WELCOME !

June 27, 2022

Genetic Counseling in ALS: Things to Consider

Guest Speaker:
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Columbia University Medical Center

The ALS Association
National Office-Care Services
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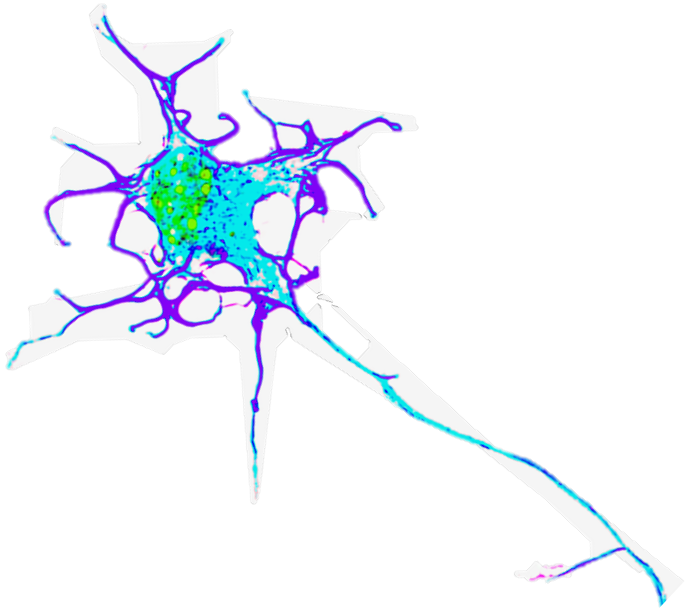


GENETICS COUNSELING & ALS

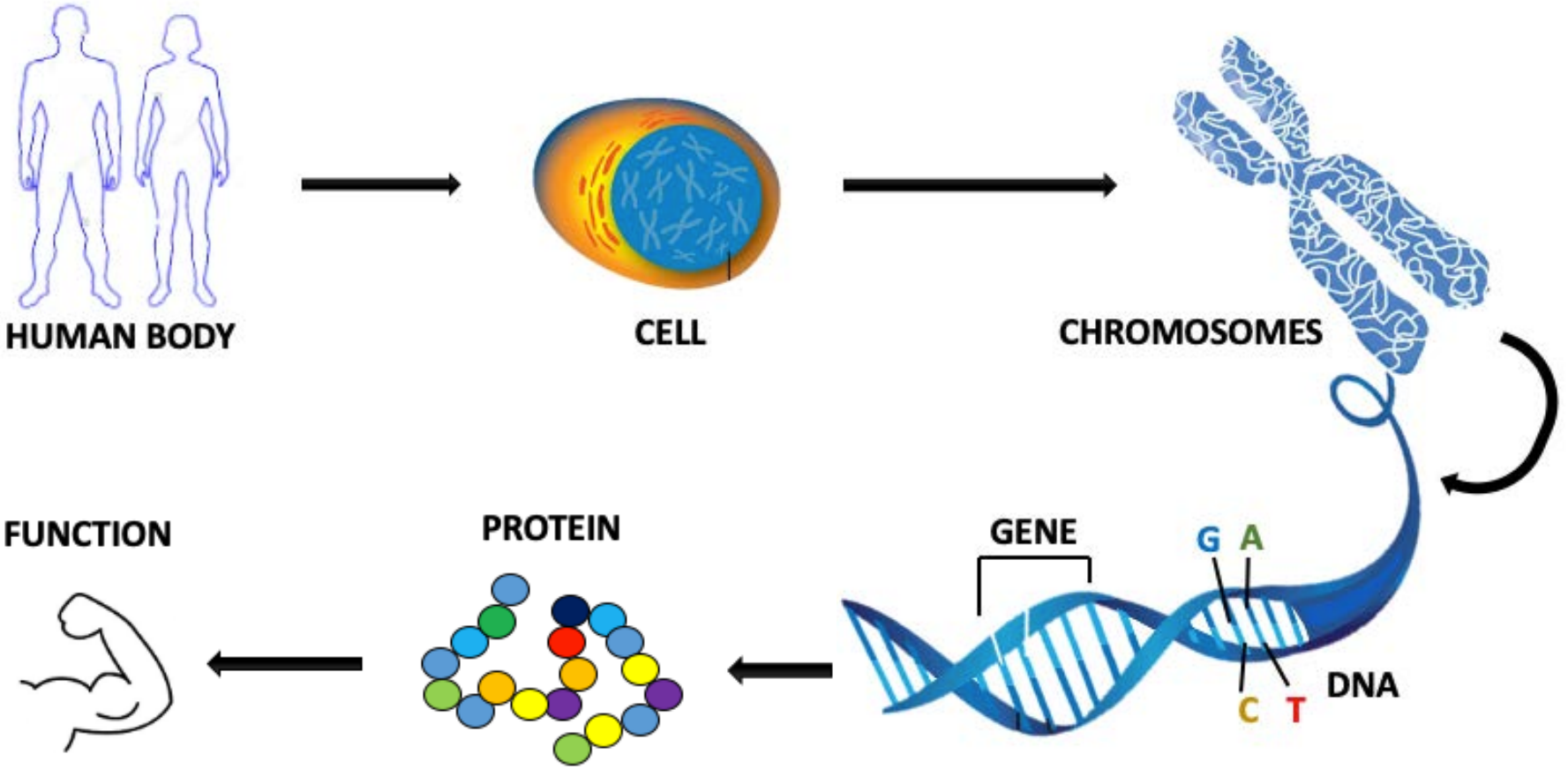
ALSA Care Services Webinars
June 27th, 2022

Elizabeth Harrington, MS, CGC
Lecturer in Genetic Counseling,
Department of Neurology

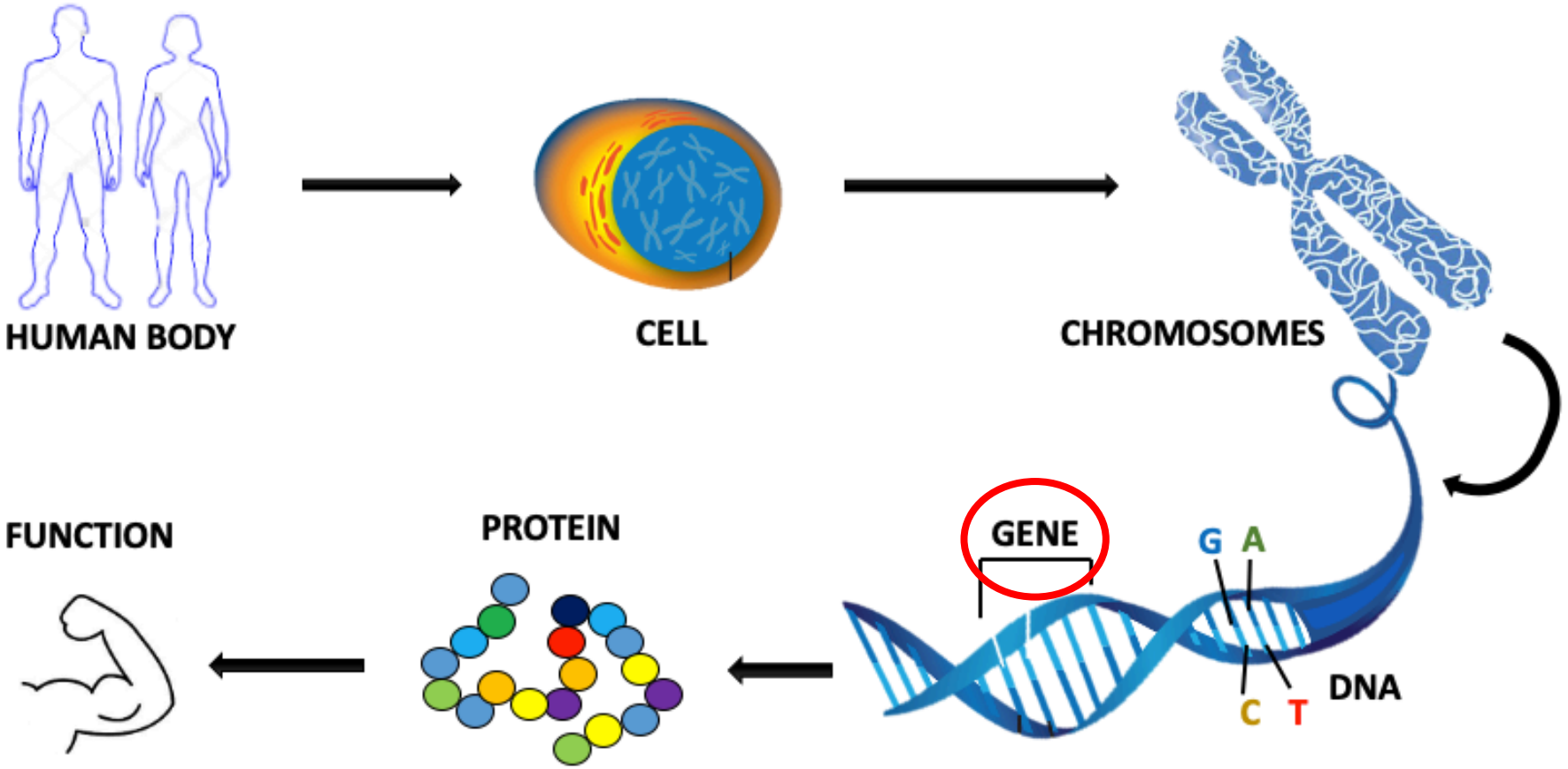
The Eleanor and Lou Gehrig ALS Center
Columbia University Medical Center

COLUMBIA

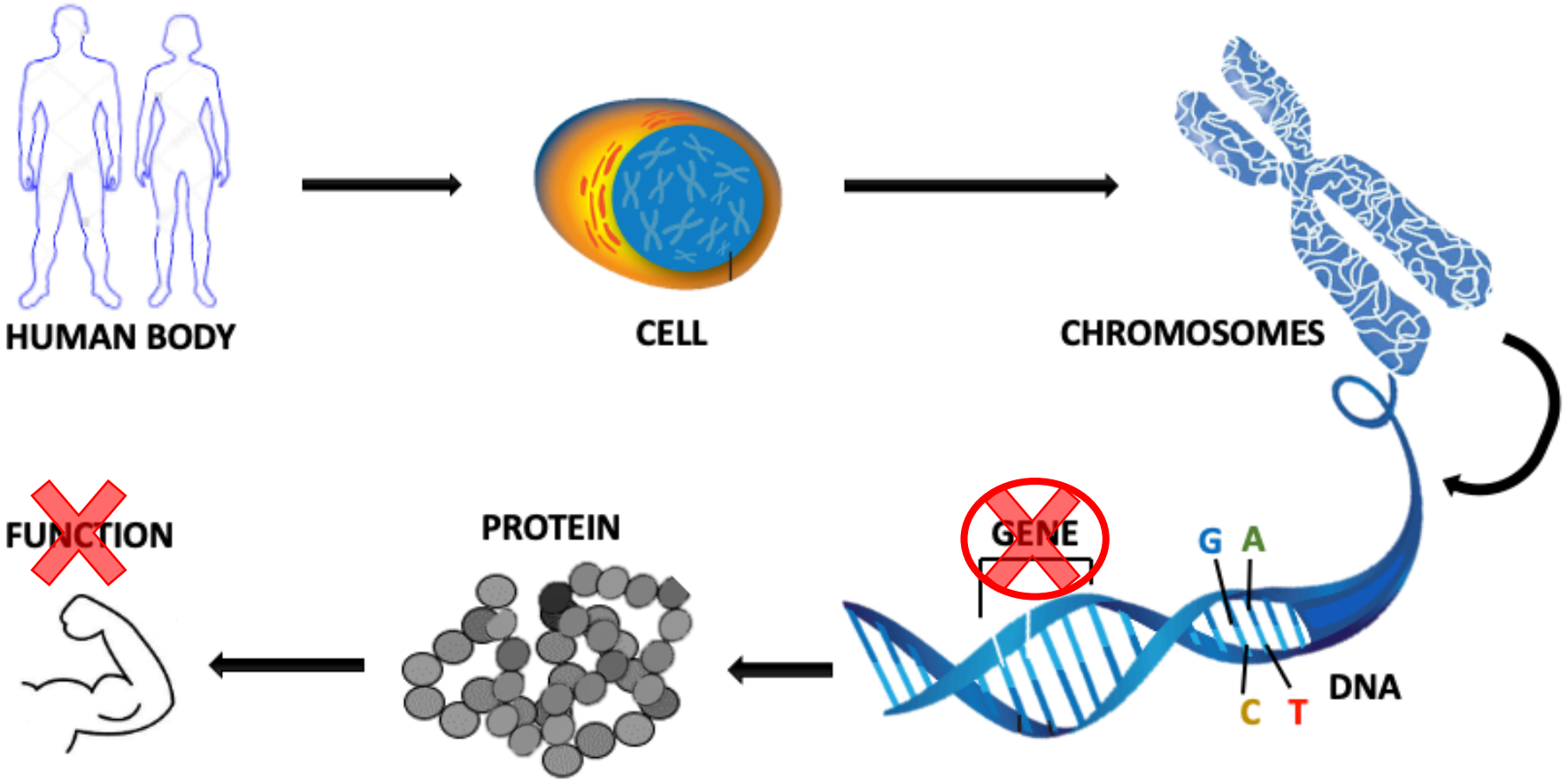
Basic genetics



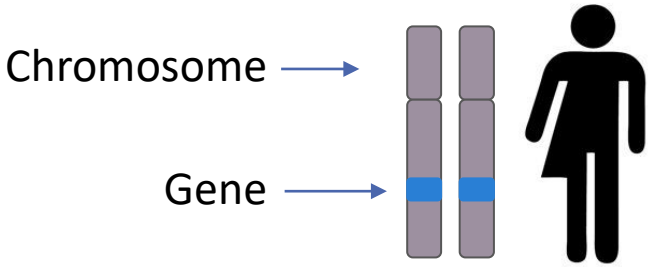
Basic genetics



Basic genetics



Basic genetics: inheritance



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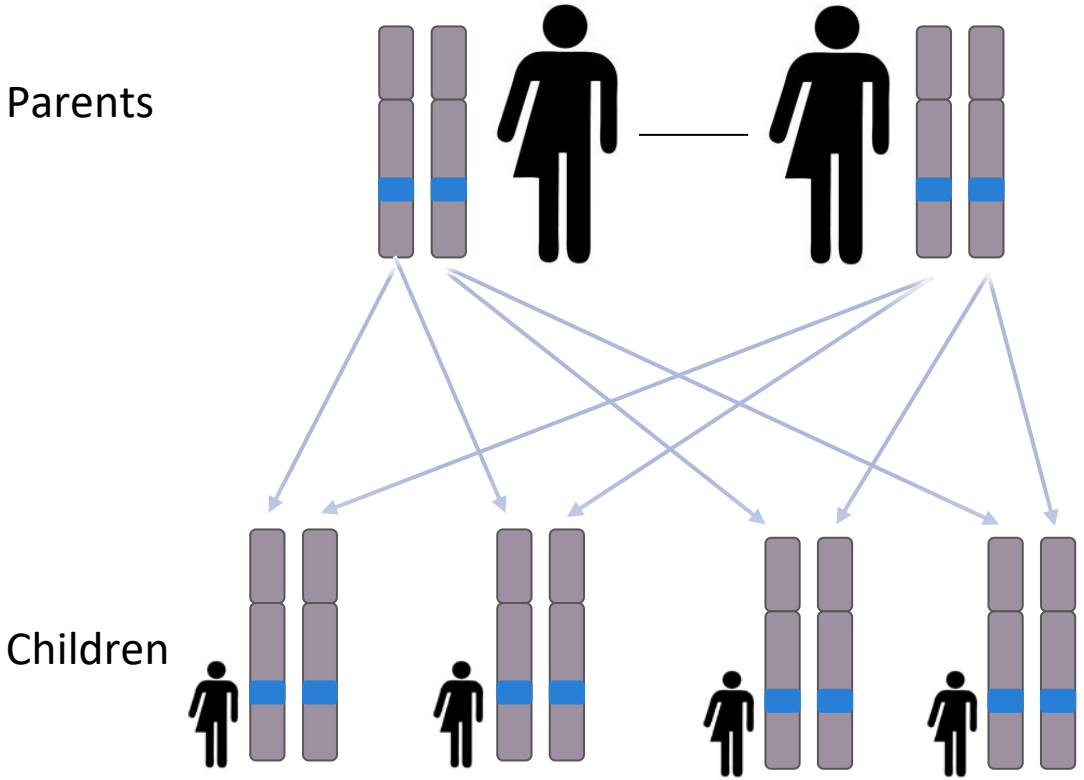
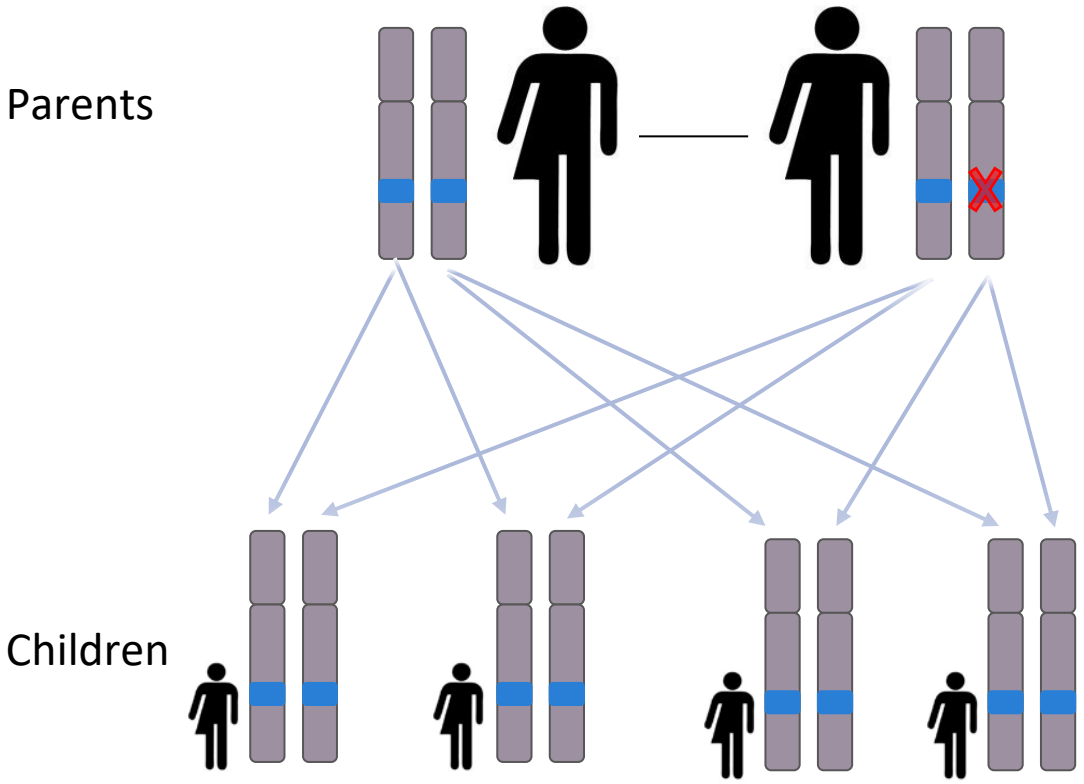
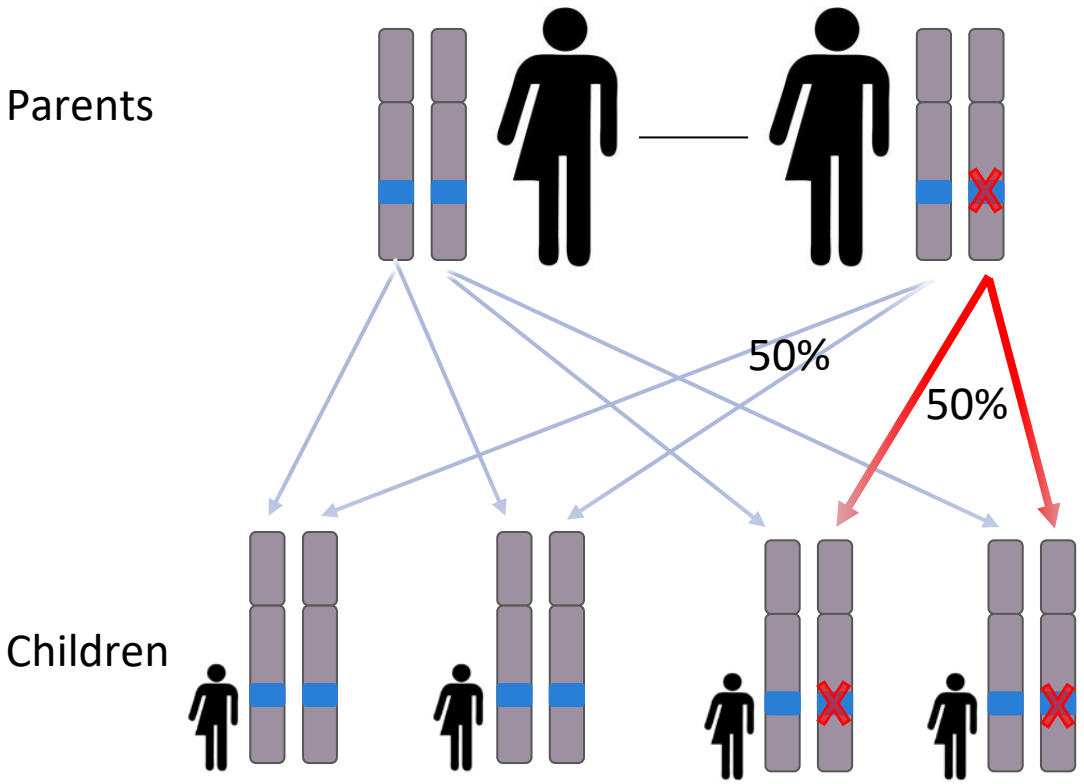


Inheritance & disease risk

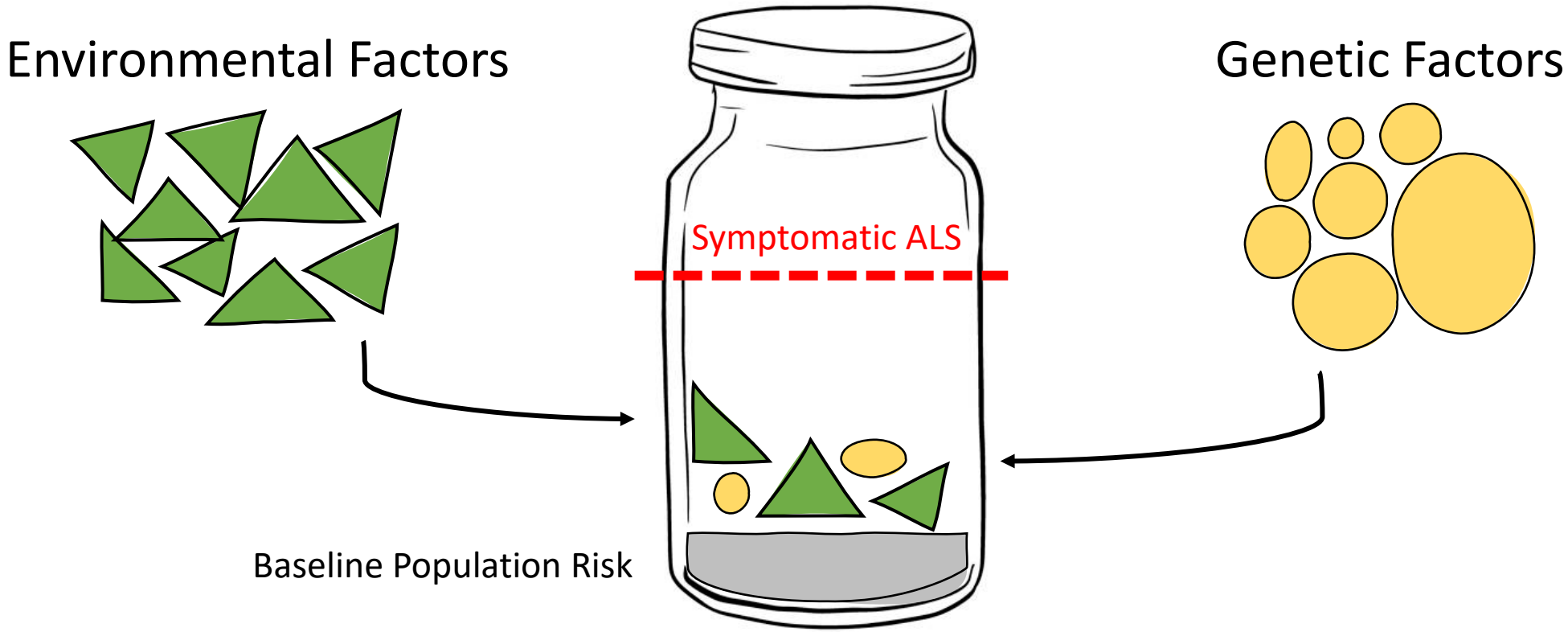


Inheritance & disease risk



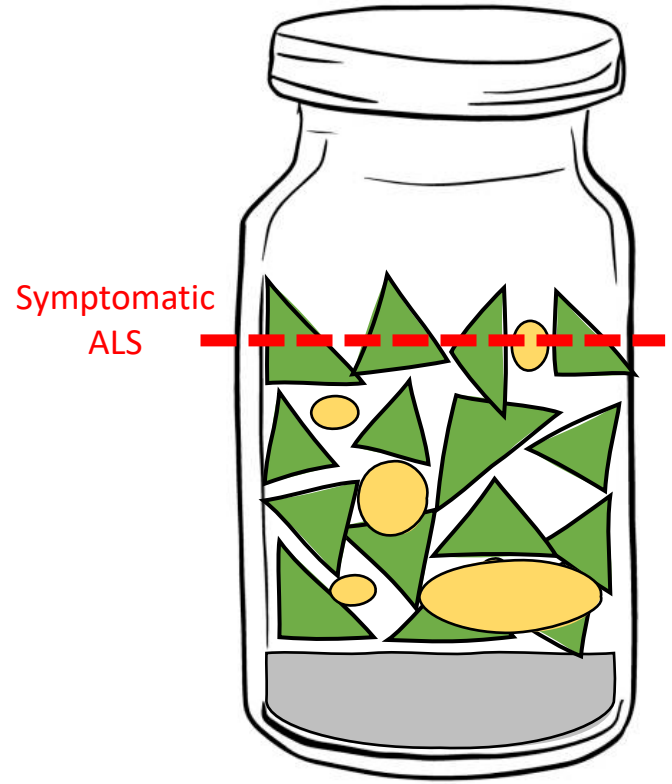
- *Inheritance*: most ALS-associated genes are autosomal dominant
  - 50% risk to 1st degree family members
- What's the risk of developing disease symptoms?
  - Varies depending on the specific ALS gene mutation – "variable or reduced penetrance"
  - Not all risk is equal

Not all risk is equal

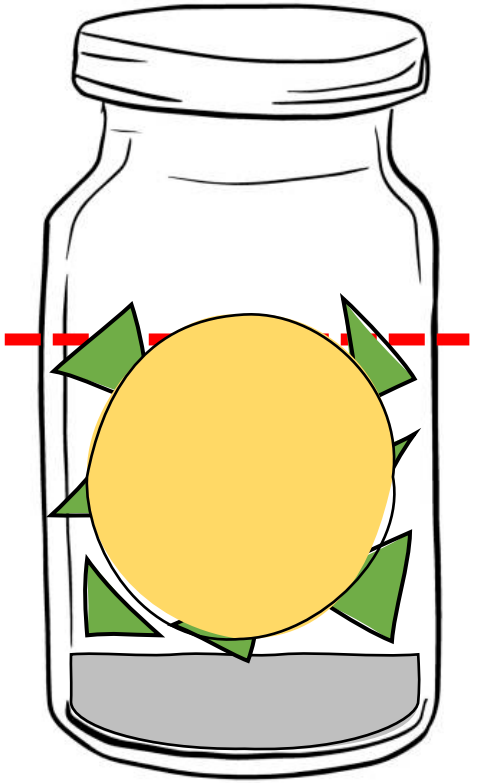


Not all risk is equal

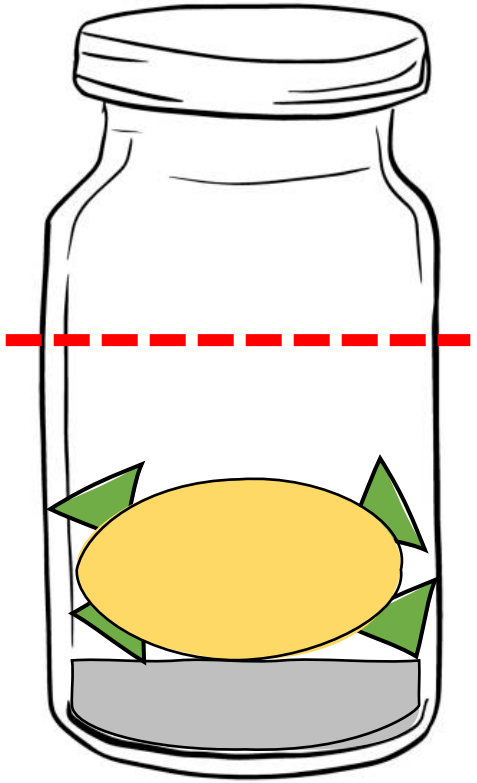
Sporadic ALS = singleton ALS
90% of ALS
Environmental factors + small genetic factors



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

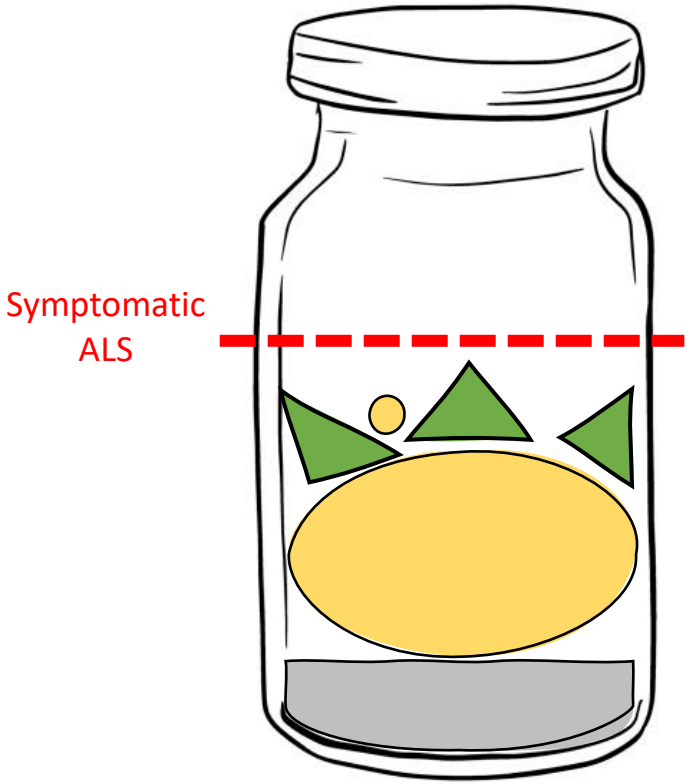


Familial ALS, “genetic ALS”
SOD1 I114T variant
Reduced penetrance

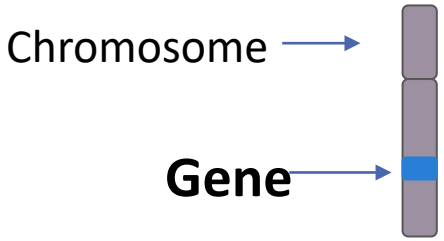


Not all risk is equal

- 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



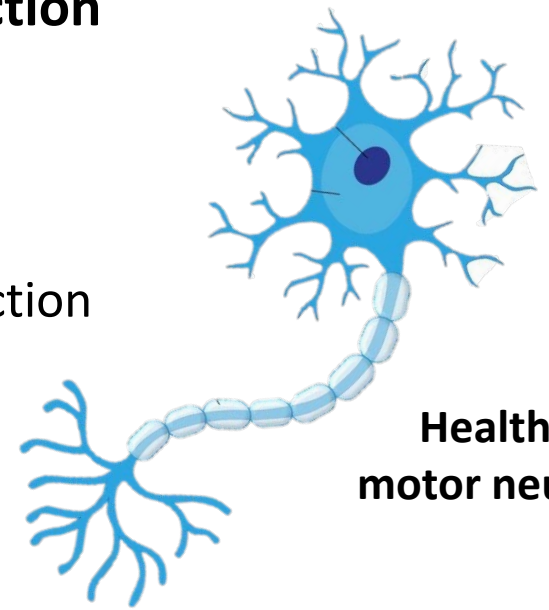
How does genetics play a role in ALS?



Protein **Function**

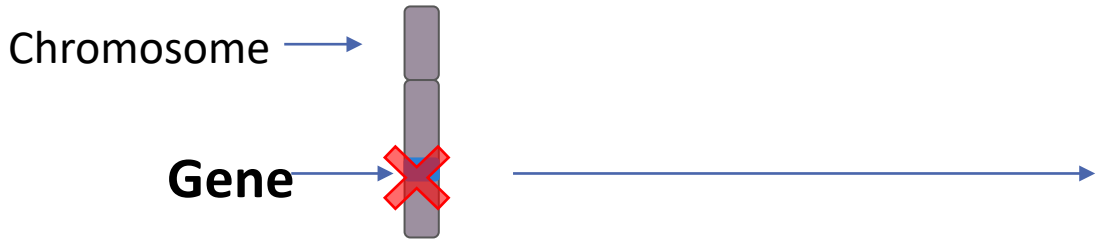
C9orf72
SOD1
FUS
TARDBP
TBK1
ALS2
ATXN2

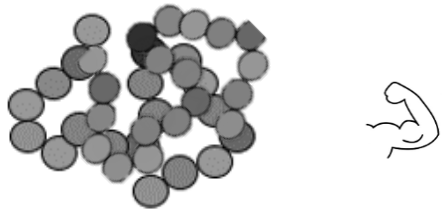
Protein transport
RNA metabolism
Mitochondrial function
Proteostasis
DNA repair



Healthy motor neuron

How does genetics play a role in ALS?





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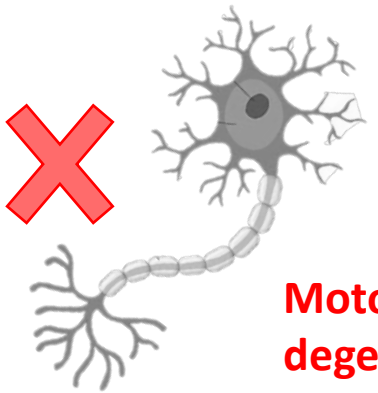
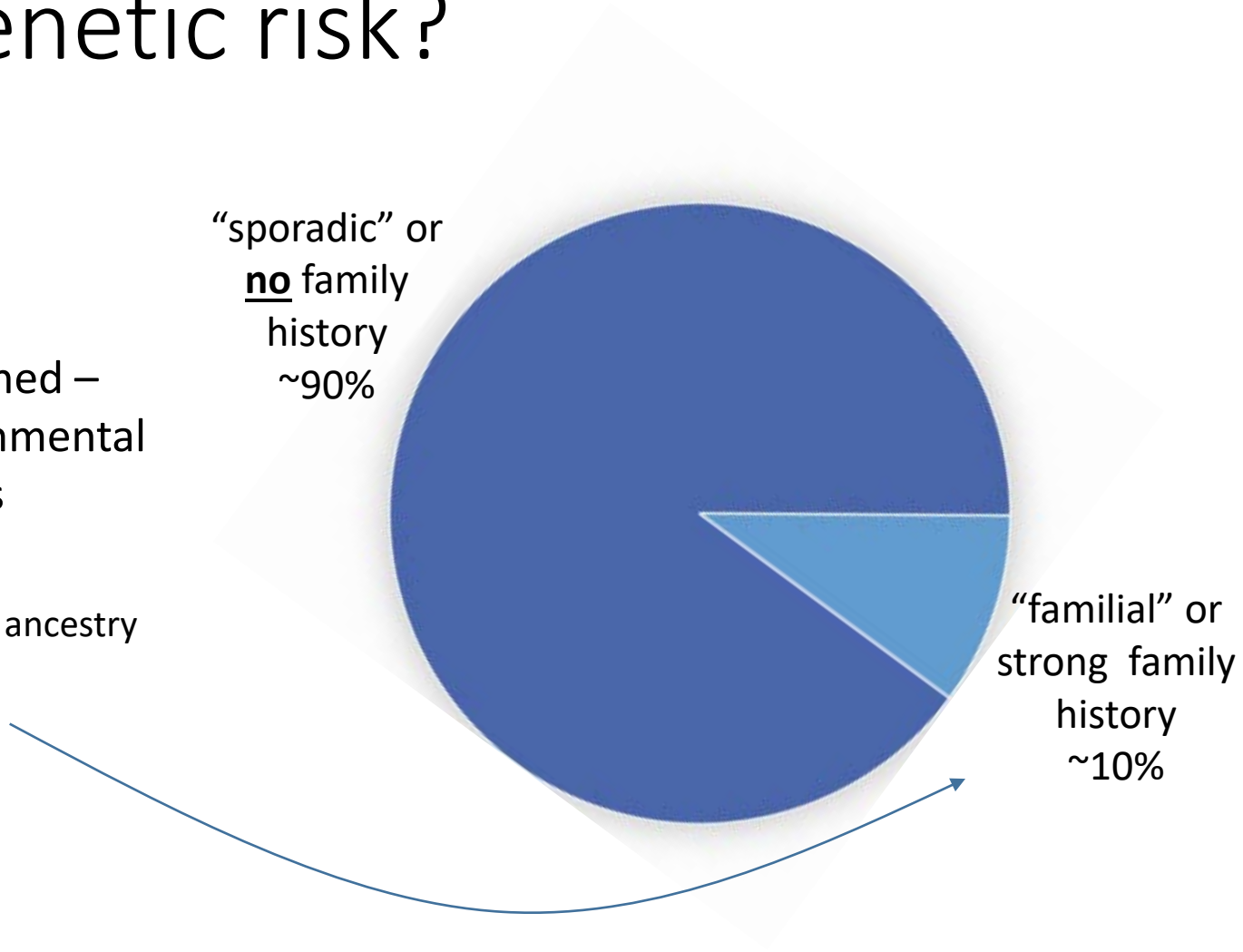


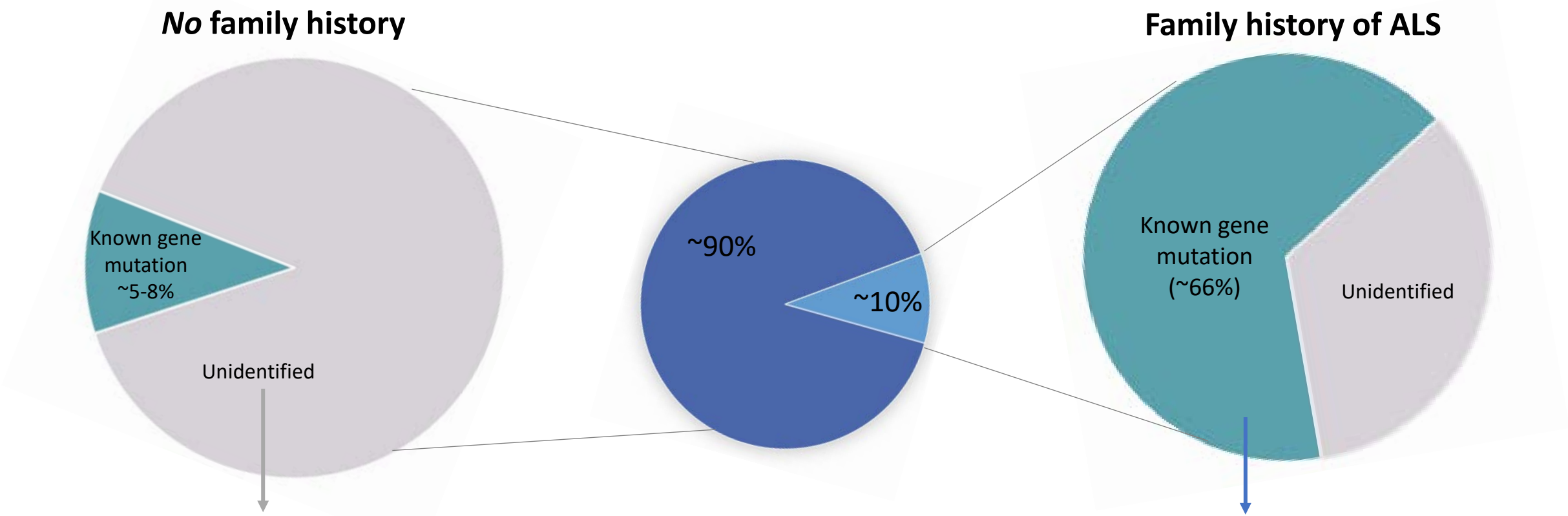
Motor neuron degeneration

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**

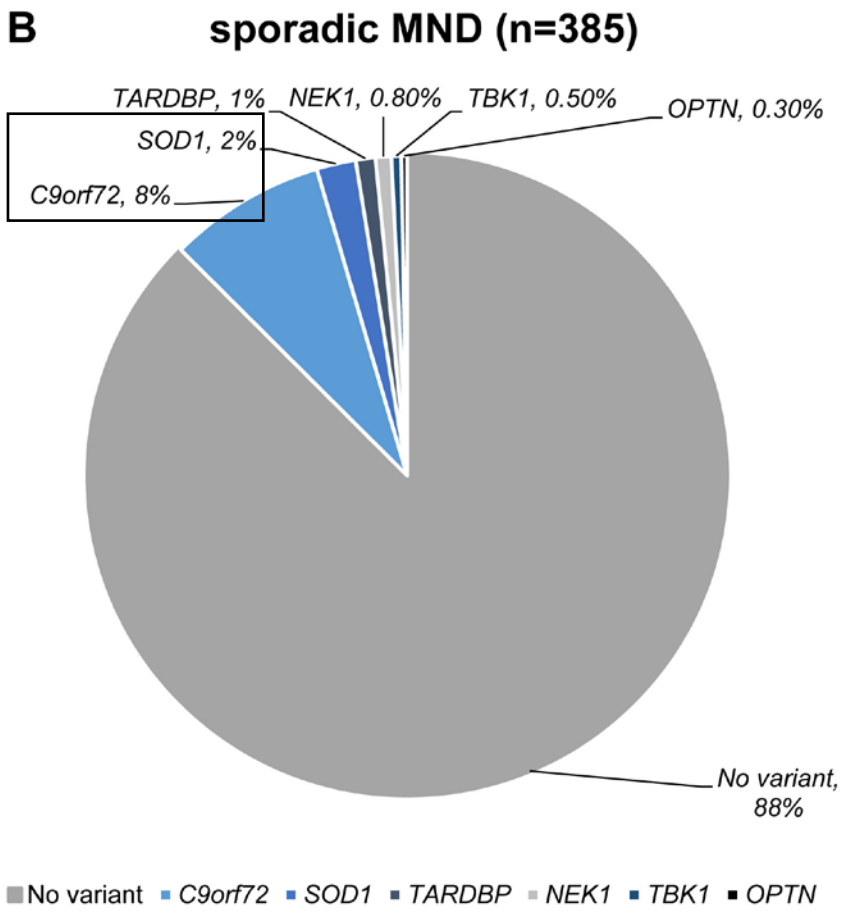


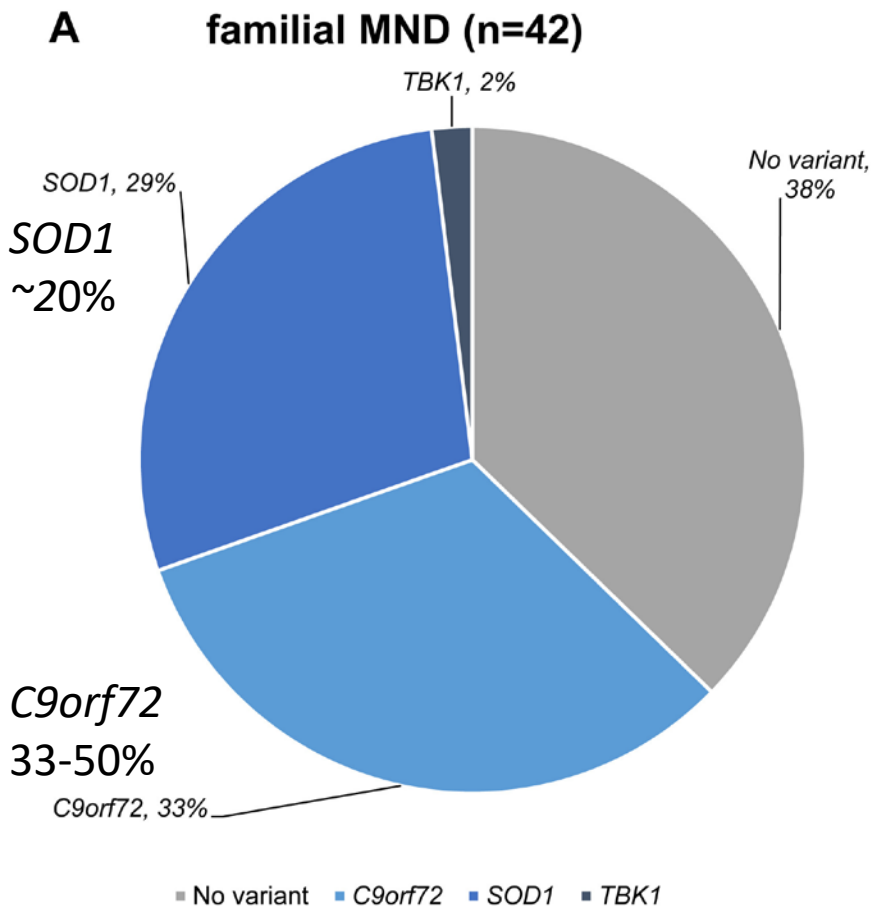
Is ALS “genetic” or “hereditary”?



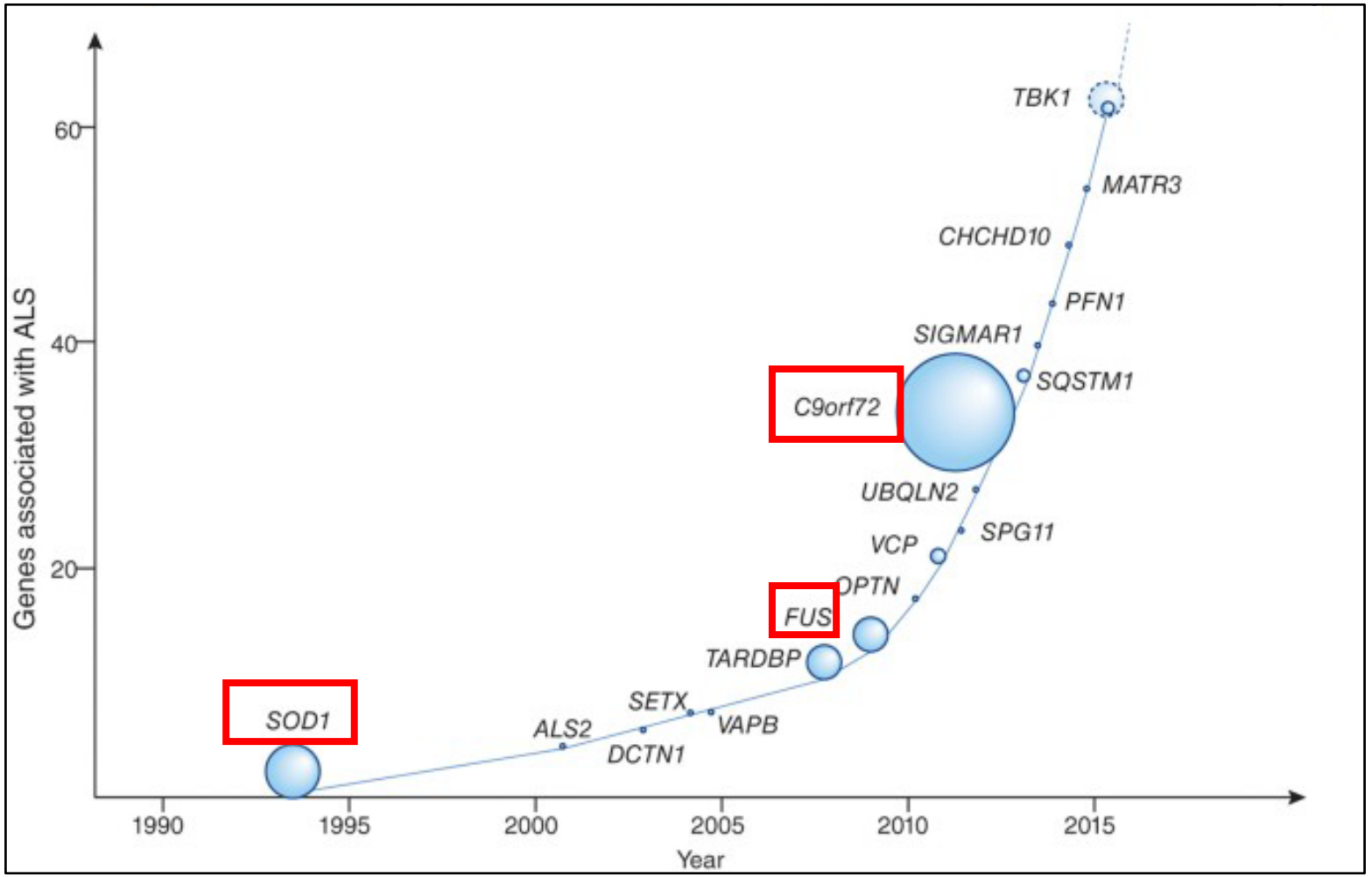
- Typically <u>not</u> monogenetic (not caused by a single gene mutation)
- More commonly monogenic (caused by a singled gene mutation)

ALS-associated genes





ALS-associated genes

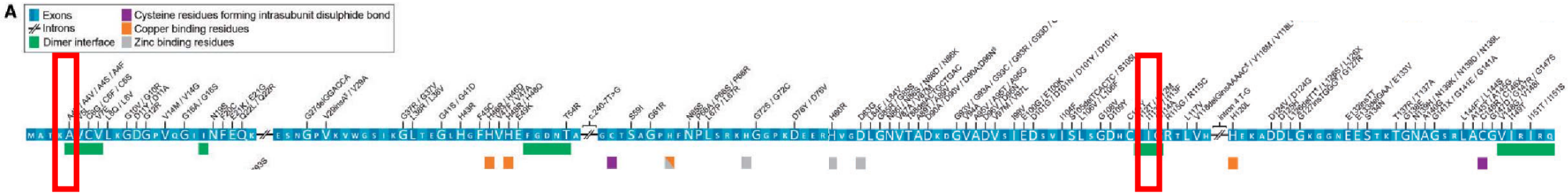


C9orf72 and *SOD1*

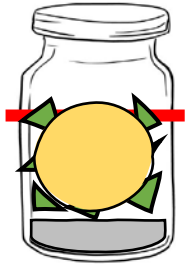
- Most common genes associated with ALS
- Active clinical drug trials for gene-specific drugs

Houlden & Battencourt. *Nat Neurosci*. 2015.

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

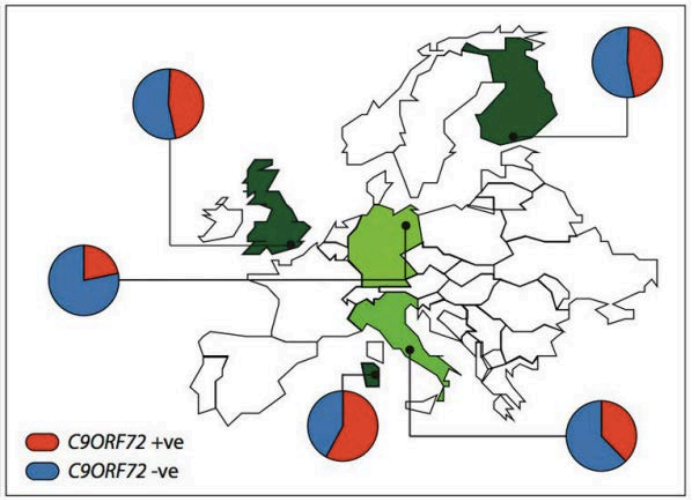


- *SOD1* I114T – extreme phenotypic variability
  - Penetrance is ~50% at age 60 and 88% at age 80
  - More slowly progressive disease

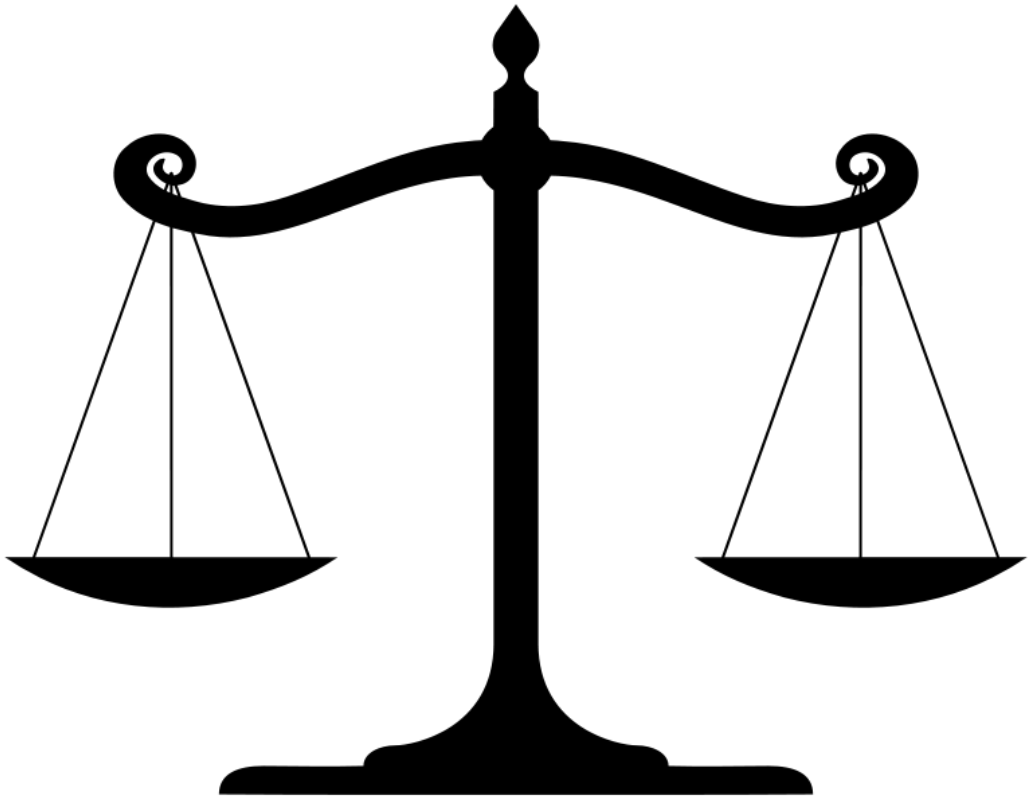
Saccon RA et al. *Brain* 2013.

C9orf72

- Identified in 2011
- GGGGCC 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

How can this information be helpful?

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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-Amyotropic Lateral Sclerosis
  - A Study of BIIB067 When Initiated in Clinically Presymptomatic Adults With a Confirmed Superoxide Dismutase 1 Mutation (ATLAS)

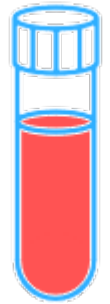
Should I get tested?

- 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 4-6weeks



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

ClinGen
Clinical Genome Resource

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