Virtual Support Group: Worthington, OH

4/7/20
6 - 7:30 pm EDT

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Myotonic Dystrophy: An Overview and Update

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Outline/Objectives

- Overview of current understanding of myotonic dystrophy
- Progress and ongoing needs
What is Myotonic Dystrophy?

- “Myotonic” muscle + tone
- “Dystrophy” degeneration

- Two types
  - Myotonic dystrophy type 1 (DM1)-later and early onset forms (congenital myotonic dystrophy)
  - Myotonic dystrophy type 2 (DM2)
Myotonic dystrophy is much more than a “muscular dystrophy”

- **Heart/Cardiac**
  - Usually a rhythm problem, not a pump problem
  - Can be asymptomatic until it isn’t
  - Routine screening is critical

- **Breathing/Pulmonary**
  - Apnea
  - Weak cough (weak muscles)

- **Eyes**
  - Cataracts

- **Gastrointestinal**
  - Swallowing, constipation, gallstones, IBS like symptoms

- **Endocrine**

- **Central Nervous System**
  - Cognitive problems, fatigue
Genetic Problem in DM1

- One copy of a genetic mutation in the *DMPK* gene
- Inherited from one parent
- Trinucleotide repeat Expansion
  - Expanded Cytosine, Thymine, Guanine (CTG) nucleotide repeats in *DMPK* gene
Effects of higher #’s of CTG repeats in *DMPK* gene

- Up to 37: No DM1
- 37-49: No Symptoms but can pass on mutation
- 50-150: Mild symptoms
- >150-1000: Typical “Classic” adult onset DM1
- >1000+: Congenital DM1
How do increased #’s CTG repeats cause DM1?

To understand how we might work on treatments for DM1, let’s first review a bit about genetics and DNA

“Everything must be made as simple as possible, but not one bit simpler” --A. Einstein
Genes and DNA

- Genes—instructions for cells how to make proteins or perform biological processes
- About 20,000 genes but not all make proteins
- Each cell has two copies of each gene
  - one from father, one from mother
- One copy of a \textit{DMPK} gene mutation results in DM1
  - Inherited from one parent
  - Autosomal dominant: means that having only one faulty copy of a gene results in a problem
-**Gene:** a “recipe” for making a proteins or performing a cellular process

-Each cell has the whole “cookbook” or **genome** but only uses certain genes

-Genes are made up of **DNA**

-A gene can make **different versions** of a particular protein

https://joyfoodsunshine.com/the-most-amazing-chocolate-chip-cookies/#wprm-recipe-container-8678
Genes to Proteins: How does it work?

“Cookie gene”

DNA
Pre-mRNA
mRNA

DNA Transcription

Alternative splicing

Translation

Protein 1: Chocolate Chip
Protein 2: Sugar
Protein 3: Peanut Butter
What causes DM1?

How do increased (expanded) CTG repeats in the \textit{DMPK} gene cause DM1?
RNA Foci and Trapped RNA binding proteins

DNA

Pre-mRNA

mRNA

RNA repeats-hairpin structures

Pettersson et al. 2015

doi.org/10.1016/j.drudis.2018.08.004
What happens to the “cookie” gene recipe in DM1?

The Best Chocolate Chip Cookie Recipe Ever
This is the best chocolate chip cookie recipe ever. No funny ingredients, no chilling time, etc. Just a simple, straightforward, amazingly delicious, doughy yet fully cooked, chocolate chip cookie that turns out perfectly every single time!

**Course**: Dessert  **Cuisine**: American  **Keyword**: best chocolate chip cookies, chocolate chip cookie recipe, chocolate chip cookies no chilling, easy chocolate chip cookie recipe

**Prep Time**: 10 minutes  **Cook Time**: 8 minutes  **Total Time**: 30 minutes  **Servings**: 36 cookies  **Calories**: 183 kcal  **Author**: Lauto

**Equipment**
- measuring spoons
- measuring cups
- KitchenAid Mixer
- spatula
- baking sheet

**Ingredients**
- 1 cup salted butter, softened
- 1 cup white (granulated) sugar
- 1 cup light brown sugar packed
- 2 tsp pure vanilla extract
- 2 large eggs
- 3 cups all-purpose flour
- 1 tsp baking soda
- 1 tsp baking powder
- 1 tsp sea salt
- 2 cups chocolate chips (or chunks, or chopped chocolate)
**Transcription:** (making an RNA copy of DNA)

**Splicing:** Trimming the copy (RNA)

**Translation:** making the protein
Multisystem effects:
Mis-splicing of different targets in different tissues

RNA Binding Proteins
Other possible mechanisms of DM1

- RAN translation
- Loss of DMPK gene function
- Inactivation of other nearby genes
- Others?
Possible Strategies for Genetic Treatments

- Decrease (or stabilize) CTG repeats in DNA
- Decrease RNA Foci
  - Decrease transcription of RNA repeats
  - Block interaction between RNA binding proteins and RNA repeats
  - Break up RNA repeats
- Others
  - Increase levels of RNA binding proteins
Ongoing Needs/Gaps

- Better animal models
  - Ideal models will replicate multisystem problems to allow testing of preclinical treatments on problems that matter most.

- Natural history studies
  - Understanding the variability between individuals
    - Are there factors (genetic or otherwise) that improve outcomes/prognosis?
  - Better understanding the different symptoms of DM1?
    - What symptoms matter most and how can we best track these symptoms in a reliable way (in clinical trials)?
Myotonic Dystrophy: Study & Trial Resource Center

Our community is involved in the first clinical trial of a targeted therapy for myotonic dystrophy, and a number of other critical studies are underway. Click on the links below and to the right to learn more about the clinical trials process, important do's and don'ts for current trial participants, and more. A list of current studies and trials can be accessed below.

Myotonic community members have been active partners in bringing the research to this point, by supporting and participating in studies, joining registries, responding to surveys, and funding patient advocacy organizations like Myotonic. The progress achieved would not be possible without the commitment and participation of people living with DM, their families, caregivers and friends.
OSU DM1
Nutrition Study
Dr. Samantha LoRusso
Nutrition study

- Muscle weakness, difficulty swallowing and gastrointestinal effects of the disease put people at risk for nutritional deficiencies.
- This study evaluates the nutritional status in people with myotonic dystrophy versus age-matched controls.
What does the study involve?

• Fasting labs
• Food questionnaire
• Resting energy expenditure calculated
• DEXA scan to evaluate lean body mass

Takes ~3 hours to complete, one-time visit
Who can be involved?

- Age 18-60
- Must have someone living in the same house willing to do the study who does not have myotonic dystrophy (to serve as a ‘control’)
Thank You