Genetics, The Duchenne Registry And Your Family

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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

[Diagram of a human karyotype showing the 23 pairs of chromosomes, with labels for autosomes and sex chromosomes (XX for female, XY for male).]
Background: the *DMD* gene

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

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DMD gene sequence

Dystrophin protein
DMD Gene Exons
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>way</strong> 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.
Reading Frame: Duchenne

The old ran. The old ran.

Deletion

The old ran.

Protein: The old ran.
Reading Frame: Becker

Deletion

The dog ran.

The dog ran.

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

Out of frame mutation
- No dystrophin
  - Duchenne

In frame mutation
- Partially functional dystrophin
  - Becker
X-linked Recessive Inheritance

Unaffected father

Carrier mother

Unaffected son

Unaffected daughter

Carrier daughter

Affected son
About 70% of boys with Duchenne have a mother who carries the mutation. The other 30% of mothers are NOT carriers.
How genetics shapes the story…

And 3 reasons why testing is important

Genetic testing is the gold standard for diagnosis

Results help other family members get testing

Mutation-specific therapies are in development

Research

Family

Diagnosis
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)

• Gene Therapy
Roles of PPMD Genetic Counselors
DECODE DUCHENNE

Free genetic testing and counseling for Duchenne and Becker muscular dystrophy

JOIN THE FIGHT. END DUCHENNE.

Parent Project Muscular Dystrophy

SAREPTA THERAPEUTICS

PTC THERAPEUTICS
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:

PerkinElmer Genetics
Over 1,000 patients tested through the Decode Duchenne program!
THE DUCHENNE 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!

THE DUCHENNE REGISTRY

Advance Research & Speed Development of New Treatments

If you have Duchenne or Becker muscular dystrophy or if you are a female carrier, join The Duchenne Registry and your data will help fuel the fight to end Duchenne. We share your anonymous Registry data with researchers to speed the development of new therapies.

THE DUCHENNE REGISTRY

Find out About Research Studies & Clinical Trials

Once you register and complete your Medical Surveys, we will let you know when you might be a good fit for research studies and clinical trials. Your data also helps drug developers know the size of the Duchenne population available for trials and helps identify new trial sites, increasing our community’s access to trials and potential therapies.

THE DUCHENNE REGISTRY

You Have the Power to Make a Difference

When you join and update your account in The Duchenne Registry, you are strengthening the power of a 10-year-old network of patient-powered data that will be used to improve care for people living with Duchenne and increase our understanding of the disorder. You become a citizen scientist by contributing to real scientific research simply by answering questions on your smartphone.

THE DUCHENNE REGISTRY

Join Patients Around the World

No one should have to navigate a Duchenne diagnosis alone. Be part of the global community to end Duchenne. The data you enter is not only shared with researchers in the United States, but is also shared with the TREAT-NMD International Neuromuscular Registry, which pools data from thousands of patients worldwide and enables more powerful data analysis and discovery.
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

Please sign using your finger on the line below.

Signature
John Doe

Clear
Done
Activities

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.

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.
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

Activity Complete!
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 w/ 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