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

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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

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## Code of Ethics

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

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## (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

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## 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)

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## Genes & NM

| Gene | Modes of Inheritance | NM Severity | Frequency (very rough!) |
|---|---|---|---|
| *NEB* | AR | Variable | ~~50% |
| *ACTA1* | AD, AR | Variable | ~25 % |
| *TPM2* | AR | Variable | <5% (2 known) |
| *TPM3* | AD, AR | Variable | <5% (4 known) |
| *TNNT1* | AR | Severe | <1% (1 known) |
| ??? | AD, AR | Variable | ??? |

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## Clinical categorization and inheritance patterns of NM patients with *ACTA1* mutations*

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

*Agrawal, Beggs et al, *Annals of Neurology* 56:86-96, 2004.

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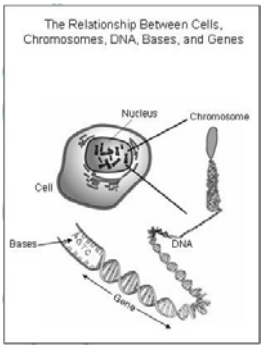
## What are genes? First a little background…

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## What are genes?

- Our chromosomes come in pairs, and therefore, so do our genes
- We inherit of each 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 e consequences for our development or health

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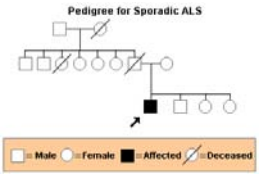
## Sporadic Cases

- 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

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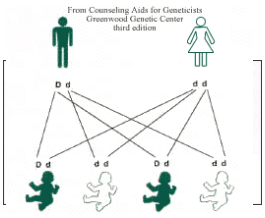
## Autosomal Dominant Inheritance

- 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

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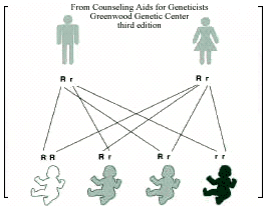
## Autosomal Recessive Inheritance

- 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

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## 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

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## 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

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## 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

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## 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)

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## 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

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## 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

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## 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

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## The Ins & Outs of Genetic Testing, cont.

- When an autosomal dominant mutation is found, cont.
  - 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

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## 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

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## 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

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## The Ins & Outs of Genetic Testing: Prenatal Diagnosis

- 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

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## 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

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## 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

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## Resources

- NM Yahoo! Group
- 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

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## Acknowledgements


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