



ALS Research Advances: Making Sense of Antisense Therapy

Kuldip Dave, Ph.D.

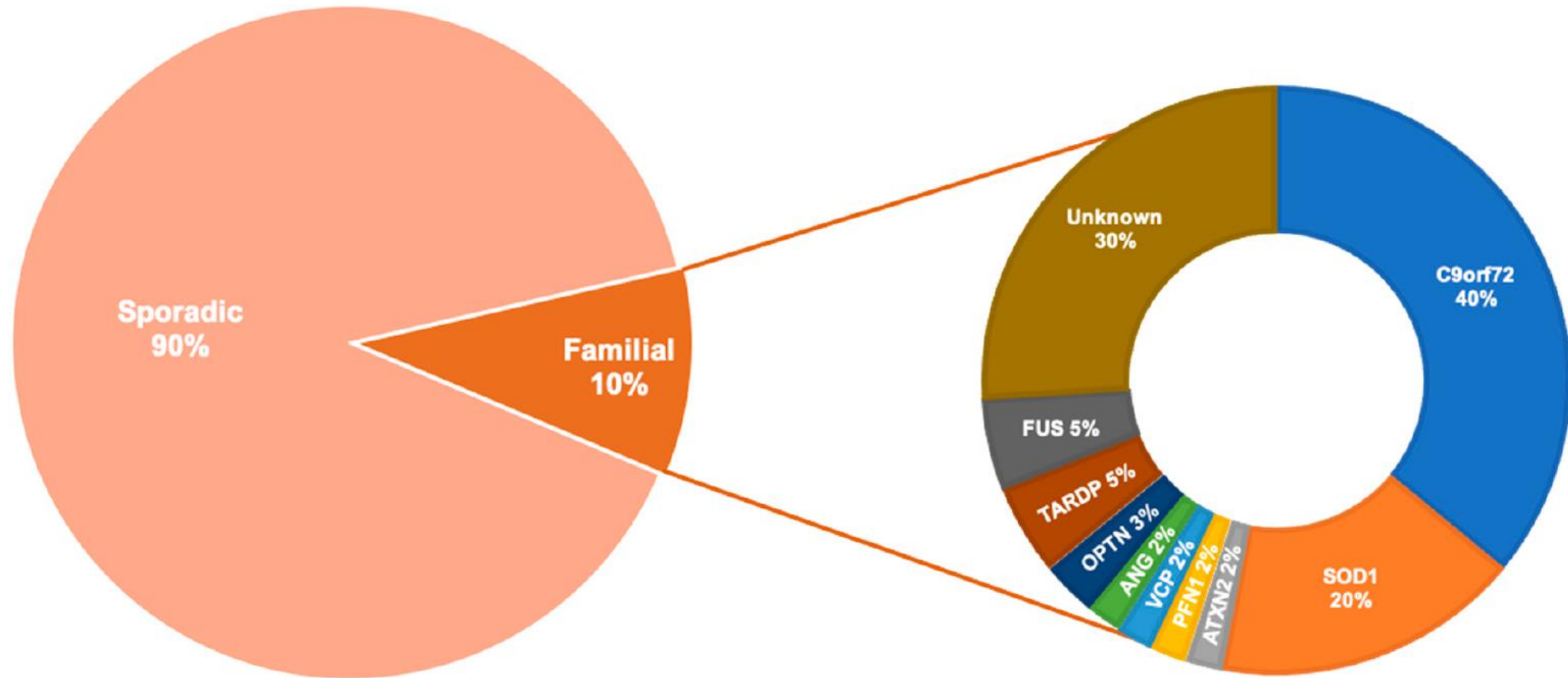
Senior Vice President, Research
The ALS Association

ALS
ASSOCIATION

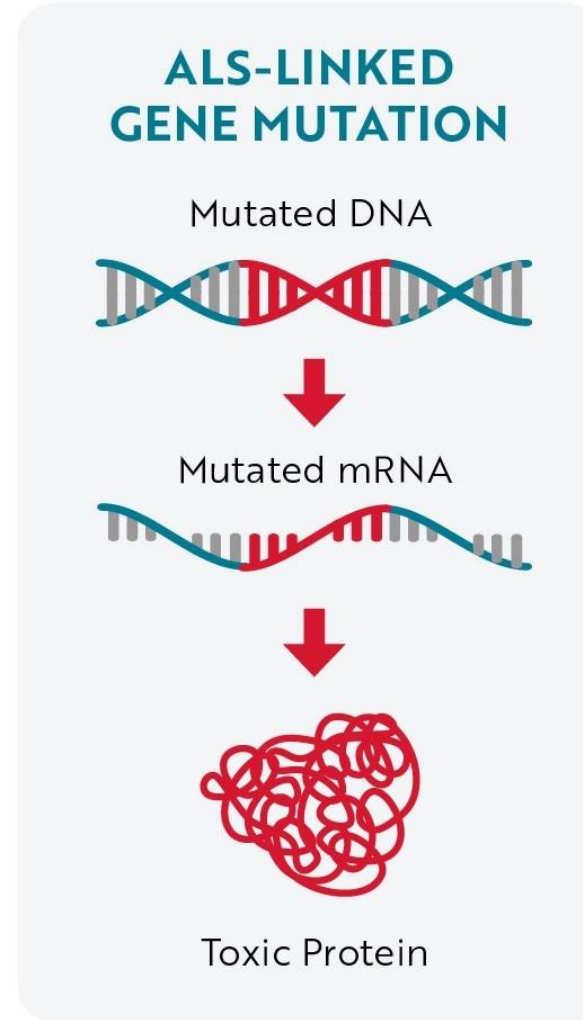
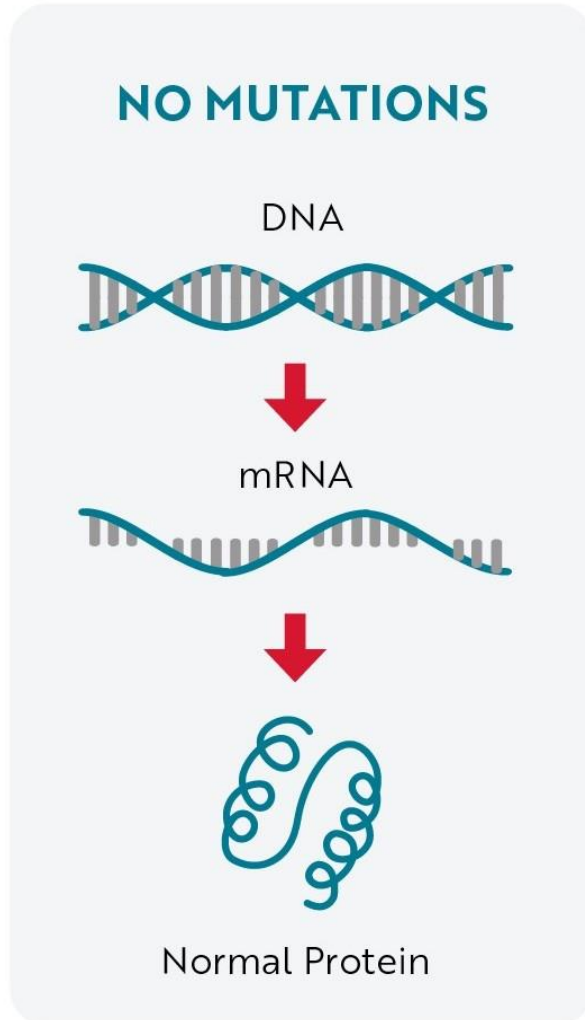
Education@ALS.org

800-782-4747

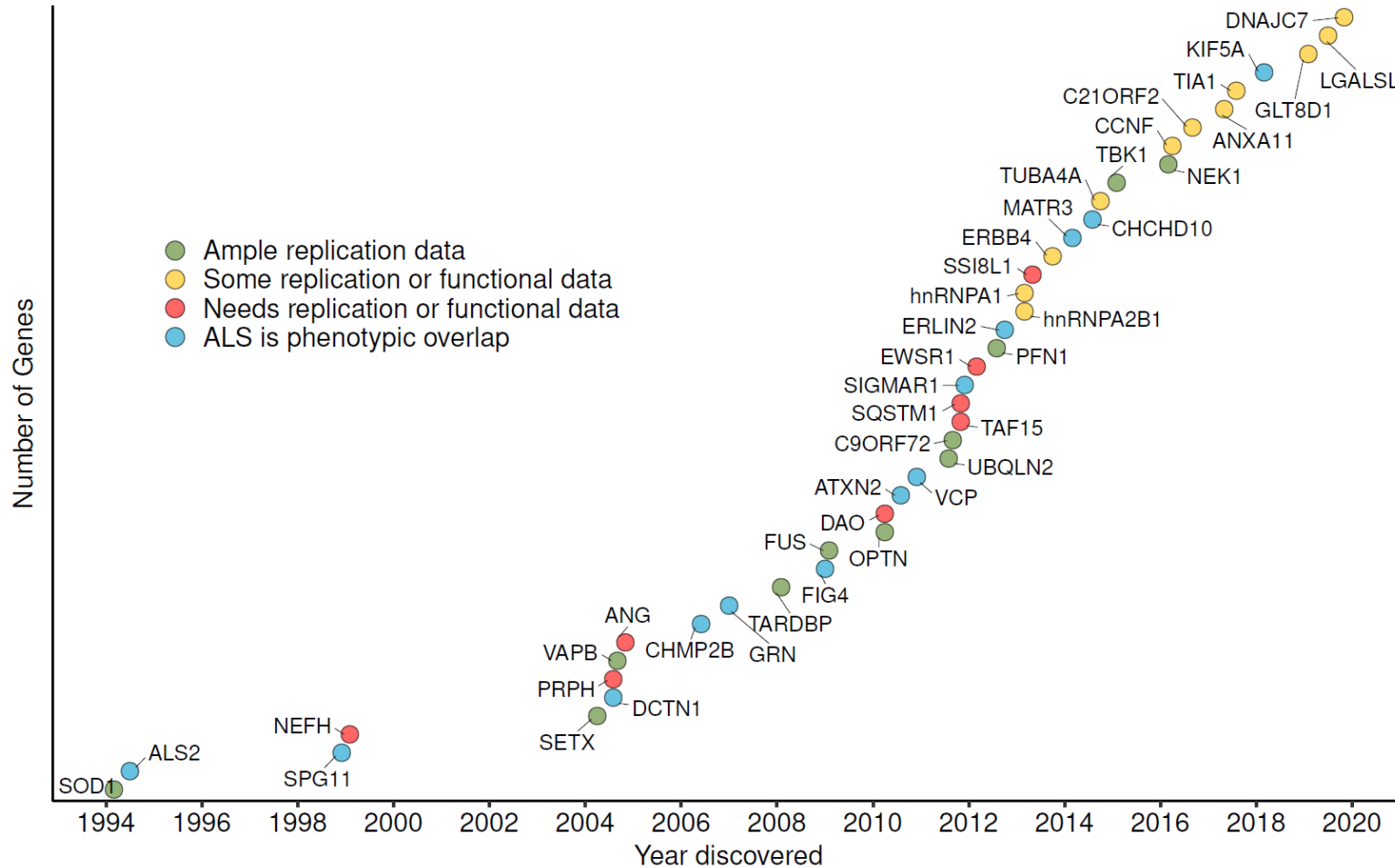
Sporadic and Familial Forms of ALS



DNA → RNA → Proteins

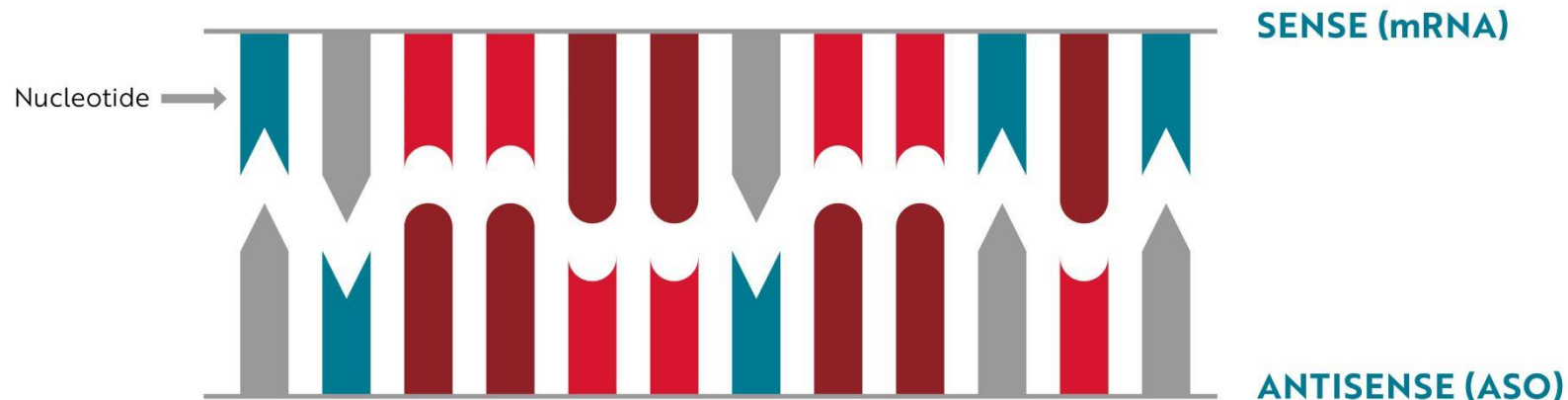


Genes Associated with Increased Risk of ALS

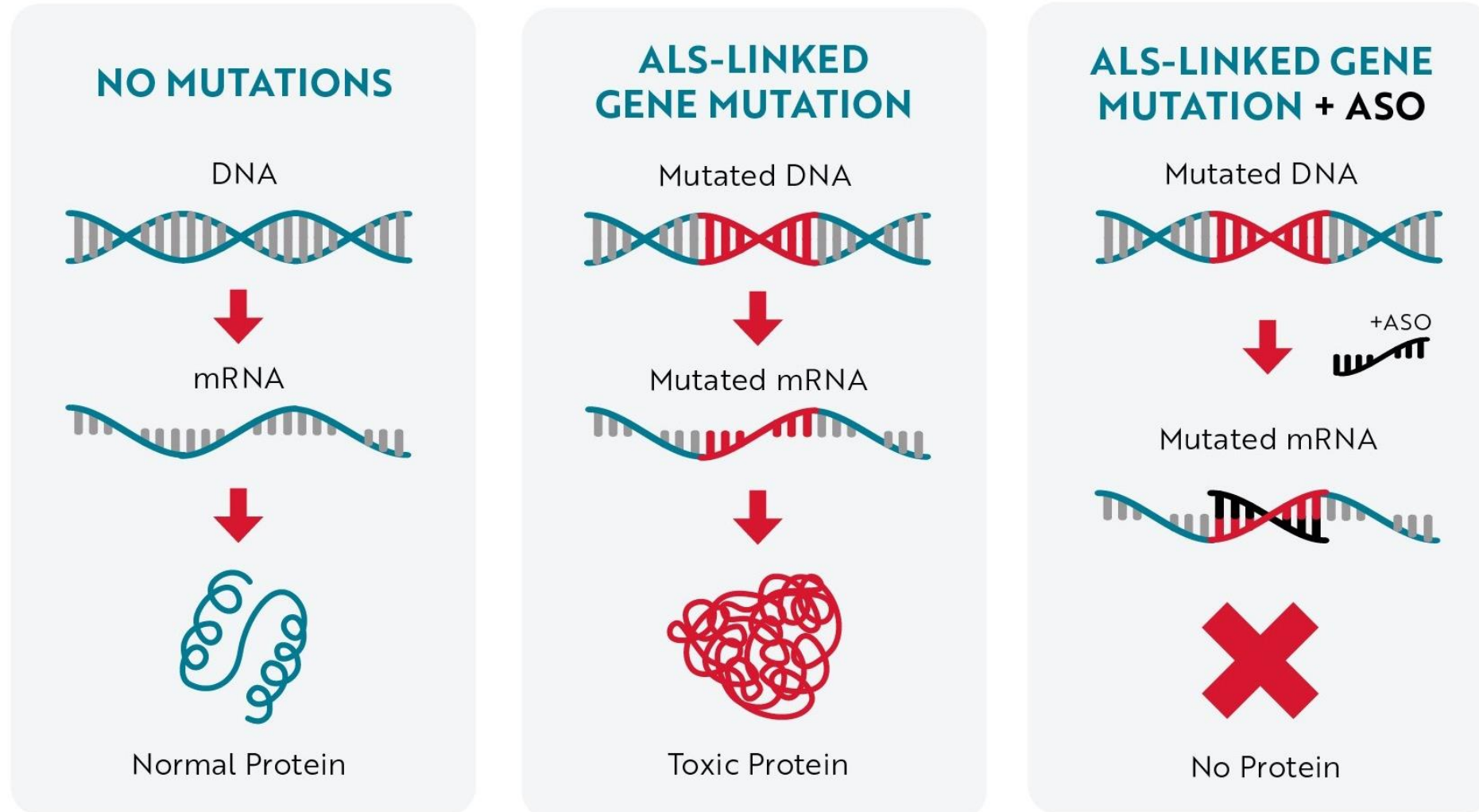


What Is Antisense Therapy?

- A way to treat ALS and other neurologic conditions using short DNA-like molecules called antisense oligonucleotides (ASOs).
- ASOs = short strings of nucleotides designed to seek out and attach to a specific sequence of RNA.
- Once an ASO binds to RNA, it can do one of two things: “knock down” the RNA or modulate its splicing.



How ASOs Work: Knockdown Approach

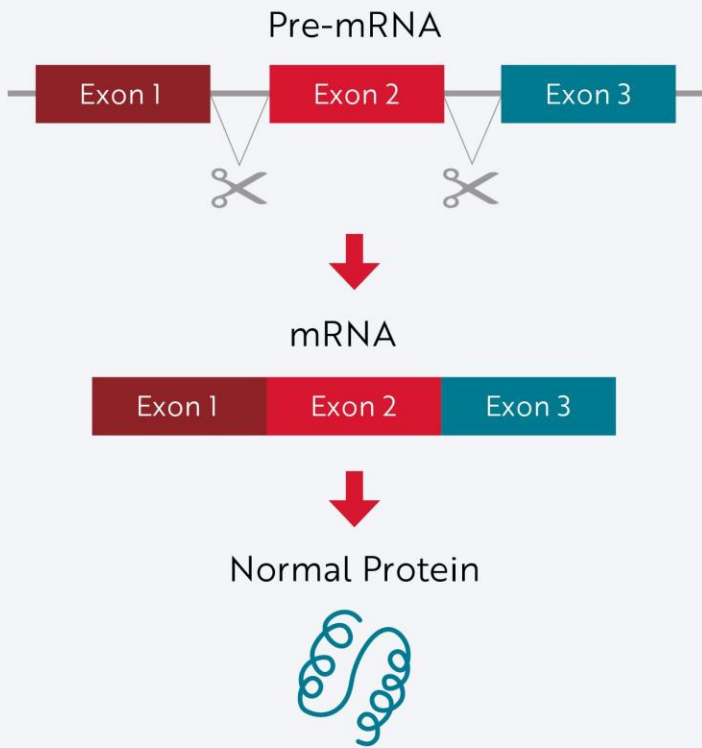


Knockdown ASOs work to eliminate the mutated, toxic protein by preventing it from being produced.

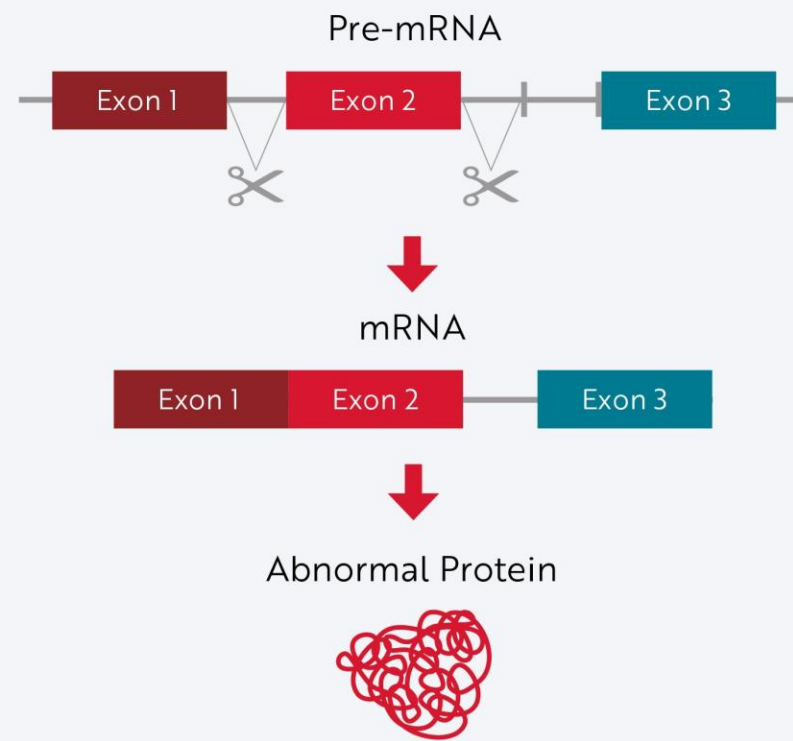
How ASOs Work: Splice Modulating Approach



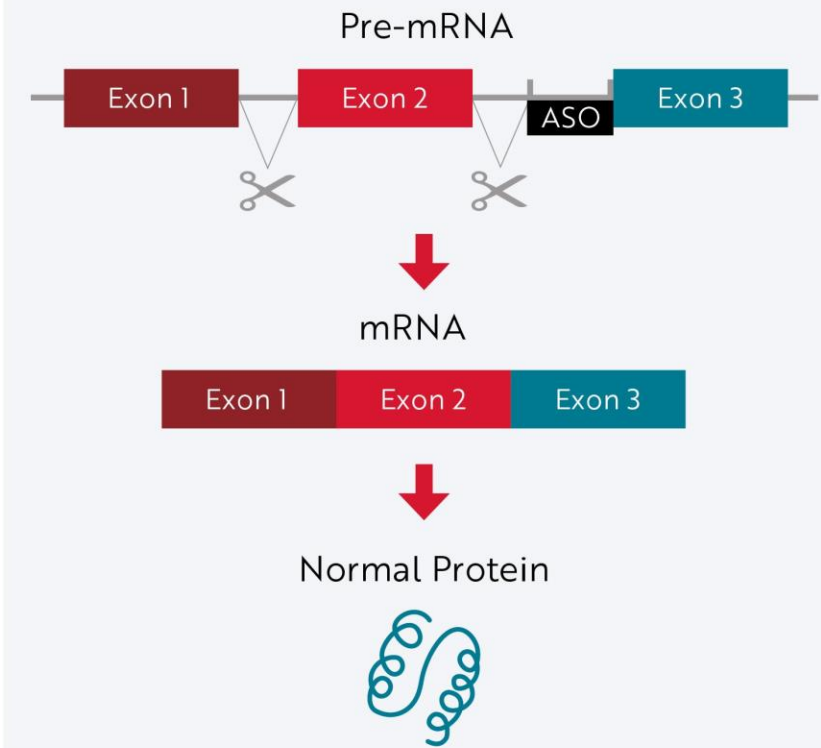
NORMAL SPLICING



ABNORMAL SPLICING



ABNORMAL SPLICING + ASO



Splice-modulating ASOs work to fix misassembled mRNA so a normal protein is produced.

SOD1 Mutations – Qalsody / Tofersen



- Second most common cause of familial ALS
- The FDA approved tofersen for the treatment of *SOD1*-ALS on April 25, 2023.
- It specifically targets the RNA produced from mutated *SOD1* genes to stop toxic SOD1 proteins from being made—“knockdown approach”.
 - In the phase 3 VALOR trial, tofersen reduced SOD1 protein levels in CSF by 35% after 8 weeks of treatment.
- Ongoing phase 3 ATLAS Study is looking at whether tofersen can delay or prevent the development of symptoms in *SOD1* gene carriers.

FUS Mutations – Jacifusen



- Mutations in the *FUS* gene are present in about 5% of familial ALS and about 1% of sporadic ALS cases.
 - Cause clumps of FUS protein that damage and destroy motor neurons.
- Jacifusen is an investigational ASO designed to reduce the production of the mutated FUS protein.
 - Ongoing phase 3 trial
- Early research showed it has the potential to delay or prevent ALS caused by a mutant *FUS* gene before symptoms appear or to slow clinical progression after disease onset.

Importance of Genetic Testing & Counseling



- Genetic testing looks for harmful changes in DNA.
 - Usually performed on a saliva sample, cheek swab, or blood sample.
- Knowing that you have a specific ALS-linked gene mutation could make you eligible for clinical trials or an FDA-approved gene-targeted therapy.
- There are also potential drawbacks, so genetic counseling is recommended before and after testing.
- Genetic counselors are trained to help people understand their family medical history, the genetics of ALS, and the potential impacts of genetic testing.

How to Get Genetic Testing & Counseling



Talk with your doctor

Genetic testing needs to be ordered by a health care professional, so start by talking with your doctor about whether testing is right for you. You can also ask for a referral to a genetic counselor.

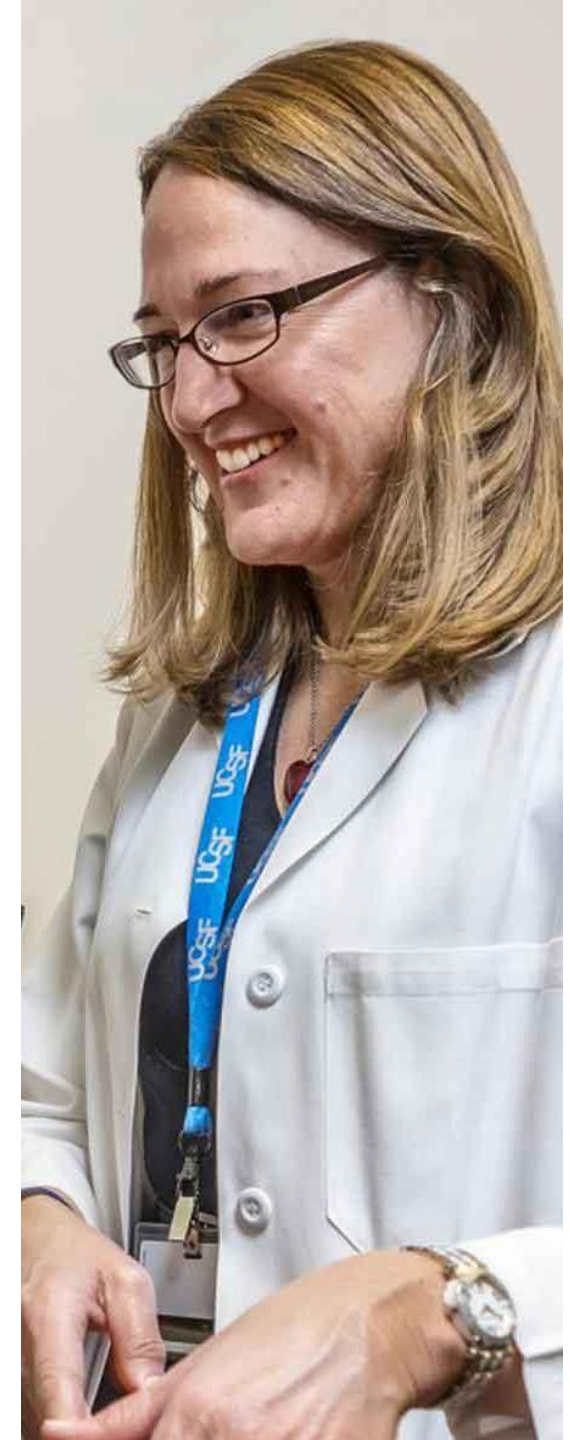


ALS Identified

This program – sponsored by Biogen and offered through the diagnostic company Invitae – provides free genetic testing and post-test counseling to people with ALS and their families.



www.als.org/genetictesting



ASOs and Sporadic ALS



- Much of this research focuses on an RNA-binding protein called TDP-43 and the RNA it targets.
- Preclinical research has shown that using knockdown ASOs to stop the production of ataxin-2 can significantly decrease the number of TDP-43 aggregates in neurons.
 - Example: BIIB105 / ION541 – phase 1/2 ALSpire Study
- Researchers also are developing splice-modulating ASOs that correct RNA mistakes cause by a loss of TDP-43 to restore normal protein levels and slow or stop neurodegeneration.
 - Example: QRL-201 (stathmin-2) – phase 1

Future Directions



- There are more than 40 genes linked to ALS that could be targeted using this technology.
 - Increased participation in genetic testing could help identify even more.
- Also important to look for other proteins impacted by TDP-43 loss of function.

More Information

 als.org/genetics

 als.org/gene-targeted-therapies

 als.org/geneticstesting



SHAPE FUTURE RESEARCH

Clinical Trials and Treatment Needs Survey

- What should matter the most when new ALS drug treatments and clinical trial designs are being developed?
- People living with ALS, current caregivers, and past caregivers are eligible to participate.
- Survey will be open April 2 – May 31.

Register today at
ALSFocus.org



ALS NEXUS

JULY 14-17, 2024 | DALLAS, TX

alsnexus.org

Questions?