Nemaline Myopathy: What are the risks? What are the tests?

Nemaline Myopathy Convention
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Genetic Counselors

- Explore the impact of genetic disorders on both affected & unaffected family members
- Assist families & individuals as they adjust to the diagnosis and make decisions
- Follow a code of ethics

Code of Ethics

- Autonomy
- Informed Consent
- Confidentiality
- Beneficience (non-maleficience)

(Very Brief) Introduction to NM

- Relatively rare in overall population
  - Estimated at 1/50,000 Finnish births (Wallgren-Pettersson)
- Many cases occur with no family history of NM
- Six forms of NM based on severity of symptoms & age of onset

Genes & NM

Nemaline myopathy can happen in a variety of ways*
  - Sporadic (72/143)
  - Autosomal dominant inheritance (41/143)
  - Autosomal recessive inheritance (29/143)

There are at least 5 genes that, when altered, can cause NM

* Combined data from Boston, Sydney and Nedlands (Ryan, et al., Annals of Neurology 50:312-320, 2001)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Modes of Inheritance</th>
<th>NM Severity</th>
<th>Frequency (very rough!)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEB</td>
<td>AR</td>
<td>Variable</td>
<td>~50%</td>
</tr>
<tr>
<td>ACTA1</td>
<td>AD, AR</td>
<td>Variable</td>
<td>~25%</td>
</tr>
<tr>
<td>TPM2</td>
<td>AR</td>
<td>Variable</td>
<td>&lt;5% (2 known)</td>
</tr>
<tr>
<td>TPM3</td>
<td>AD, AR</td>
<td>Variable</td>
<td>&lt;5% (4 known)</td>
</tr>
<tr>
<td>TNNT1</td>
<td>AR</td>
<td>Severe</td>
<td>&lt;1% (1 known)</td>
</tr>
<tr>
<td>???</td>
<td>AD, AR</td>
<td>Variable</td>
<td>???</td>
</tr>
</tbody>
</table>
Clinical categorization and inheritance patterns of NM patients with ACTA1 mutations*

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Total NM cases studied</th>
<th>NM cases with ACTA1 mutations</th>
<th>% cases with ACTA1 mutations</th>
<th>No. of ACTA1 mutations by mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sporadic AR AD</td>
</tr>
<tr>
<td>Severe</td>
<td>25</td>
<td>14</td>
<td>56</td>
<td>13 1 0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>23</td>
<td>3</td>
<td>13</td>
<td>3 0 0</td>
</tr>
<tr>
<td>Typical</td>
<td>50</td>
<td>10</td>
<td>20</td>
<td>6 0 4</td>
</tr>
<tr>
<td>Mild/childhood</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Adult onset</td>
<td>3</td>
<td>1</td>
<td>33</td>
<td>1 0 0</td>
</tr>
<tr>
<td>Unknown/other</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>28</td>
<td>26</td>
<td>23 1 4</td>
</tr>
</tbody>
</table>


What are genes? First a little background...

What are genes?

- Our chromosomes come in pairs, and therefore, so do our genes
- We inherit one pair from each parent
- Each gene is a length of DNA that spells out a specific code for that gene’s function
- If the code is altered, there may be consequences for our development or health

Sporadic Cases

- Caused by a new mutation
- No family history of the condition
- Condition can be caused by one mutation (dominant) or two (recessive)
- About 1/2 of NM cases are sporadic

Autosomal Dominant Inheritance

- One mutation will cause the condition
- Children of an affected parent have 50% chance of being affected
- Can be passed from mother or father
- May be considerable variation in presentation

Autosomal Recessive Inheritance

- Both genes must carry mutation to cause condition
- Carriers are unaffected - no signs or symptoms of disease
- Children of 2 carrier parents have a 1/4 (25%) chance of being affected
- Typically no family history of the condition
Genetic Testing & NM

- Clinical diagnosis of NM still very important
- Genetic testing may still be considered
- Why Pursue Genetic Testing?
  - Establish diagnosis
  - Confirm diagnosis
  - Prenatal diagnosis
  - Implications for other family members

Genetic Testing: Clinical vs. Research

- Clinical testing is done by a CLIA approved lab
- Tests have a specified TAT
- Results are released to patients/physicians for clinical/diagnostic use
- Research testing labs are not CLIA approved
- Testing may not have specified TAT
- Results may or may not be released
- Results must be confirmed by CLIA approved lab for clinical use

Genetic Testing & NM

- Clinical testing available for ACTA1 mutations
  - GeneDX, Maryland USA
    (www.genedx.com)
  - Laing Lab, Nederlands, W. Australia
  - Universita degli Studi di Firenze, Italy
  - ? Orphan disease testing labs

Genetic Testing & NM

- Research testing available for all other genetic forms of NM
  - Children’s Hospital, Boston (Beggs)
  - Univ. Helsinki, Finland (Wallgren-Pettersson)
  - Nedlands, Western Australia (Laing)

The Ins & Outs of Genetic Testing

- Visit a geneticist/genetic counselor
- Testing starts with the affected patient (proband)
- Clinical testing for ACTA1 mutations first
- Samples also sent to research labs for testing of additional genes, known and unknown

The Ins & Outs of Genetic Testing, cont.

- When an autosomal recessive mutation is found:
  - Screen the parents to r/o new mutation
  - If both parents are carriers:
    • 25% chance to have an affected child in each pregnancy
    • Parents’ siblings have 50% chance of being a carrier as well
The Ins & Outs of Genetic Testing, cont.

- When an autosomal dominant mutation is found:
  - Evaluate the parents to r/o inherited mutation
    - Clinical evaluation
    - Genetic testing
    - Muscle biopsy
  - If neither parent is affected/has the same mutation, we may estimate ~1% recurrence risk in future pregnancies to account for possible gonadal mosaicism
  - When a parent has an AD mutation, they have a 50% chance of having an affected child in each pregnancy

Potential Benefits of Genetic Testing

- Establish/confirm diagnosis
  - Other conditions with similar presentations may require very different treatment/management
- Future family planning
- Genetic testing through a research lab may also have other benefits
  - Contributes to general scientific knowledge, understanding of the condition
  - May aide in development of treatments, therapies

The Ins & Outs of Genetic Testing: Prenatal Diagnosis

- Chorionic Villus Sampling (CVS)
  - Done at 10-12 weeks of pregnancy
  - Sample of the placenta taken for genetic testing of the fetal cells
  - Results may take ~4 weeks
  - 1% risk of miscarriage

- Amniocentesis
  - Done 15-20 weeks of pregnancy
  - Genetic testing done on fetal skins cells isolated from amniotic fluid
  - May take ~4 weeks for results
  - 0.5% risk of miscarriage

The Ins & Outs of Genetic Testing: Prenatal Diagnosis

- Preimplantation genetic diagnosis
  - IVF and genetic testing/screening used to only implant pre-embryos (8 cell stage) that do not have NM
  - CVS or amniocentesis performed to verify the diagnosis
Limitations of Genetic Testing

- Time
- Cost
- May find nothing (i.e., “low sensitivity”)
  - Not all genes can currently be effectively screened
  - More genes yet to be found
- More genes yet to be found
- No special treatments/ therapies offered based on a molecular genetic diagnosis of NM
- Risk to fetus for PNDx

Resources

- NM Yahoo! Group (www.nemaline.org)
- David McDougall (www.nemaline.org)
- Local support groups
- Research labs
  - Boston, MA – Beggs Lab (www.childrenshospital.org/research/beggs)
  - Finland
  - Australia
- MDA/MDC
- NSGC (www.nsgc.org) or CAGC (www.cagc-accg.ca/)
  - Find a genetic counselor near you

Acknowledgements

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- NMC04 organizers
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