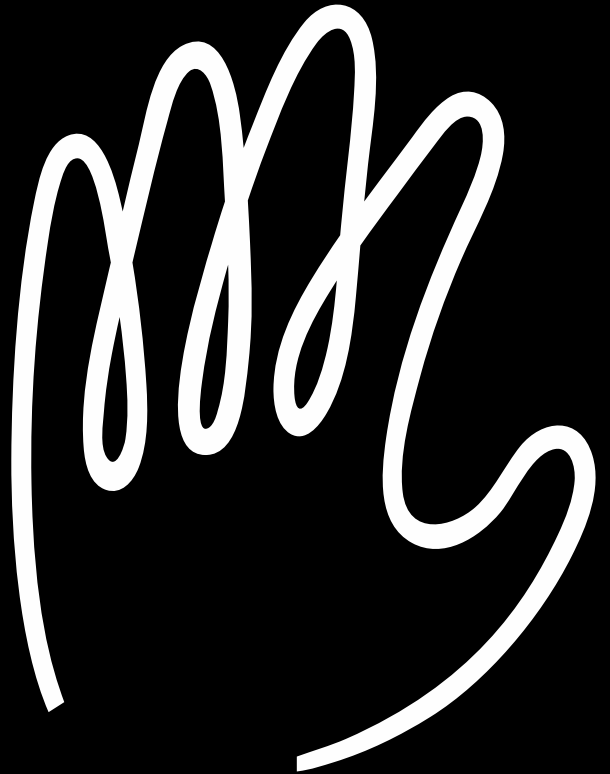


Virtual Support Group:
Worthington, OH

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

Phone: (631) 992-3221
Code: 353-903-853

Myotonic





Myotonic Dystrophy: An Overview and Update

W. David Arnold, MD

April 7, 2020



Outline/Objectives

- Overview of current understanding of myotonic dystrophy
- Progress and ongoing needs



What is Myotonic Dystrophy?

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

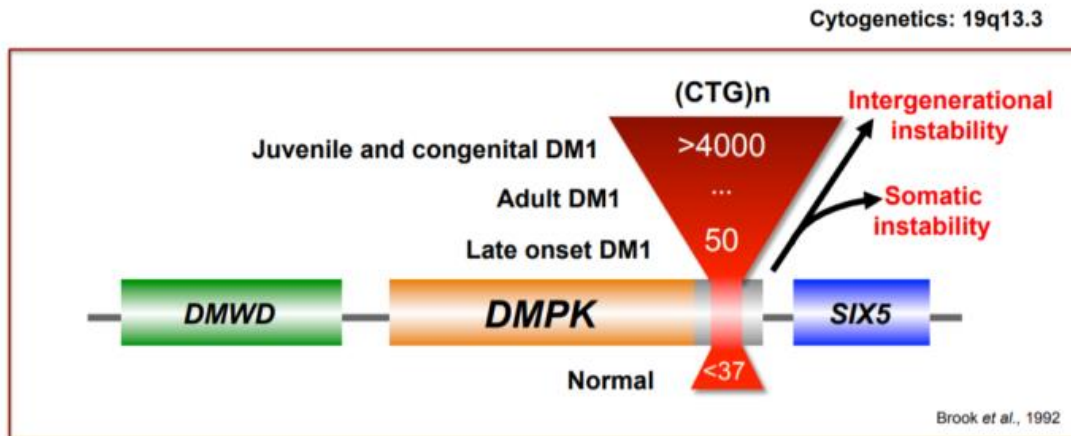
- **Two types**
 - **Myotonic dystrophy type 1 (DM1)**-later and early onset forms (congenital myotonic dystrophy)
 - **Myotonic dystrophy type 2 (DM2)**

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

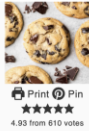
“Everything must be made as simple as possible, but not one bit simpler” --A. Einstein

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 *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

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 still 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	183kcal
👤 Author	Laura

Equipment

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

Ingredients

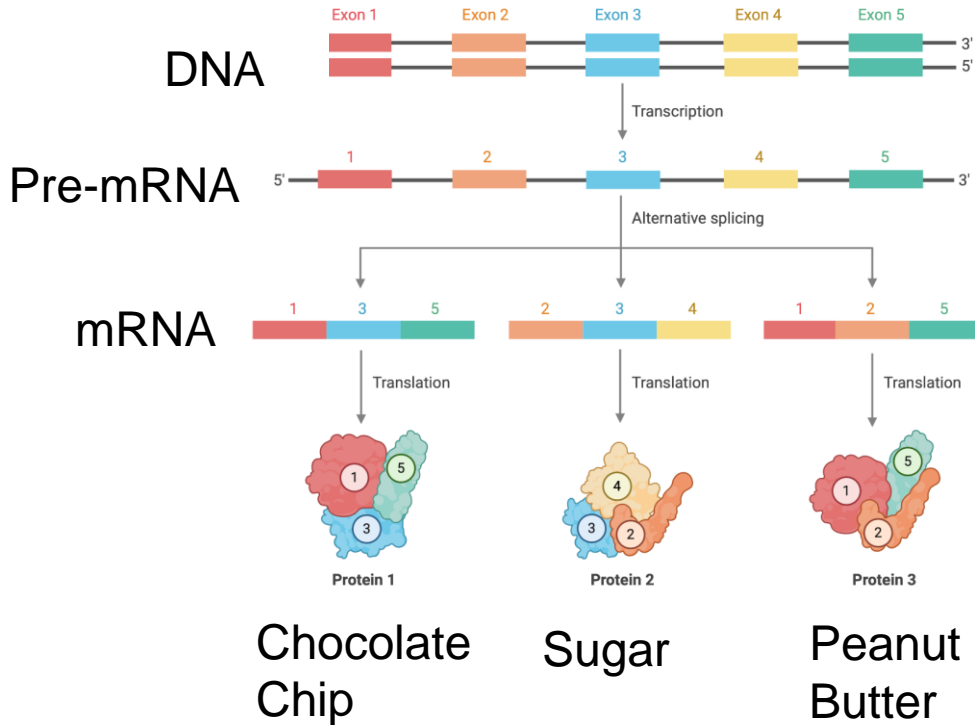
- 1 cup salted butter* softened
- 1 cup white (granulated) sugar
- 1 cup light brown sugar packed
- 2 tsp pure vanilla extract
- 2 large eggs
- 3 cups all-purpose flour
- 1 tsp baking soda
- ½ tsp baking powder
- 1 tsp sea salt***
- 2 cups chocolate chips (or chunks, or chopped chocolate)



- 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

Genes to Proteins: How does it work?

“Cookie gene”

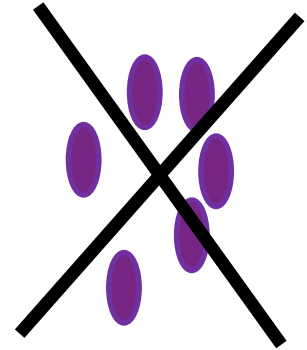
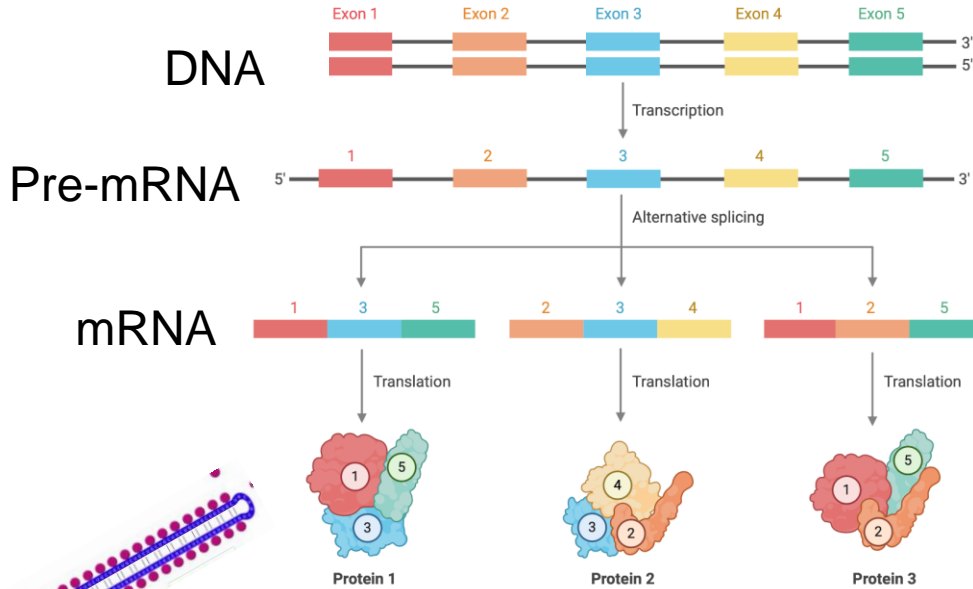


RNA
Binding
Proteins

What causes DM1?

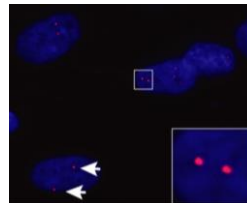
How do increased (expanded) CTG repeats in the *DMPK* gene cause DM1?

RNA Foci and Trapped RNA binding proteins



RNA
Binding
Proteins

RNA repeats-
hairpin structures












Petterson et al. 2015

doi.org/10.1016/j.drudis.2018.08.004

What happens to the “cookie” gene recipe in DM1?

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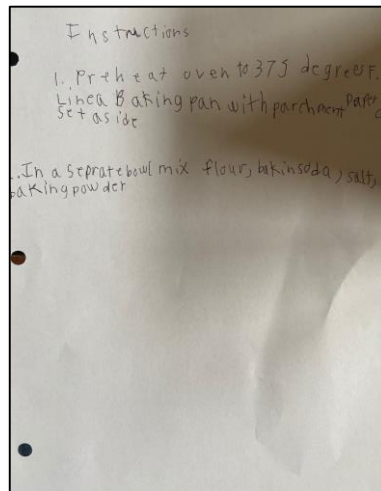
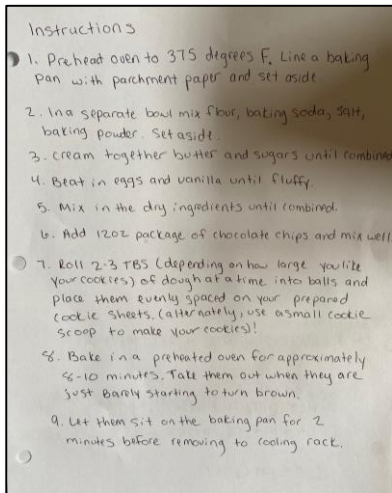
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Transcription: (making an RNA copy of DNA)

Splicing: Trimming the copy (RNA)

Translation: making the protein

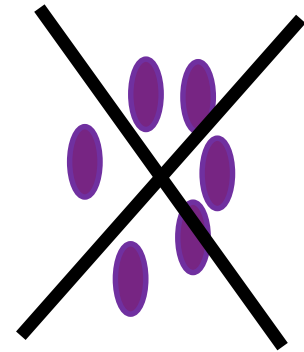


Mis-splicing

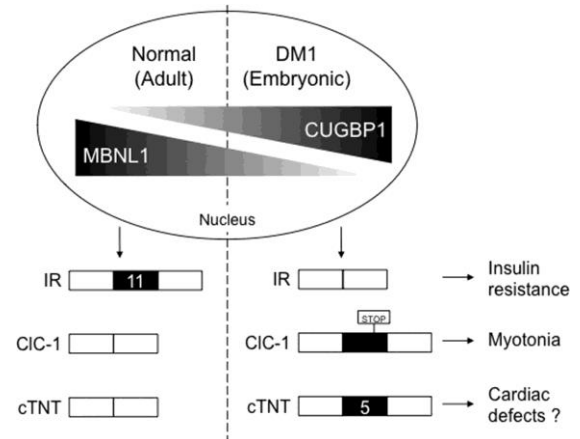
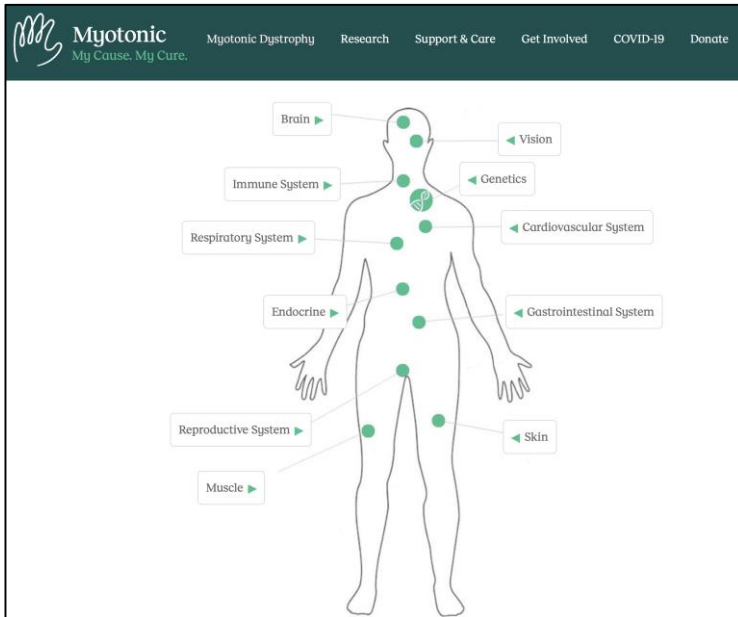


Multisystem effects:

Mis-splicing of different targets in different tissues



RNA Binding Proteins

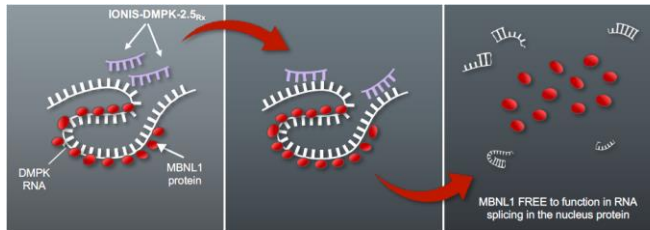


Other possible mechanisms of DM1

- 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
My Cause. My Cure.

Myotonic Dystrophy

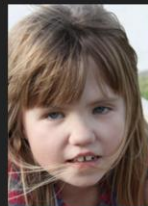
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FOR RESEARCHERS

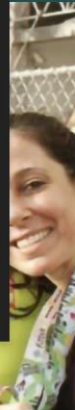
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Myotonic Dystrophy: Study & Trial Resource Center

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.

Myotonic Dystrophy News

March 23, 2020

[Respiratory Care Recommendations for Myotonic Dystrophy Patients During the COVID-19 Pandemic](#)

We understand that this is a very challenging time and we would like to provide tips for patients, caregivers, and medical providers on the use of noninvasive positive pressure ventilation (NIPPV) if you have been exposed to this virus or have symptoms of COVID-19 infection.

March 20, 2020

[A Message from Myotonic's CEO about COVID-19](#)

Residents of the Bay Area in California, including Myotonic staff, are under strict Public Health orders to Shelter in Place for the next several weeks. We want to be sure you know that all Myotonic staff are prepared for this shift and have been successfully working from home. Myotonic is open, our website is active, and our resources are available.

March 20, 2020

[Myotonic Publishes Clinical Care Recommendations for Cardiologists](#)

10 leading DM1 cardiologists in Canada, Japan, Western Europe, the United Kingdom, and the United States joined Myotonic to create the Consensus-based Care Recommendations for Cardiologists Treating Adults with Myotonic Dystrophy Type 1.

March 20, 2020

[2020 Congressional Leadership Award & Advocacy Update](#)

The 2020 Myotonic Congressional Leadership Award was presented to Rep. Adam Schiff, an early supporter of our efforts to add myotonic dystrophy to the DoD's Peer Reviewed Medical Research Program (PRMRP) who recently

<https://www.myotonic.org/study-trial-resource-center>

The background of the slide is white and decorated with various colorful illustrations of fruits and vegetables. These include a blueberry cluster, an orange slice, a green leaf, a watermelon slice, a lime, a lemon, an avocado, a banana, a strawberry, a kiwi slice, an orange, and a cherry. Each illustration is rendered in a simple, stylized line-art style with flat colors.

OSU DM1 Nutrition Study

Dr. Samantha LoRusso

Nutrition study

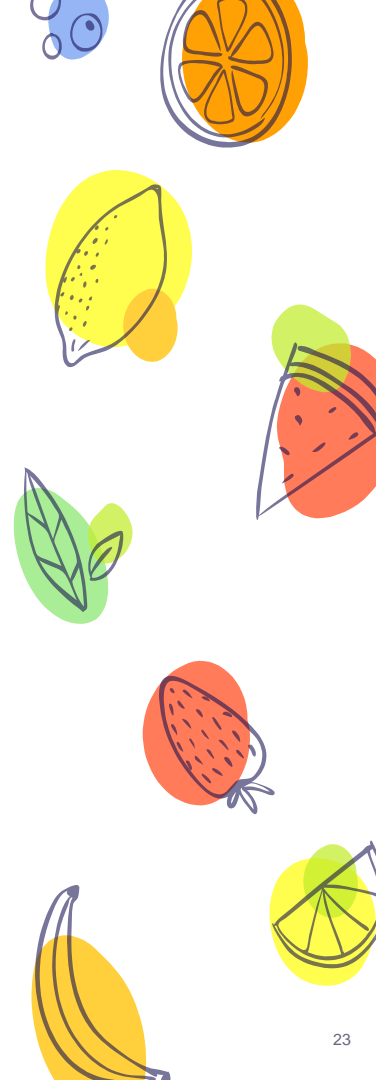
- Muscle weakness, difficulty swallowing and gastrointestinal effects of the disease put people at risk for nutritional deficiencies
- This study evaluates the nutritional status in people with myotonic dystrophy versus age-matched controls



What does the study involve?

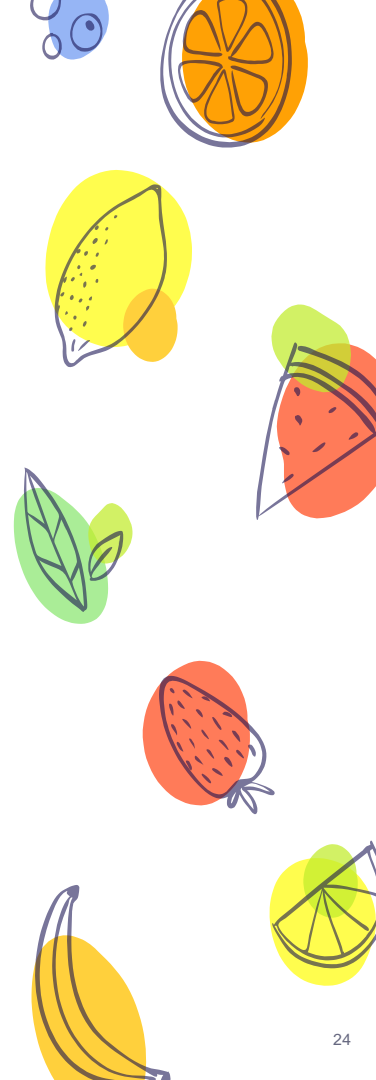
- Fasting labs
- Food questionnaire
- Resting energy expenditure calculated
- DEXA scan to evaluate lean body mass

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

