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HST.161 Molecular Biology and Genetics in Modern Medicine
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Lecture 14

Myotonic Dystrophy

Genetic basis of myotonic dystrophy:

Type 1: CTG repeats; normal is 5-30, 50-80 is mild, more than 2000 is severe

Type 2: specifics?

CUG repeats form intranuclear foci

“Expansion42” (Exp42) binds to CUG repeats

Mbnl1 (muscle blind – a drosophila gene) binds to CUG repeats normally found in some genes. Splicing factor; regulates some mRNA processes, such as alternative splicing.

There are a number of diseases caused by disruptions in alternative splicing, including MD. In MD, all those extra CUG soak up Mbnl1 protein, so it can't do its real job in alternative splicing of certain genes.

- in MD, insulin transcription is disrupted and MD's have insulin resistance
- a chloride channel is also disrupted, causing myotonia

Overexpression of Mbnl1 can force a normal splicing pattern.

Targeted disruption of Mbnl1 in mice caused 4 serious symptoms of MD – myotonia, cataracts, intranuclear foci, and loss of chloride channels.

- Subsequent Mbnl1 overexpression rescued the phenotype, to some extent.

Treatments?

- Antisense oligomers to force the splicing out of CUG repeats?
- Destroy Mbnl1/CUG-repeat interaction (but don't destroy its ability to bind to its normal targets)

Presentation by guest lecturer

Ptosis: droopy eyelids

Investigating the pedigree of a baby who died of congenital myotonic dystrophy.

Baby had 2480 repeats in muscle; had different numbers of repeats in different tissues.

Heart muscle was most affected, with over 3000 repeats.

- Mom had 750 repeats.
- Mom's sister had 99 repeats; brother only had ptosis.

Older-onset symptoms:

- Neuromuscular:
 - o Muscle weakness, myotonia
 - o Mental retardation
- Eye:
 - o Cataracts
 - o Ptosis
- Endocrine:
 - o Diabetes

- Testicular atrophy
- Cardiac:
 - Arrhythmias
 - Conduction block
- Skin:
 - Frontal balding

MD Management: treat the symptoms (diabetes, myotonia, cardiology and ophthalmology).