WELCOME!

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Genetic Counseling in ALS: Things to Consider
GENETICS COUNSELING & ALS

ALSA Care Services Webinars
June 27th, 2022

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Basic genetics

HUMAN BODY → CELL → CHROMOSOMES

FUNCTION → PROTEIN → GENE

DNA (G, A, C, T)
Basic genetics
Basic genetics
Basic genetics: inheritance

Chromosome

Gene
Basic genetics: inheritance
Inheritance & disease risk
Inheritance & disease risk

- **Inheritance**: most ALS-associated genes are autosomal dominant
  - 50% risk to 1st degree family members

- What’s the risk of developing disease symptoms?
  - Varies depending on the specific ALS gene mutation—“variable or reduced penetrance”
  - Not all risk is equal

Parents

Children

50%
Not all risk is equal

Environmental Factors

Baseline Population Risk

Symptomatic ALS

Genetic Factors
Not all risk is equal

Sporadic ALS = singleton ALS
90% of ALS
Environmental factors + small genetic factors

Familial ALS, “genetic ALS”
*SOD1* A5V variant
Highly penetrant

Familial ALS, “genetic ALS”
*SOD1* I114T variant
Reduced penetrance
Not all risk is equal

- Genetic ALS
  - “variable or reduced penetrance”
    - *Penetrance* is proportion of individuals carrying a particular gene variant that also express associated disease symptoms
  - Not all who have certain variant may go on to develop ALS
How does genetics play a role in ALS?

Chromosome → Gene → Protein → Function

- **C9orf72**
- **SOD1**
- **FUS**
- **TARDBP**
- **TBK1**
- **ALS2**
- **ATXN2**

- **Protein transport**
- **RNA metabolism**
- **Mitochondrial function**
- **Proteostasis**
- **DNA repair**
How does genetics play a role in ALS?

Chromosome → Gene

C9orf72
SOD1
FUS
TARDBP
TBK1
ALS2
ATXN2

Protein Function

Protein transport
RNA metabolism
Mitochondrial function
Proteostasis
DNA repair

Motor neuron degeneration

Healthy motor neuron → Motor neuron degeneration
Is ALS “genetic” or “hereditary”? What is my genetic risk?

- Specific cause is undetermined – likely a combination environmental and multiple genetic factors
- Risk factors:
  - Age, gender, military service, ancestry
  - Strong family history of ALS
Is ALS “genetic” or “hereditary”?

No family history

- Known gene mutation (~5-8%)
- Unidentified

- Typically not monogenetic (not caused by a single gene mutation)

~90%

~10%

Family history of ALS

- Known gene mutation (~66%)
- Unidentified

- More commonly monogenetic (caused by a single gene mutation)
ALS-associated genes

B  sporadic MND (n=385)

- TARDBP, 1%
- NEK1, 0.80%
- TBK1, 0.50%
- OPTN, 0.30%
- C9orf72, 8%
- SOD1, 2%

A  familial MND (n=42)

- SOD1, 29%
- C9orf72, 33-50%
- No variant, 38%
- TBK1, 2%

No variant, 88%
ALS-associated genes

C9orf72 and SOD1
- Most common genes associated with ALS
- Active clinical drug trials for gene-specific drugs

**SOD1**

- Over 180 disease causing variants
- **SOD1 A5V** – rapidly progressive and aggressive form of ALS
  - Mean age of onset is 49
  - Survival time of less than 2 years after disease onset
  - Responsible for 50% of SOD1 mutations associated with fALS in North America
- **SOD1 I114T** – extreme phenotypic variability
  - Penetrance is ~50% at age 60 and 88% at age 80
  - More slowly progressive disease

C9orf72

- Identified in 2011
- GGGGCCC hexanucleotide repeat expansion
- “Out of Finland” theory – most common in those of Scandinavian ancestry
- Variable penetrance
  - ~50% by age 58
  - Risk of developing disease increases with age
- Most common genetic cause of ALS and frontotemporal dementia (FTD)
Should I get tested?
How can genetic information be helpful?

1. Information for family members
   • Autosomal dominant inheritance and variable penetrance
   • Provide knowledge of risk for family
     • Presymptomatic clinical drug trials
   • Considerations for future and family planning options
     • Financial planning
     • In vitro fertilization and preimplantation genetic testing options
2. Gene-targeted clinical drug trials

- **C9orf72**
  - A Phase 2a Study of TPN-101 in Patients With C9ORF72 ALS/FTD
  - Safety and Therapeutic Potential of the FDA-approved Drug Metformin for C9orf72 ALS/FTD
  - Study of WVE-004 in Patients With C9orf72-associated Amyotrophic Lateral Sclerosis (ALS) or Frontotemporal Dementia (FTD) (FOCUS-C9)
  - Study of Safety, Tolerability, and Biological Activity of LAM-002A in C9ORF72-Associated Amyotrophic Lateral Sclerosis

- **FUS**
  - A Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of ION363 in Amyotrophic Lateral Sclerosis Participants With Fused in Sarcoma Mutations (FUS-ALS)

- **SOD1**
  - Expanded Access Program for Tofersen in Participants With Superoxide Dismutase 1-Amyotrophic Lateral Sclerosis
  - A Study of BIB067 When Initiated in Clinically Presymptomatic Adults With a Confirmed Superoxide Dismutase 1 Mutation (ATLAS)
Should I get tested?

- May help determine the underlying cause of disease
- May inform you about potential clinical trial opportunities
- Provide knowledge of risk for family
- Considerations for future and family planning options
- Results may not change care plan
- Clinical trial options also carry a risk
- Anxiety surrounding genetic diagnosis and risk to family members
- Potential cost of testing
  - Now minimal to none
- Potential insurability risks
  - GINA.org
How would I get tested and what’s involved?

• Speak with your neurologist/ALS specialist/genetic counselor

• Signed informed consent by you and neurologist

• Blood draw or saliva collection – test sent to commercial, CLIA approved genetic testing laboratory

• Results returned in 4-6 weeks
Genetic test results

• Negative result – “normal”
  • No variants identified within known and tested genes

• Positive result – “abnormal”
  • Disease causing variant identified in ALS-related gene
  • Confirms diagnosis

• “Variant of uncertain significance” (VUS)
  • Genetic variant identified through testing but whose significance to the gene function is not certain
  • Not enough scientific evidence to determine if the VUS is related to disease or normal variation in the genetic code
Genetics & ALS Takeaways

• Single genetic causes for ALS are most commonly identified in individuals with a strong family history of ALS

• Actual disease risk for families with a known gene mutation depends on the specific ALS-associated gene

• Genetic testing is increasingly performed given emerging drugs in clinical trials

• Genetic testing is optional, and all potential benefits and risks should be considered prior to pursuing testing