DM 101: GETTING A HANDLE ON THE BASICS

Nicholas Johnson, MD, MSCI
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 CTG...
**Myotonic Dystrophy Type 1**

**CTG**

- **5-37 repeats**: No Myotonic Dystrophy
- **38-49 repeats**: No symptoms
- **~50-150 repeats**: Mild Myotonic Dystrophy
- **~100-1000 repeats**: Classic Myotonic Dystrophy
- **730-4300 repeats**: Congenital Myotonic Dystrophy

*Range where expansion is possible*
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
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”
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

CLCN1 mRNA

6

7a

7

CLCN1 pre-mRNA

6

7a

7

Decreased CIC-1 density (myotonia)

Retained fetal isoform

MBNL1

Normal splicing to adult isoform

CLCN1 mRNA

6

7

MBNL1 Sequestration in DM1

(CUG)_n

MBNL1

DMPK
Splicopathy

DNA

DM1

DMWD | DMPK | SIX5

CTG

(CTG)_n

DM2

ZNF9

CCTG

(CCTG)_n

Pre-mRNA

(CUG)_n

(CCUG)_n

Altered activity of RNA binding proteins regulating splicing, including CUG-BP and MBNL 1

Aberrant splicing

Insulin Receptor

Chloride Channel CLCN1

Cardiac Troponin T

RYR1

MTMR1

NMDAR1

Tau APP

Disease features

Insulin Resistance

Myotonia

?cardiac abnormalities

?Muscle weakness and wasting

CNS effects
Treatment Targets
Multi-systemic Disease
<table>
<thead>
<tr>
<th></th>
<th>DM 1</th>
<th>DM 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>common</td>
<td>Facial weakness</td>
<td>rare</td>
</tr>
<tr>
<td></td>
<td>common</td>
<td>Difficulty swallowing, speaking</td>
<td>rare</td>
</tr>
<tr>
<td></td>
<td>common</td>
<td>Difficulty breathing</td>
<td>rare</td>
</tr>
<tr>
<td></td>
<td>common</td>
<td>Heart problems</td>
<td>variable</td>
</tr>
<tr>
<td></td>
<td>rare</td>
<td>Pain</td>
<td>common</td>
</tr>
<tr>
<td></td>
<td>common</td>
<td>Difficulty thinking, memory</td>
<td>uncommon</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>Congenital form</td>
<td>No</td>
</tr>
</tbody>
</table>
How does it affect the muscles?

- **DM1—distal muscles**
  - Hands, ankles, but also neck

- **DM2—proximal muscles**
  - Hips and shoulders
- Myotonia ("muscle stiffness") – delayed muscle relaxation
- Myotonia ("muscle stiffness") – delayed muscle relaxation
- Dystrophy – progressive weakness and loss of muscle mass
- Swallowing – difficulty swallowing with risk of aspiration and slurred
How does it affect the eyes?

- Cataracts
  - “Christmas tree”
  - tinsel effect

www.neuro.wustl.edu/neuromuscular
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 recommendations
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](http://www.clinicaltrials.gov)
    - Registries
    - Surveys
    - Observational studies
    - Treatment studies