GLOSSARY OF TERMS

Amino acid: Amino acids are the building blocks of proteins; a specific order of amino acids is required to make a functional protein.

ASO (antisense oligonucleotide): A short synthetic RNA that uses a specific DNA sequence to locate a specific region (gene) where it can hide a mutation that is present in the gene.

Central dogma: The process by which your genetic code, or DNA, is transcribed into messenger RNA (mRNA) using complementary nucleotides (individual components of DNA or RNA). mRNA is understood by the translational machinery, which takes every three bases and translates it into an amino acid. Amino acids are linked on a growing chain, which becomes a protein. Every protein that the body needs has a sequence of DNA that undergoes this process. *See Figure 1.*

Exon: A sequence of protein-encoding nucleotides within a gene. Exons are separated by introns, which are removed by splicing, so translation can occur. *See Figure 2.*

Gene therapy: A therapeutic approach that aims to correct the gene that is dysfunctional. There are a few different methods to do this.

Intron: A sequence of nucleotides within a gene that separates exons. It was once thought that these sequences were junk, simply removed during protein synthesis. It is now understood that sequences within the introns have many functions. *See Figure 2.*

Leukodystrophy: A category of diseases and disorders that predominantly affect the white matter of the brain and spinal cord.

Leukoencephalopathy: A term that describes all diseases of the white matter.

Missense mutation: A missense mutation is a type of mutation in which the altered nucleotide changes the protein code. This change can alter the structure of a protein, which can affect function.

Mutation: A mutation is a change in the DNA sequence. Generally, all people carry mutations, the vast majority of which have no consequence. But certain mutations in important areas of the DNA sequence, or in areas that are shared across many species (known as highly conserved DNA), can have debilitating consequences.

Nanoparticle (dendrimer): Nanoparticles are a diverse category of very, very small molecules. They can be used to encapsulate or carry drugs or other small particles through tissues. Nanoparticles can be designed to have certain properties that make them uniquely suited to function in certain tissues or under certain conditions. The dendrimer nanoparticles that we work with are about 4–6 nm in diameter. For reference, one human hair is approximately 70,000 nm in diameter.

Natural history study: A study that follows a group of people over time who have, or are at risk of developing, a specific medical condition. A natural history study collects health information in order to understand how the medical condition develops and how to treat it.

Organoid (or mini-brain): This is essentially a ball of cells that are allowed to differentiate, or mature, as they would in a brain. An organoid begins with pluripotent stem cells, which can become any type of cell (neurons, astrocytes, etc.). The stem cells replicate and change into different cell types, forming a cellular organization similar to that of a brain. Organoids are very useful to our work, because they allow us to observe interactions between different types of cells, as would occur in a brain, and to observe the effects of disease, injury and treatment on these cellular interactions.

Respiratory chain complex (or the electron transport chain): A series of protein complexes that operate in sequence to produce energy for the cell. A very large number of these protein groups are contained in our mitochondria, and cells can have hundreds to hundreds of thousands of mitochondria.

RNA sequencing (RNAseq): RNA sequencing is a commonly used technique in research to analyze RNA. RNA sequencing tells us which genes are being made and how many copies are made, and can even tell us if splicing is affected. This information must be compared to a baseline sample. In LBSL research, we compare patient cell sequences to the sequences of age- and sex-matched people without LBSL.

Splice site (and splice site mutation): A splice site is the area in a sequence where splicing cuts are made to either remove introns or link exons. In LBSL, a common mutation is located in the splice site, which affects the ability of the protein to be made correctly.

Splicing: Splicing is the process by which protein-making machinery removes unneeded nucleotides from a gene sequence (called an intron), leaving only the sequences (called exons) that code for proteins. Many proteins can be made from the same gene sequence, but when the exons are in a different order, a unique protein, called an alternative splice product, is produced. When a sequence doesn't make any sense, the cell will usually degrade. *See Figure 3.*

tRNA: Transfer RNAs (tRNAs) are small molecules that match the genetic code to the appropriate amino acid. tRNAs help build chains of amino acids that become proteins. *See Figure 4.*

tRNA synthetase: Synthetases, like the DARS2 gene, link tRNAs to an amino acid for protein translation. For DARS2, this happens in the cell's mitochondria. Other tRNA synthetases exist outside the mitochondria, in the cell body. *See Figure 4.*

White matter: White matter is the fatty (lipid-rich) tissue that wraps around nerve cell axons. Information and communication between cells can be sent and received quickly when traveling via these insulated "highways."

FIGURES

Figure 1: The Central Dogma

DNA

Provides the code or "recipe" for all the proteins our bodies need to make

mRNA

DNA must be transcribed into mRNA to be understood by the cell's translation machinery

protein

Proteins are the final product, responsible for the structure, function and regulation of tissues and organs

Figure 2: Introns and Extrons

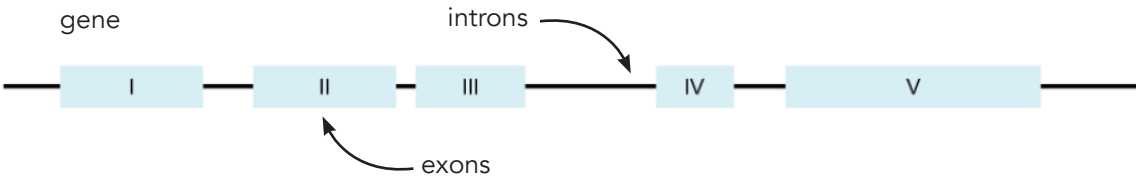


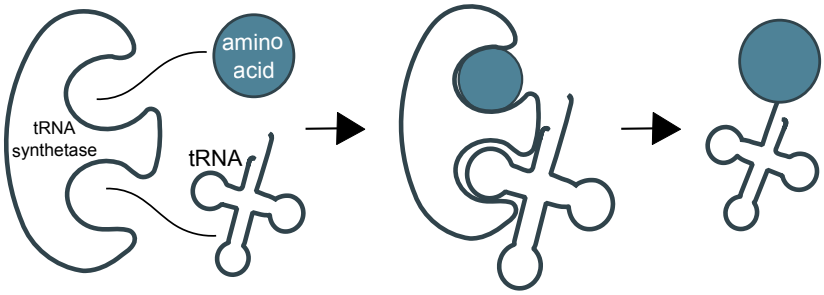
Figure 3: Splicing

Full mRNA sequence

Alternatively spliced transcripts still make sense, come from the original full sequence, and will produce unique proteins.

These transcripts do not make sense and will be degraded. These products may have been made as a result of a mutation.

Figure 4: tRNA Synthetases



tRNA synthetases catalyze the binding of amino acids to tRNAs.

CURE LBSL

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