Genetics, The Duchenne Registry And Your Family

Niki Armstrong, MS, CGC
May 30, 2020
Topics for Today:

1. Duchenne and Becker 101
2. Genetics and the importance of genetic testing
3. Connecting to research through The Duchenne Registry
4. Answer your questions!
What is Duchenne?

Duchenne and Becker muscular dystrophies are genetic conditions caused by problems with the gene that makes dystrophin (DMD). As a result, dystrophin is not made or is made incorrectly. Without dystrophin, muscles are not able to function or repair themselves properly.
Duchenne and Becker are dystrophinopathies

Fairclough et al, *Translational Genetics*, 2013
DUCHENNE’S EFFECT ON MUSCLES

Without dystrophin, muscle cells are damaged, and, over time, are replaced with scar tissue and fat in a process called fibrosis.
Duchenne is not just a disease of the muscles. It affects every system in the human body.
Genetics Review
Typical Human Karyotype
Background: the *DMD* gene

The *DMD* gene has 79 exons… but what is an exon?

*Exon* and *Intron*:

- **Exon**: A section of DNA that codes for an amino acid sequence. In the *DMD* gene, there are 79 exons.
- **Intron**: A section of DNA that does not code for an amino acid sequence. Exons and introns alternate in the *DMD* gene sequence.

*DMD* gene sequence:

- The *DMD* gene sequence consists of exons and introns, with 79 exons in total.

*Dystrophin protein*:

- The *DMD* gene encodes the dystrophin protein, which is involved in muscle function and plays a crucial role in maintaining muscle integrity.

Diagram:

- The diagram illustrates the alternating pattern of exons and introns in the *DMD* gene sequence, with each exon representing a section that codes for an amino acid sequence, and each intron representing a non-coding section.
Types of Changes in the *DMD* gene

- More than 4000 unique genetic changes (*aka* mutations, variants)
- Fall into categories

<table>
<thead>
<tr>
<th>Type of Change</th>
<th>% of Duchenne cases</th>
<th>% of Becker cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large deletions</td>
<td>60-70%</td>
<td>80-85%</td>
</tr>
<tr>
<td>Large duplications</td>
<td>10%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Point mutations and other small changes</td>
<td>15-30%</td>
<td>10-15%</td>
</tr>
</tbody>
</table>
### Types of Genetic Mutations

<table>
<thead>
<tr>
<th>The old dog ran too far.</th>
<th>Original</th>
</tr>
</thead>
<tbody>
<tr>
<td>The old ___ ran too far.</td>
<td>Deletion</td>
</tr>
<tr>
<td>The old dog <strong>dog</strong> ran too far.</td>
<td>Duplication</td>
</tr>
<tr>
<td>The old.</td>
<td>Nonsense</td>
</tr>
<tr>
<td>The old dog ran too <strong>fat.</strong></td>
<td>Missense</td>
</tr>
<tr>
<td>The old dog ran too <strong>fat.</strong></td>
<td>Missense</td>
</tr>
<tr>
<td>The old dog ran too far.</td>
<td>Insertion</td>
</tr>
</tbody>
</table>
Reading Frame Rule: What is supposed to happen.

Exons

The old dog ran.

Protein: The old dog ran.
The old ran.  

Deletion  

The old ran.  

Protein: The old ran.
Reading Frame: In frame Becker

Deletion

The dog ran.

The dog ran.

Protein: The dog ran.
Does my mutation predict the severity?

Out of frame deletion:
- No dystrophin
  - Duchenne

In frame deletion:
- Partially functional dystrophin
  - Becker
X-linked Recessive Inheritance

Unaffected father

Carrier mother

Unaffected son

Unaffected daughter

Carrier daughter

Affected son
If I don’t have any family history of Duchenne, what are the chances I am a carrier?

About 70% of boys with Duchenne have a mother who carries the mutation. The other 30% of mothers are NOT carriers.
Why is it important to know if I am a carrier?

- Family planning and determining risk for other family members
- Some carriers have muscle symptoms and may need additional support or care
  - Manifesting carrier or female with dystrophinopathy
- Carriers have an increased risk of heart disease and should have screening in early adulthood
How genetics shapes the story…
And 3 reasons why testing is important

Genetic testing is the gold standard for diagnosis

Mutation-specific therapies are in development

Results help other family members get testing

Diagnosis

Research

Family
Genetic Approaches to Therapies

• **For Nonsense Mutations:**
  - Nonsense mutation read-through
    - PTC Therapeutics (Translarna®)
• **For Deletions**
  - Exon skipping
    - Sarepta Therapeutics (exon 51: Exondys 51)
    - Sarepta Therapeutics (exon 53: Vyondys 53)
    - NS Pharma (exon 53: Viltolarsen)
• **Gene Therapy**
Roles of PPMD Genetic Counselors
Free genetic testing and counseling for Duchenne and Becker muscular dystrophy
DECODE DUCHENNE

Criteria for Free Testing:

- Male with a confirmed or suspected diagnosis of Duchenne or Becker,
  OR
- Female with a relative with Duchenne or Becker with a known mutation
- Never had genetic testing OR previous genetic testing has not confirmed a mutation
- Any financial barrier
- Legal resident of US or Canada

All testing performed at:
Over 1,000 patients tested through the Decode Duchenne program!
THE DUCHEENNE REGISTRY

THE STRENGTH OF THE REGISTRY IS YOU

Your data is critical in the fight to end Duchenne
Our Impact

5000+ Registrations since launch

115+ Countries Represented

12YRS of Longitudinal Data

100+ Trials & Studies Recruited
NEW Registry App!

THE DUCHENNE REGISTRY

The Duchenne Registry

The Duchenne Registry is an international, self-report registry and resource for individuals with Duchenne or Becker muscular dystrophy.
Welcome Screens

Click Join Study!
By providing your name and signature, you confirm that you read the information contained herein and that you wish to take part in this research study.

First Name: John
Last Name: Doe

Signature
By providing your name and signature, you confirm that you read the information contained herein and that you wish to take part in this research study.

Please sign using your finger on the line below.

Signature: [John Doe]

Clear

Done
Muscle Function

By "you" in this survey we mean the person being registered; the person with Duchenne or Becker, or the carrier of Duchenne or Becker.

Next

Heart Module

By "you" in this survey we mean the person being registered; the person with Duchenne or Becker, or the carrier of Duchenne or Becker.

It would be helpful to have the results handy of the most recent echocardiogram or MRI.

Next
How do you or your child (the person with Duchenne or Becker) usually get around? Please choose one answer below.

I usually or always walk on my own without help or mobility devices.

I can get around on my own but I sometimes need help from a mobility device.

I use a wheelchair or other mobility device and rarely or never walk.

My child is an infant/toddler and has not yet taken his/her first steps.

During the last week, has it been easy or hard for your child to RUN SHORT DISTANCES without help:

- Easy
- A little hard
- Very hard
- Can't do at all
- Too young for this activity
Why YOU should join the Registry

1. Be a citizen scientist
2. Get specific information on clinical trials and drug approvals
3. Better understanding of EVERYONE with Duchenne/Becker/Carriers
Activation Code needed to join!

- Previous registrants already received invitation email with a code.
- New registrants must first pre-register on our website.
ALL New Registrants:

Go to www.DuchenneRegistry.org

Click “JOIN”

Enter your email under Pre-Registration

Invitation email will come from no-reply@threadresearch.com, which will contain link & activation code.
Thank you!

coordinator@parentprojectmd.org

888-520-8675

Schedule a phone appointment at duchenneregistry.org