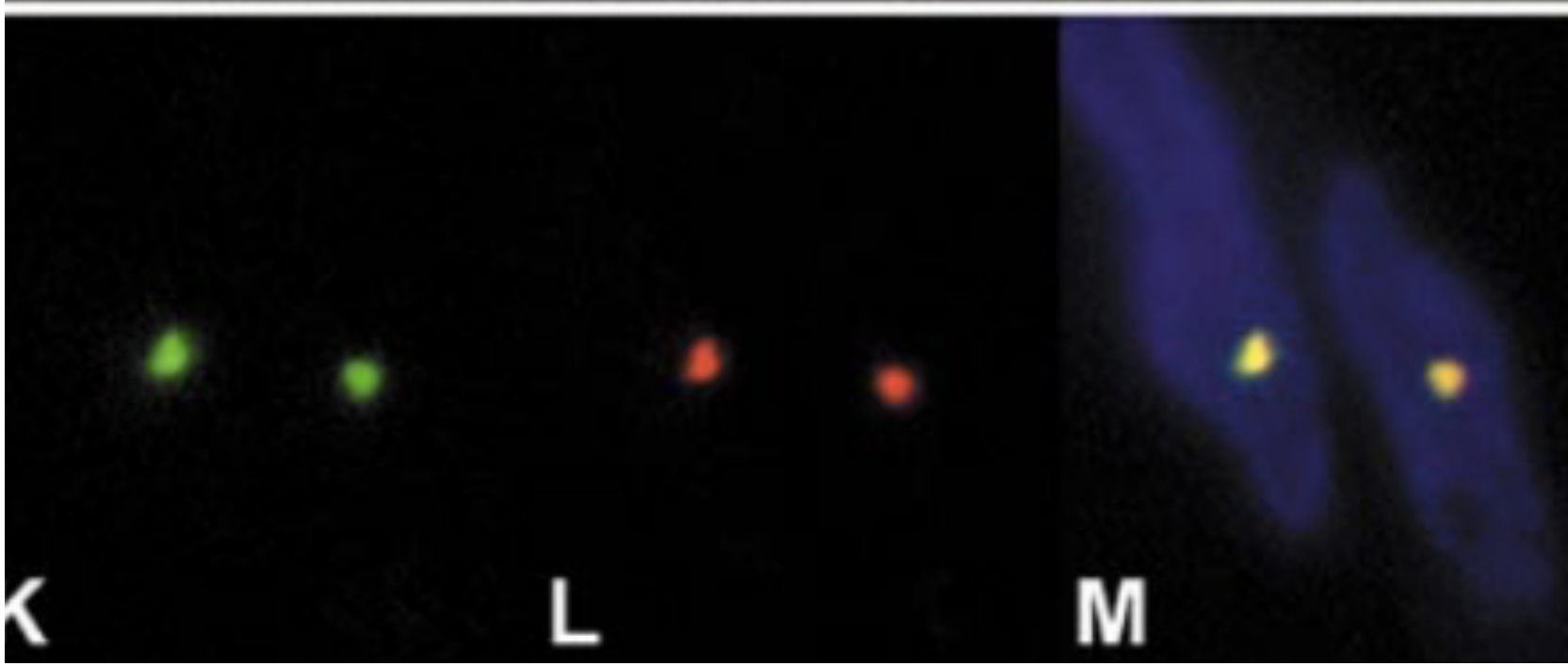


Mankodi et al. 2001

DM1



DM2



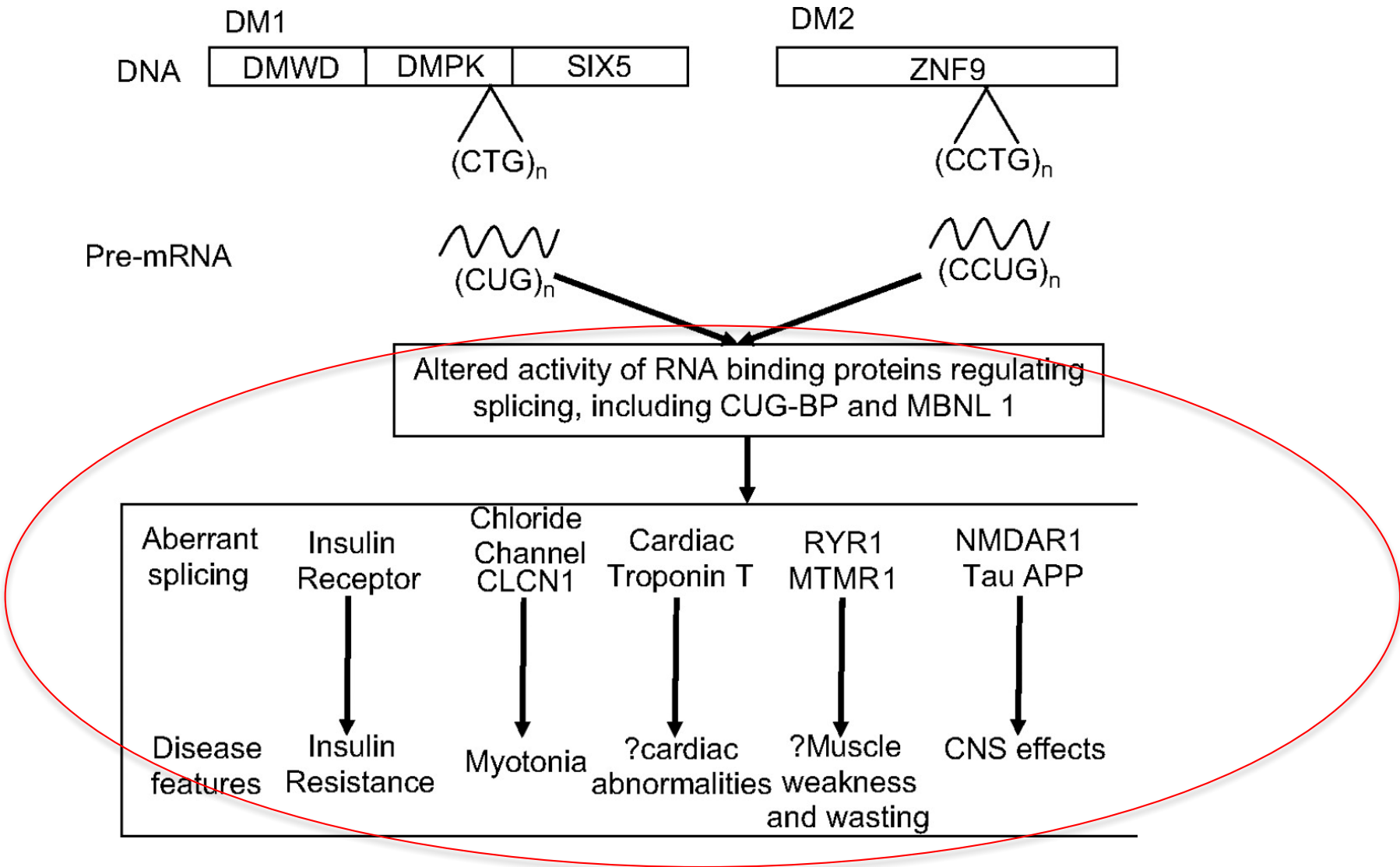
RNA

MBNL

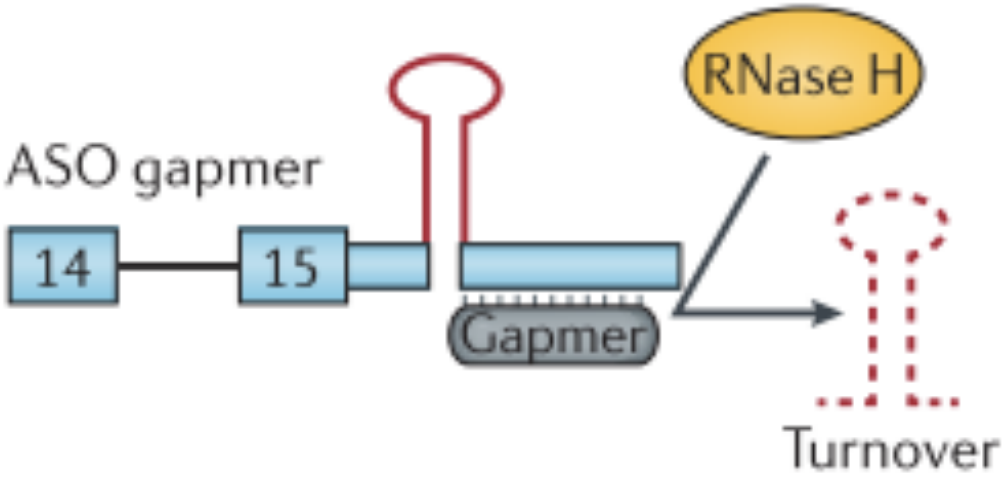
both

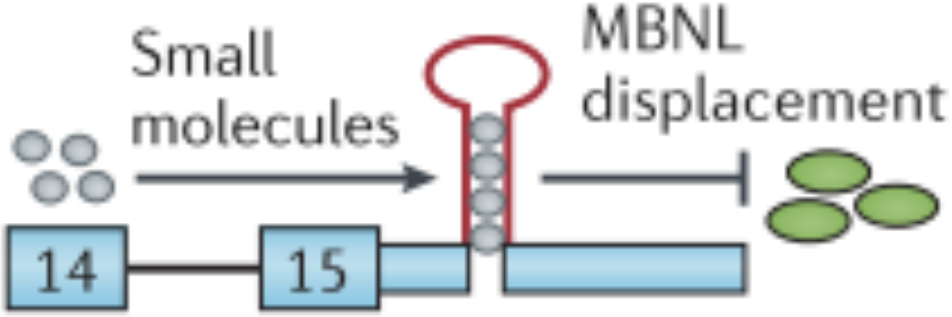
Mankodi et al. 2001

Splicopathy



Treatment Targets





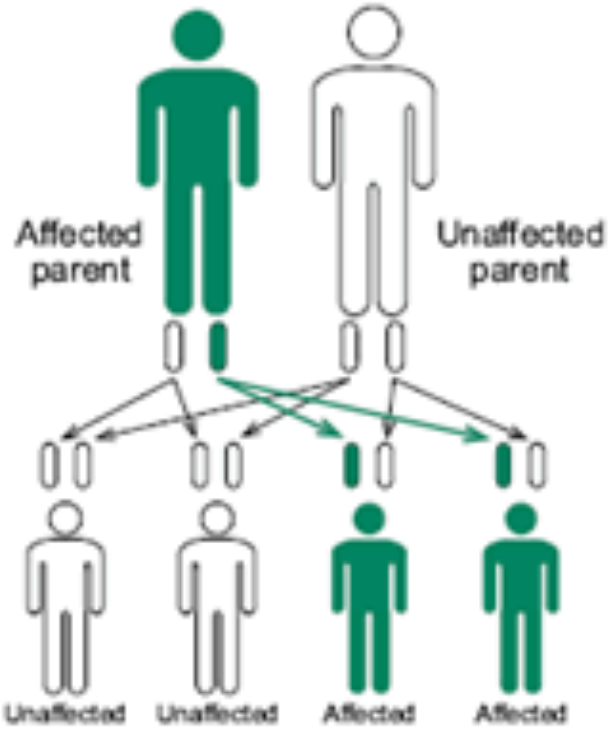
2 concepts to explain differences in disease severity

- 1. Anticipation

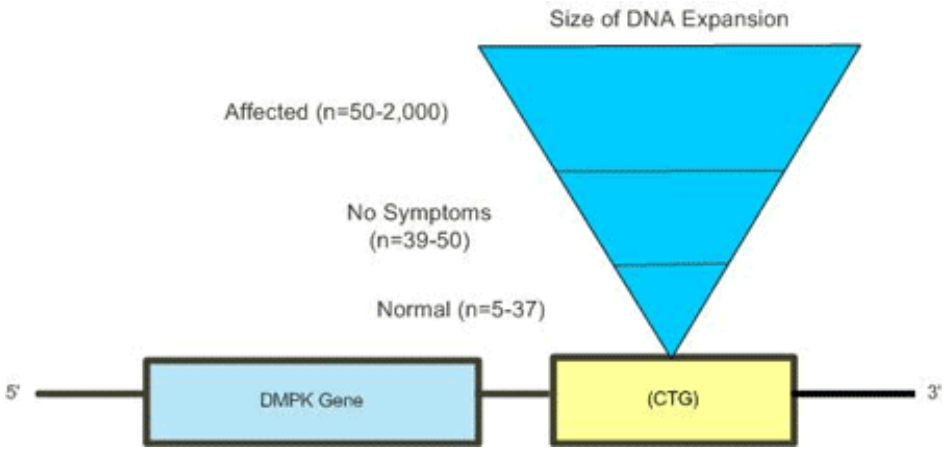
- 2. Somatic instability

How is DM inherited?

DM1 and DM2: autosomal dominant



DM1: Anticipation



Harper 2001

A few concepts to explain differences in disease severity

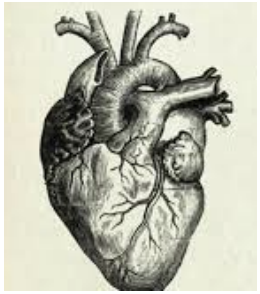
- 1. Anticipation

- 2. Somatic instability

DM1: Somatic Instability

- CTG repeat expansion size changes in some body tissues throughout a patients life

- This happens at different rates in different types of cells, which leads to variability of repeat length in different tissues within one individual



DM1: Somatic Instability

- Skeletal muscle: > 2,000 repeats by age 20,

40 years: average repeat length > 4,000 repeats, (3 to 25-fold larger than in blood)

- This may explain how the disease worsens in different ways in various organs over time.

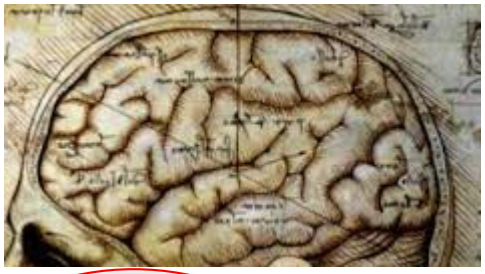
Myotonic dystrophy (Dystrophia Myotonica)

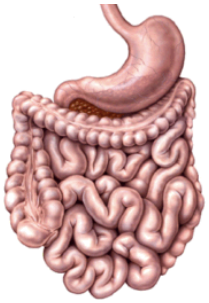
1. DM1 and DM2: 2 types of diseases

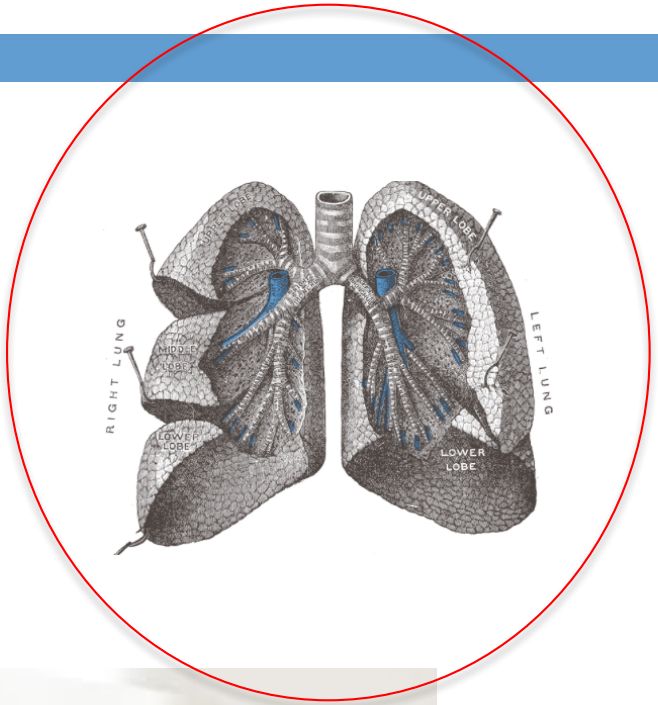
2. Inherited diseases caused by a genetic abnormality

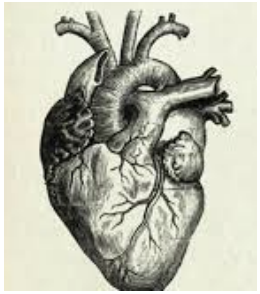
3. Multi-systemic diseases: not only the muscle is affected but multiple other organ systems

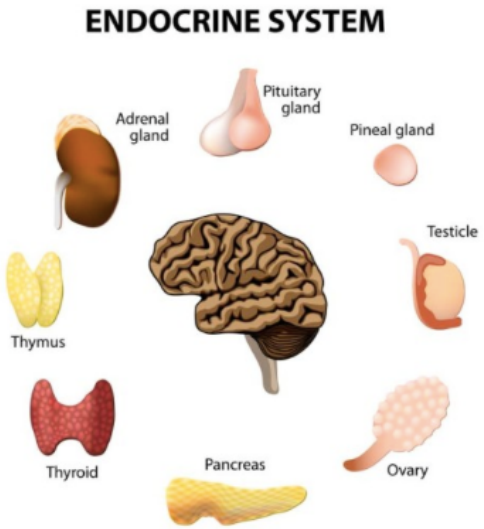
Multi-systemic Disease

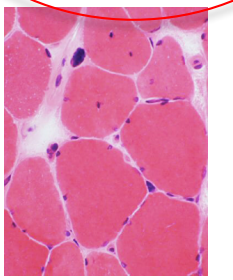


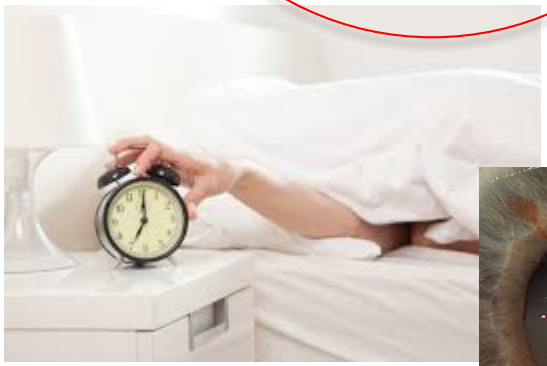


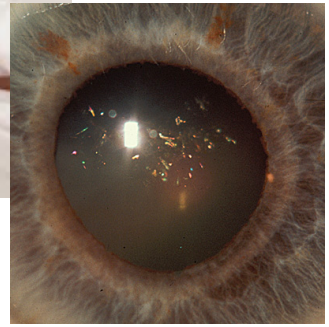




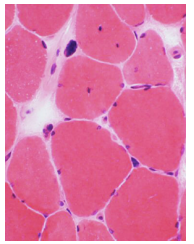






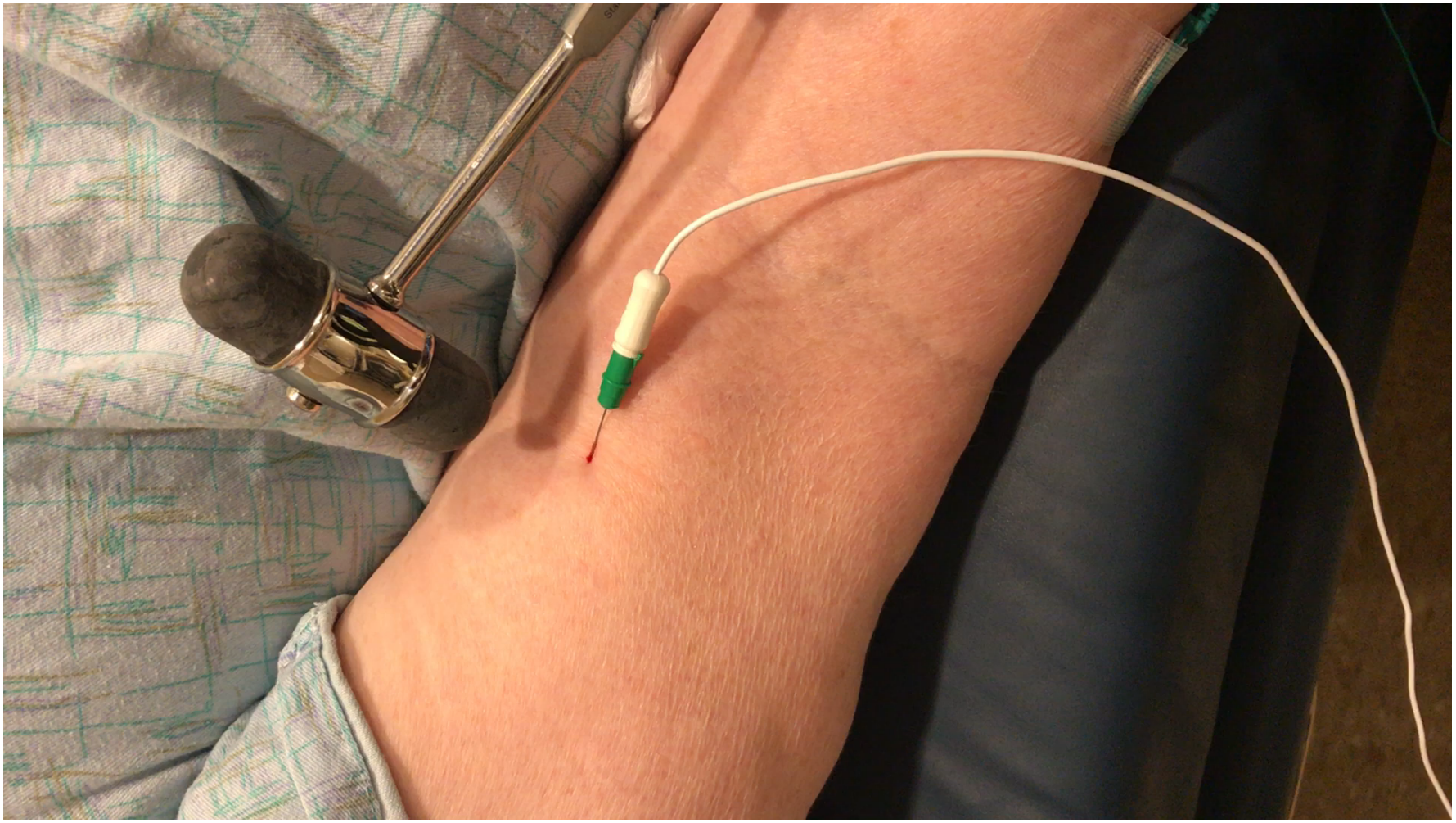


MUSCLE



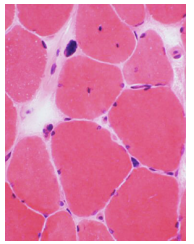
- Myotonia ("muscle stiffness") – delayed muscle relaxation

CONTINUUM 2012



Provided by Dr. Logigian

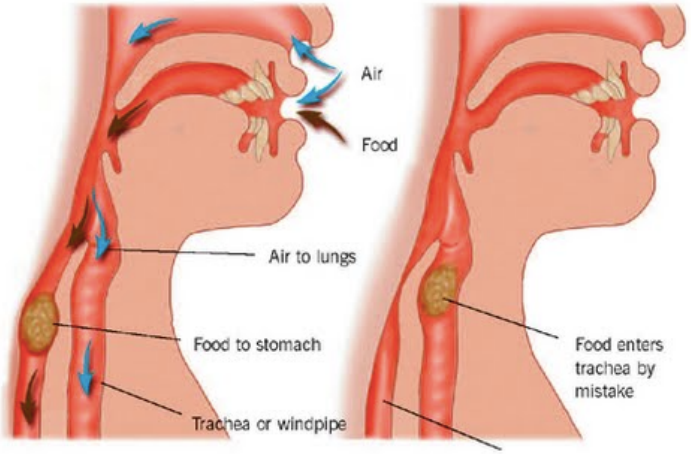
MUSCLE



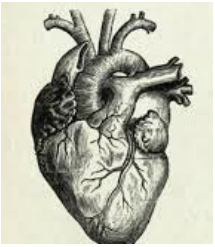
- Myotonia ("muscle stiffness") – delayed muscle relaxation

- Dystrophy – progressive weakness and loss of muscle mass

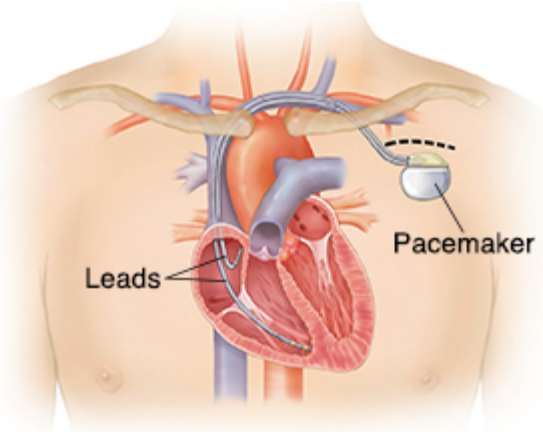
- Swallowing – difficulty swallowing with risk of aspiration and slurred



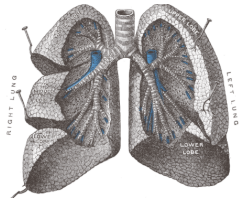
HEART



- Slow, fast or irregular heart beat
- Heart failure
- Can be present early with little other symptoms
- Yearly EKG
- Risk of sudden cardiac death



BREATHING



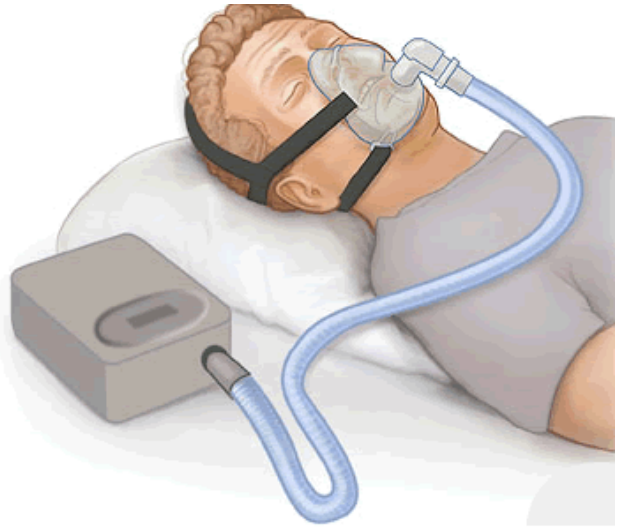
- Weakness of the diaphragm
- Disordered breathing in sleep

→

- Insufficient breathing at night (nocturnal hypoventilation)
- Monitoring breathing function

at clinic visits

- Assisted breathing at night

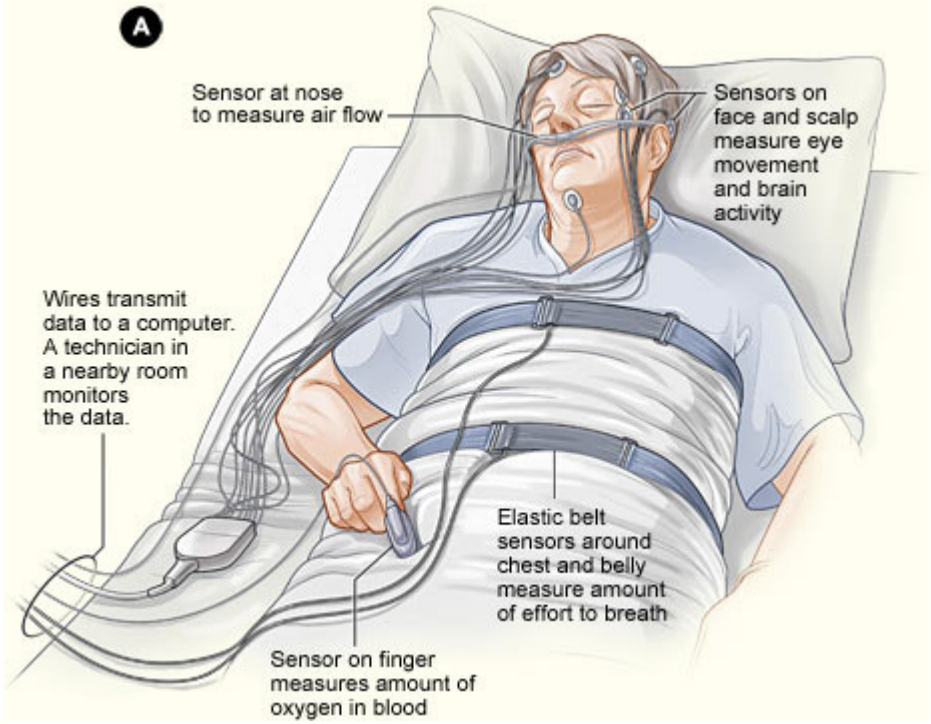


SLEEP/ hypersomnolence

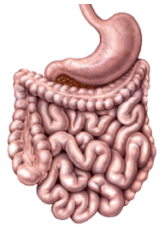
- Excessive daytime sleepiness
- Hypersomnia (sleeping too much)
- Sleep is not restorative
- Due to abnormal sleep regulation

→

- Sleep study

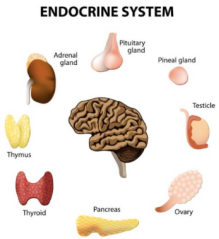


GASTROINTESTINAL SYMPTOMS



- risk of problems with gallbladder
- Bowel urgency with diarrhea, alternating with constipation (symptoms like irritable bowel syndrome)

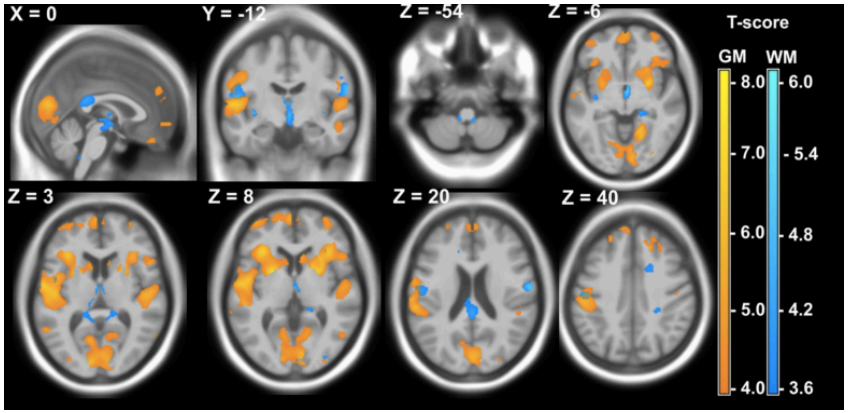
ENDOCRINE SYSTEM



- Difficulty with fertility (more common in men)
- Balding
- Insulin resistance (risk for diabetes)

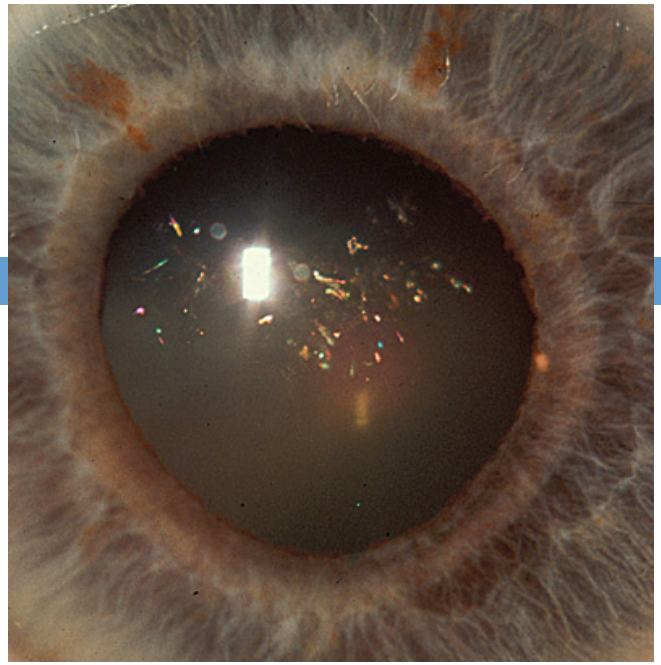
BRAIN

- Difficulty with problem solving
- Difficulty with emotions and behavior
- Changes on brain MRI



Gourdon, G and Meola, G. 2017

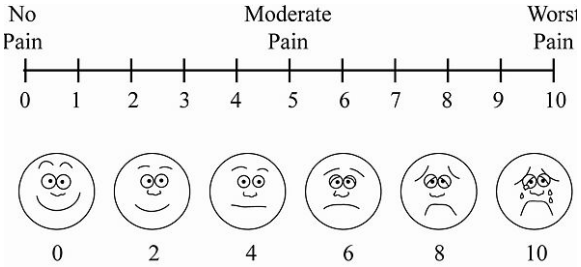
EYES - Cataract



- Cataract: clouding of the lens resulting in decreased vision
- In DM: Cataracts before age 55
- "Christmas tree cataract" – multicolored spots

Others

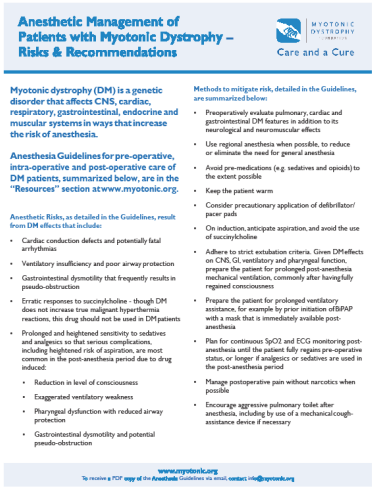
- **Pain:** DM2 > DM1



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

- **Anesthesia complications:**

www. myotonic.org



Anesthetic Management of Patients with Myotonic Dystrophy – Risks & Recommendations

Care and a Cure

Myotonic dystrophy (DM) is a genetic disorder that affects CNS, cardiac, respiratory, gastrointestinal, endocrine and muscular systems in ways that increase the risk of anesthesia.

Anesthesia Guidelines for pre-operative, intra-operative and post-operative care of DM patients, summarized below, are in the "Resources" section at www.myotonic.org.

Anesthetic Risks, as detailed in the Guidelines, result from DM effects that include:

- Cardiac conduction defects and potentially fatal arrhythmias
- Ventilatory insufficiency and poor airway protection
- Gastrointestinal dysmotility that frequently results in pseudo-obstruction
- Erratic responses to succinylcholine - though DM does not increase true malignant hyperthermia reactions, this drug should not be used in DM patients
- Prolonged and heightened sensitivity to sedatives and analgesics so that serious complications, including heightened risk of aspiration, are most common in the post-anesthesia period due to drug induced:
  - Reduction in level of consciousness
  - Exaggerated ventilatory weakness
  - Pharyngeal dysfunction with reduced airway protection
  - Gastrointestinal dysmotility and potential pseudo-obstruction

Methods to mitigate risk, detailed in the Guidelines, are summarized below:

- Preoperatively evaluate pulmonary, cardiac and gastrointestinal DM features in addition to its neurological and neuromuscular effects
- Use regional anesthesia when possible, to reduce or eliminate the need for general anesthesia
- Avoid pre-medications (e.g. sedatives and opioids) to the extent possible
- Keep the patient warm
- Consider precautionary application of defibrillator/ pacer pads
- On induction, anticipate aspiration, and avoid the use of succinylcholine
- Adhere to strict extubation criteria. Given DM effects on CNS, GI, ventilatory and pharyngeal function, prepare the patient for prolonged post-anesthesia mechanical ventilation, commonly after having fully regained consciousness
- Prepare the patient for prolonged ventilatory assistance, for example by prior initiation of BiPAP with a mask that is immediately available post-anesthesia
- Plan for continuous SpO2 and ECG monitoring post-anesthesia until the patient fully regains pre-operative status, or longer if analgesics or sedatives are used in the post-anesthesia period
- Manage postoperative pain without narcotics when possible
- Encourage aggressive pulmonary toilet after anesthesia, including by use of a mechanical cough-assistance device if necessary

www.myotonic.org
To receive a PDF copy of the Anesthesia Guidelines via email, contact: info@myotonic.org

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