Genetic Counseling for ALS: Things to Consider

Ellie Harrington, MS, CGC
Genetic Counselor
The Eleanor and Lou Gehrig ALS Center
eh2769@cumc.columbia.edu

Andrea Smith, MS, CGC
Outreach Professional
ALS Association of North Carolina
asmith@alsnc.org

January 28th, 2019
Outline

• Genetics and Genetic Counseling 101
• ALS Genetics – What We Know
• Genetic Counseling for ALS
• Clinical trials
• Resources
Genetic Counseling

Genetic Counseling is the practice of helping individuals and families understand the medical, psychological, social and reproductive implications of genetic and congenital conditions.

1. **Education** (information giving) about inheritance, natural history, testing options, medical management, prevention, social support and research;

2. **Assessment** of the chance for recurrence or occurrence of a condition, after information gathering and establishing/verifying the diagnosis, and

3. **Counseling** and psychological support to help clients adapt to their situation and choices, and to the psychological, familial and social issues that stem from the risk or condition in the family.
Education – Basic Genetics

HUMAN BODY → CELL → CHROMOSOMES

FUNCTION

PROTEIN

GENES

DNA

Harrington, Elizabeth MS, CGC, 2019
Google Images
Assessment – familial or sporadic ALS (fALS/sALS)

- Pedigree analysis
  - Is there a family history?
- Familial vs. Sporadic (fALS/sALS)
Sample – family history example

[Family tree diagram showing genetic inheritance of diseases such as ALS and Alzheimer’s disease.]
Assessment – familial or sporadic ALS (fALS/sALS)

• Pedigree analysis
  • Is there a family history?
• Familial vs. Sporadic (fALS/sALS):
Features of fALS

• Generally, the symptoms of FALS are the same as the symptoms of SALS though exceptions exist
• The average age that individuals with FALS begins to have symptoms of ALS is 46 compared to the average age of symptom onset in individuals with SALS which is 56
• Variability in the age of symptom onset and disease progression between families and between members of the same family is common
ALS gene discovery

Renton et al. Nature Neuroscience 2013
Genetic risk

• Inheritance
  • Autosomal dominant > autosomal recessive >> X-linked

• Penetrance
  • The proportion of individuals carrying a particular variant of a gene that also express the associated symptoms or phenotype
• European founder effect detected in Scandinavia (Finland)
• Accounts for \(~40\%\) fALS and \(~7-10\%\) sALS

Frontotemporal dementia
• Also major genetic cause for frontotemporal dementia (FTD)
  • Accounts for \(~25.9\%\) of familial FTD
• Incomplete penetrance
  • 50% by age 58, nearly 100% by age 80
• Autosomal dominant inheritance

Van Blitterswijk et al., *Curr Opin Neurol*. 2012
Autosomal dominant C9orf72

Typical C9orf72 (GGGGCC) repeat size

Expanded C9orf72 (GGGGCC GGGGCC) repeat size

Typical C9orf72 (GGG GCCC) repeat size

Expanded C9orf72 (GGGGCC GGGGCC) repeat size
SOD1

- Accounts for ~20% of fALS
- Causes typical ALS
- ~50% of individuals with SOD1 mutation are symptomatic by age 46 years; 90% are symptomatic by age 70 years
- Autosomal dominant inheritance
Genetic counseling

- **Counseling** and psychological support to help clients adapt to their situation and *choices*, and to the psychological, familial and social issues that stem from the risk or condition in the family.

- Help individuals decide if genetic testing is right for them
  - Review benefits and risks
  - Discuss implications for individual and their family members
Genetic testing

• **Reasons some chose to test**
  - Find out “what” the cause of disease is or “why” it occurred
  - Potential to enroll in clinical trials
  - Knowledge of risk for family members
  - Family planning

• **Reasons some chose not to test**
  - Psychological considerations – increased anxiety
  - Result wouldn’t change care plan
  - Insurability risks → GINA
    - (Genetic Information Nondiscrimination Act) 2008
      www.ginahelp.org
    - Protects individuals against health insurance companies and employers from discrimination against genetic information
    - Does NOT include: life insurance, long-term care, or disability insurance
Drug Development and Research for fALS

• BIIB078 (IONIS-C9Rx) for c9orf72
• BIIB067 (IONIS-SOD1Rx ) for SOD1
• Pre-fALS: The Pre-symptomatic Familial ALS Study

How to find out more:
• http://www.alsa.org/research/clinical-trials/?state=
• www.clinicaltrials.gov
• ALS trial liaison: Carly Doyle, (855) 437-4823, alstrials@neals.org
• http://www.alsa.org/research/research-news/research-webinars.html
Presymptomatic genetic testing

• Testing at risk family members who do not exhibit symptoms
Pre-symptomatic genetic testing - example

d. ALS + C9orf72 gene mutation
50% chance inherited C9orf72 mutation

Example family tree with gene mutation and disease prevalence.
Presymptomatic genetic testing

• Testing at risk family members who do not exhibit symptoms
  • Confirmed familial mutation

• Genetic Counseling for family members
  • Explore individuals experience with ALS in family
  • Discuss the reasons and desire to learn this information
    • Is this a good time in their life to learn their genetic status?
  • Explore how this result may impact their life –
    • Impact on relationships and family
    • Family planning
    • Insurances

“Genetic Testing Protocol for Huntington’s Disease”,
© 2016 Huntington’s Disease Society of America
Presymptomatic genetic testing – family planning
Genetic counseling session(s)

1. **Why test?**
   - Find out “what” the cause of disease is or “why” it occurred
   - Potential to enroll in clinical trials
   - Knowledge of risk for family members
   - Family planning

2. **Informed consent**
   - Implications for individual
   - Implications for family members

3. **Return of results**
   - Where to go from here?
     - Processing of the personal genetic test result
     - Conversations with family members
     - Clinical trial opportunities and hope for future
Summary

• Sporadic ALS is most common (~90%)
  • Causative gene mutation found in ~11% of sALS and ~66% of fALS
    • 20+ ALS associated genes – variable inheritance, penetrance, expressivity
    • C9orf72 is the most common gene associated with ALS and FTD

• Clinical genetic testing may be useful for:
  • Participation in clinical trials
  • Knowledge for at-risk family members

• Genetic testing for at-risk family members may be possible when a gene mutation is first confirmed in a family member with ALS

• Talk to your physician about questions regarding genetic testing
  • Find a genetic counselor through the National Society of Genetic Counselors
    • NSGC website: https://www.nsgc.org/
Questions?

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