Familial ALS 101

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Questions about familial ALS

- What is fALS?
- What causes fALS?
- How common?
- Which genes?
- Genetic Testing?
- fALS vs sALS?
- Registries?
- Twin studies?
- Research?
- Resources for families?
What is fALS?

• Definitions
  – Familial vs. sporadic
  – Genetic vs. non-genetic

• Examples
Sporadic vs. Familial ALS

• sALS and fALS are clinically indistinguishable
• All genetic mutations found in fALS, have also been found in patients with sALS
• First-degree relatives of sALS patients have an increased risk of ALS
• Classification into sALS and fALS
  – is convenient
  – has limited biological meaning
  – is largely artificial
How Common is fALS?

• Incidence
  – 2 per 100,000
  – Number of new ALS diagnoses/year ≈ 6,000
  – If fALS accounts for 5% of all ALS
  – Number of new fALS diagnoses/year ≈ 300

• Prevalence
  – 6 per 100,000
  – Number of ALS patients in the US ≈ 18,000
  – If fALS accounts for 5% of all ALS
  – Number of fALS patients in the US ≈ 900

• Proportion of fALS pedigrees with living affected individual ≈ 75%

• Estimated number of fALS pedigrees ≈ 1,200
Is fALS Underestimated?

• Incomplete recording of family history
• Loss of contact between members of family
• Misdiagnosis of family members with ALS
• Reluctance to report hereditary disease
• Small family size
• Early deaths due to other causes
• Incomplete disease penetrance
What is the Cause of fALS?

DNA is the genetic code, the material that we inherit from our parents.

A gene is a stretch of DNA.

fALS is caused by DNA mutations (permanent changes) in specific genes.
Genetic Causes of fALS

- SOD1: 40%
- C9ORF72: 30%
- FUS/TLS: 5%
- TDP-43: 4%
- Others: 1%
- Unknown: 20%

Percentages are approximate
How is fALS Inherited?

Risk $\approx 50\%$

Risk $\approx 25\%$
If I Have the Gene, will I Definitely Develop ALS?

• Depends on penetrance of the genetic mutation

• Penetrance varies based on gene and specific mutations within these genes
Is Genetic Testing Possible?

• Yes, but there are caveats?
• Different genes in different families, but always the same gene within a single family!
• Genetic testing should always start with an affected individual
  - determine the genetic cause of ALS in this individual and the family
• Role of genetic counseling
Pre-Symptomatic Genetic Testing?

- Only if gene in family is already known
- Important to be clear about motivation for undergoing testing
- Importance of psychosocial readiness to undergo testing and learn the results
- Genetic counseling is essential
- Being offered as part of the Pre-fALS Study
Twin Studies?

- Twin studies allow us to estimate “heritability” – a measure of the relative contributions of genetic and non-genetic factors to overall phenotypic variation
- Heritability of sALS is estimated to be 0.61 (95% confidence interval 0.38 – 0.78)
- Interpretation: genes are responsible for about 60% of variability between people
Information in ALS Registries?

• National ALS Registry
  – Documents presence/absence of a family history of ALS & other neurodegenerative diseases

• Familial ALS Registry

falsconnect.org
The fALS Connect registry aims to connect fALS families with scientists who are engaged in fALS research. The goal of the registry is to accelerate progress towards finding a cure for this disease. We encourage both affected individuals and unaffected family members to sign up for the registry.

Registered members may complete a profile in order to provide basic information about themselves and how the disease has affected them and their family. There is also an opportunity to upload the results of genetic testing and medical records. Registered members may view anonymous summary information about other people who have joined the registry. fALS Connect will periodically send registered members information about opportunities to participate in research studies for which they may be eligible.

It is important to note that participation in the fALS Connect Registry does not mean that you also have enrolled in the National ALS Registry, which is maintained by the U.S. Centers for Disease Control and Prevention (CDC). The registries are different and information in fALS Connect is not shared with the National ALS Registry. If you are a person with ALS, we encourage you to sign up for both registries, as the National ALS Registry also has a component focused on familial ALS. To enroll in the National ALS Registry, visit the CDC's ALS Registry website at www.cdc.gov/als or click on the link below.

Register Now!
Research Opportunities?

Currently there are many opportunities to participate in clinical research. These include three ongoing clinical trials for people who are affected with familial ALS, a study of people who are at genetic risk for developing ALS, as well as multiple efforts to identify new genes that may cause ALS. Click on the adjacent links to learn more or email us at coordinator@falsconnect.org.
Pre-fALS

- Pre-Symptomatic familial ALS Study
- Enrolls people at genetic risk for developing ALS
- Goals
  - Characterize pre-symptomatic disease
  - Ascertain incidence rate of progression to manifest disease
  - Explore genetic/environmental modifiers of risk
  - Establish repository of samples for ‘wet’ biomarker discovery
  - Use knowledge gained to design early therapeutic/preventative trial
Unaffected family members at high likelihood of being gene mutation carriers

Known gene-

Exclude

Known gene+

Gene status unknown

Gene results

Gene+/-

Non-disclosure

Disclosure

Genetic counseling

Gene+

Gene-

Exclude

Pre-fALS Cohort (longitudinal follow-up)
Arimoclomol

- Phase II/III clinical trial enrolling people with rapidly progressive ALS associated with specific mutations in the SOD1 gene
- Funded by ALSA and FDA
- Randomized, double-blind, placebo-controlled
- 200mg three times/day x 12 months
- Nearing completion of phase II
- Interim analysis expected within next 9-12 months
Pyrimethamine

- Phase I/II trial
- Aims to evaluate safety of drug and extent to which it suppresses CSF levels of SOD1
- Eligibility: fALS with any SOD1 mutation
- Up to 75mg/day x 36 weeks
- No placebo
- PI: Dale Lange (NY)
C9ORF72

• Most common (identified to date) cause of both fALS and sporadic ALS
• Amenable to gene therapy using e.g. antisense oligonucleotides
• Currently in pre-clinical development
  – ISIS
  – U Miami (ALSA funded)
Hunting for New Genes

• Goal is to identify genetic causes of ALS, at least in the 40% of fALS families in which gene is currently unknown

• Many efforts ongoing
  – U Mass. (Dr. Robert Brown)
  – Northwestern (Dr. Teepu Siddique)
  – NIH (Dr. Bryan Traynor)
  – And others in the US and Europe
Choosing a Study

- Talk to the investigators
- Understand the rationale for the study and its goals
- Understand the study procedures, including potential risks and benefits
- Ask questions
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More Information

• ALS Association
  – ALSA.org
  – fals@alsa-national.org

• falsconnect.org

• ALS Research Collaboration at U Miami
  – ALS-research.org
  – fals@med.miami.edu
  – 1-888-413-9315