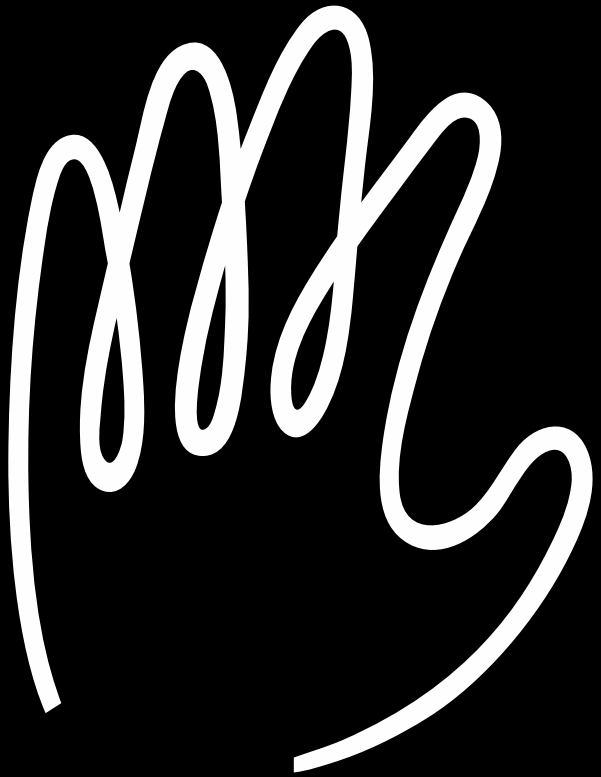
Virtual Support Group:
Worthington, OH

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

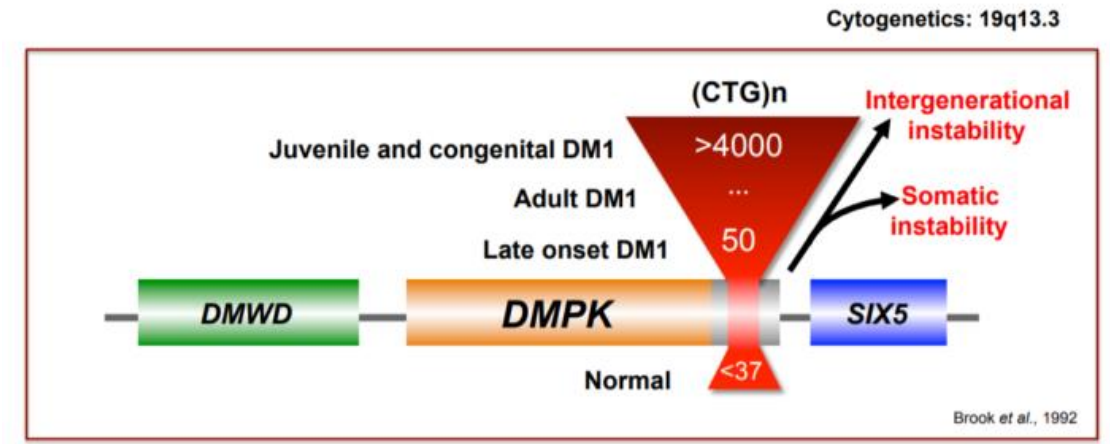
- **Two types**
  - **Myotonic dystrophy type 1** (DM1)-later and early onset forms (congenital myotonic dystrophy)
  - **Myotonic dystrophy type 2** (DM2)

# 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 **C**ytosine, **T**hymine, **G**uanine (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!

Print Pin

★★★★★

4.93 from 610 votes

**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

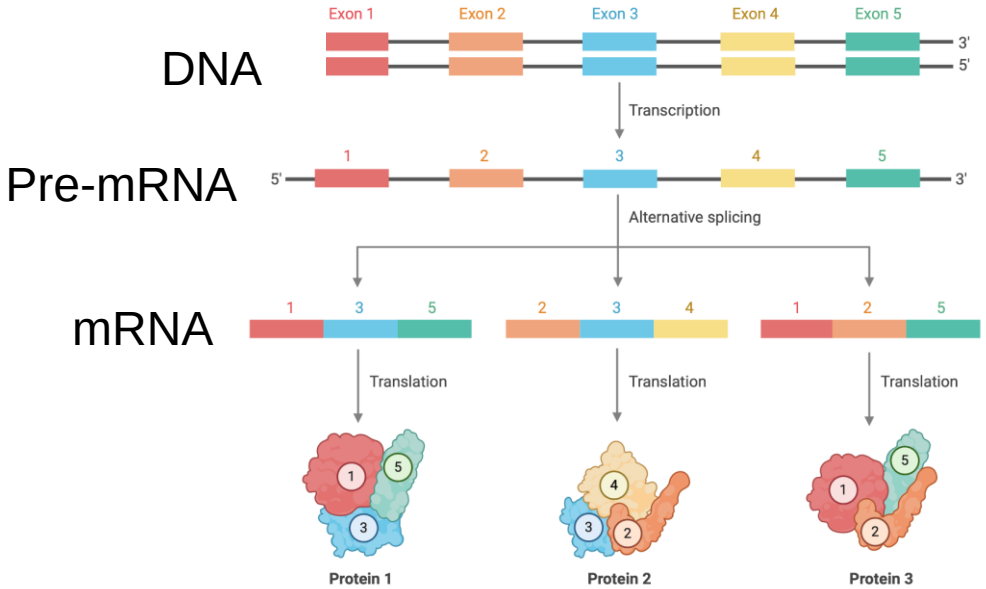
-Genes are made up of DNA

-A gene can make different versions of a particular protein

https://joyfoodsunshine.com/the-most-amazing-chocolate-chip-cookies/#wprm-recipe-container-8678

# Genes to Proteins: How does it work?

## “Cookie gene”




Chocolate Chip

Sugar

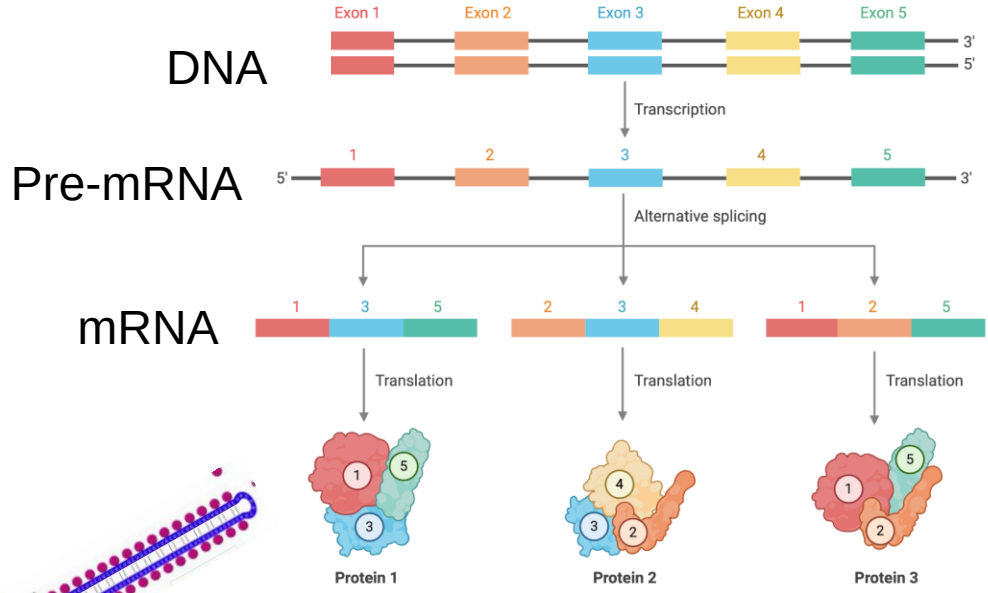
Peanut Butter

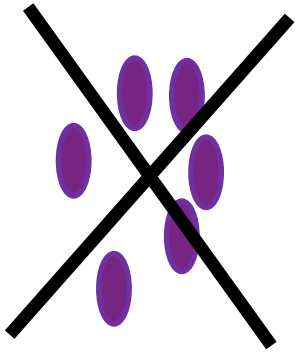
RNA Binding Proteins

# What causes DM1?

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

# RNA Foci and Trapped RNA binding proteins

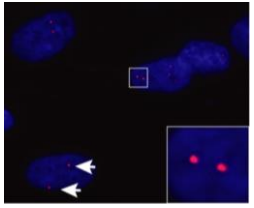


RNA Binding Proteins



RNA repeats- hairpin structures



Pettersson 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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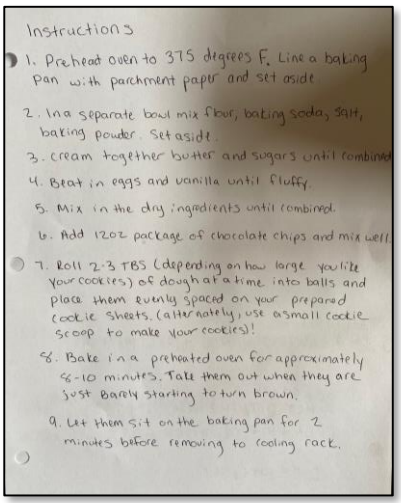
https://joyfoodsunshine.com/the-most-amazing-chocolate-chip-cookies/#wprm-recipe-container-8678

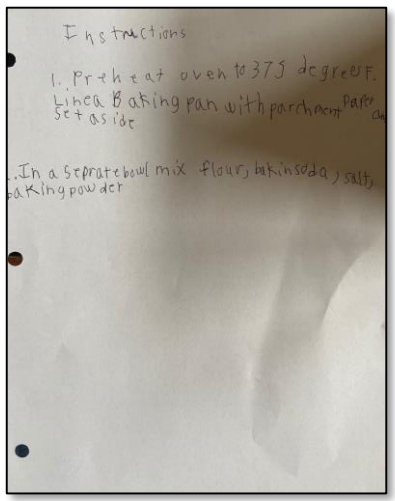
**Transcription:** (making an RNA copy of DNA)

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

**Translation:** making the protein


Instructions

1. Preheat oven to 375 degrees F. Line a baking pan with parchment paper and set aside.
2. In a separate bowl mix flour, baking soda, salt, baking powder. Set aside.
3. Cream together butter and sugars until combined.
4. Beat in eggs and vanilla until fluffy.
5. Mix in the dry ingredients until combined.
6. Add 12oz package of chocolate chips and mix well.
7. Roll 2-3 TBS (depending on how large you like your cookies) of dough at a time into balls and place them evenly spaced on your prepared cookie sheets. (alternately, use a small cookie scoop to make your cookies)!
8. Bake in a preheated oven for approximately 8-10 minutes. Take them out when they are just barely starting to turn brown.
9. Let them sit on the baking pan for 2 minutes before removing to cooling rack.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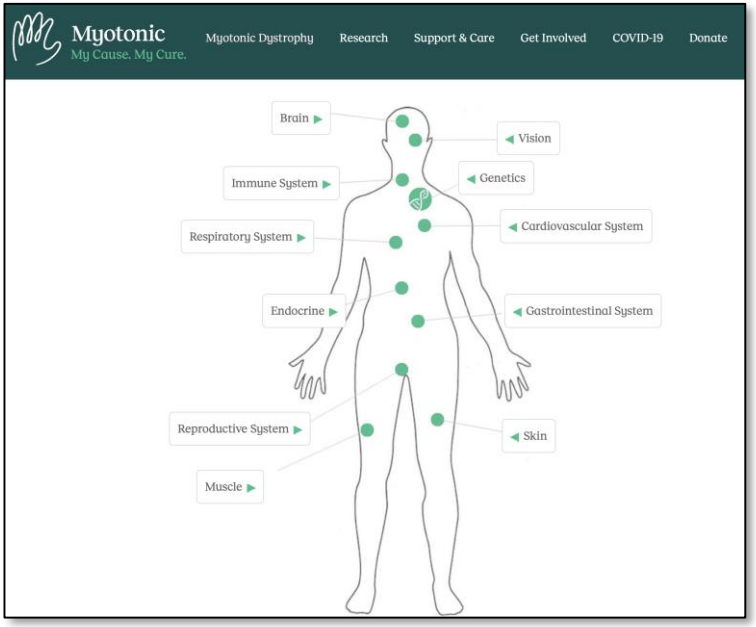
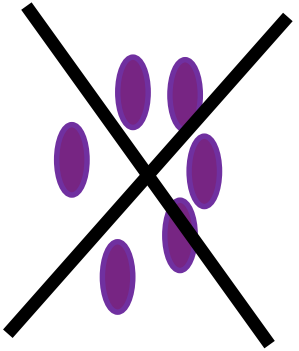
.In a seprate bowl mix flour, bakinsoda, salt, baKing powder

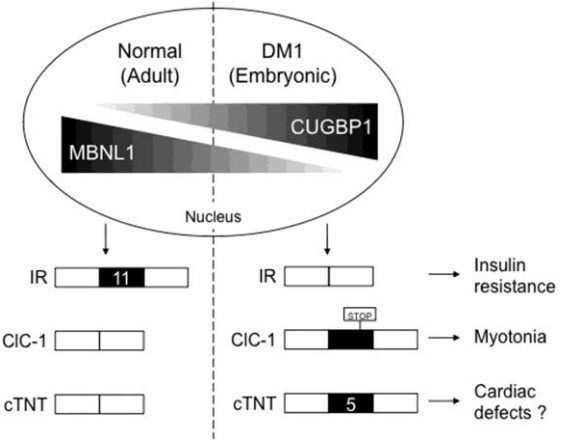
Mis-splicing

**Multisystem effects:**
Mis-splicing of different targets in different tissues



RNA Binding Proteins

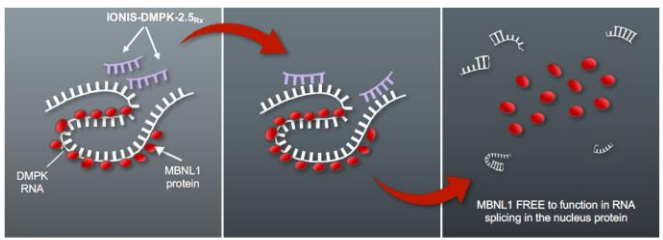


# Other possible mechanisms of DM1

- 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




Cooper, T.. (2009) *Science*, 325:272-273

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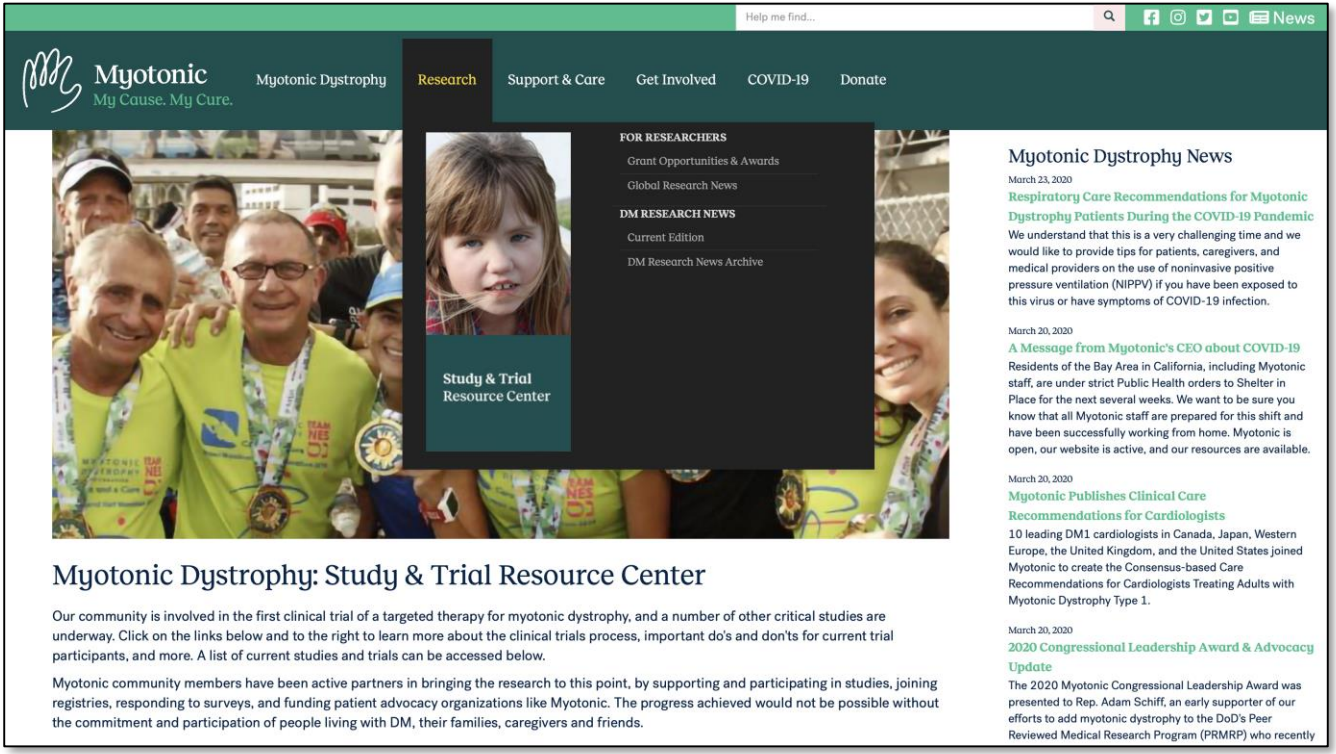
# Ongoing Needs/Gaps

- **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)?




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

# OSU DM1 Nutrition Study

Dr. Samantha LoRusso

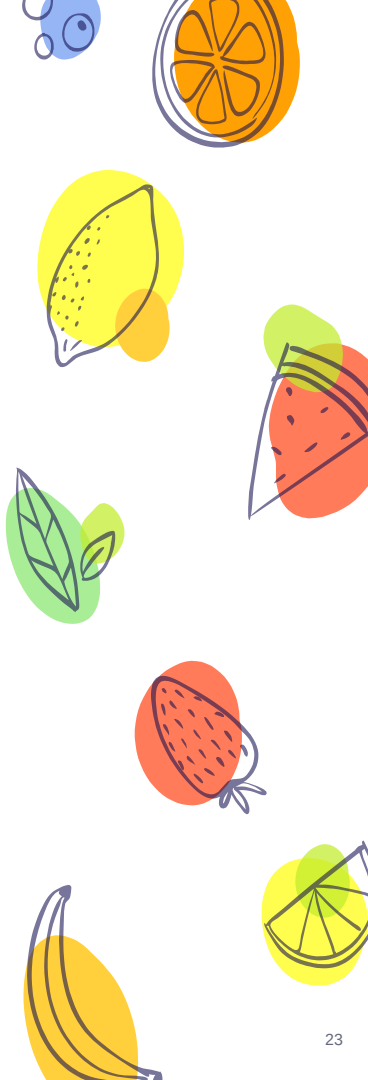
# Nutrition study

- 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