**INTRODUCTION TO GENETICS**

### WHAT IS YOUR GENOME?

- **Your genome** can be thought of as a book that contains the instructions to life.
- **Chromosomes** are the chapters in this book.
- **DNA** are the words written across the pages.
- The 3,000,000,000 units of DNA that make up your genome are packaged into 23 pairs of chromosomes and exist in every cell of your body.

### WHAT ARE GENES & WHAT DO THEY DO?

- **Genes** are important paragraphs interspersed throughout the book and only makeup 1.5% of your genome. You have 20,000 – 25,000 genes.
- Genes contain information for human traits and the biological building blocks for your cells.
- To make these building blocks, your body makes a photocopy of the required paragraphs, generating a copy of the gene called **RNA**.
- The RNA is then used by your body to make your biological building blocks called **proteins**.

These resources have been developed by the International Alliance of ALS/MND Associations. The material has been adapted by Kristiana Salmon and Helmut Bernhard from a presentation given by Dr. Kelly Williams, Macquarie University, Australia.
INTRODUCTION TO GENETICS

WHAT IS GENETIC VARIATION?

Your DNA is made up of individual units. There are 4 types of DNA units: A, T, C, and G.

Everyone has the same genes, but a gene can be spelled out slightly differently in different individuals, due to genetic variation.

These are considered different “versions” of the genes, and give us our unique traits as humans.

When your DNA is copied, mistakes can happen and this is a normal process.

When a mistake in your DNA occurs, and results in a detrimental outcome such as a disorder, this is called a mutation or pathogenic variant.

These detrimental mistakes can be caused by a change in your DNA units (such as a single nucleotide variant), a portion of your DNA deleted or inserted, or a small region of DNA units repeated multiple times.

HOW ARE GENES INHERITED?

You have 46 chromosomes in which your DNA is packaged.

You inherited one set of 23 chromosomes from your mother, and the remaining set of 23 chromosomes from your father.

Depending on which version of a gene you inherited from each parent, the gene will result in a different trait.

HOW DO WE INHERIT GENETIC DISORDERS?

Some genetic disorders only need one copy of a mutant version of the gene to be present for an individual to be affected by the disorder. This is called autosomal dominant inheritance.

Some genetic disorders need two copies of a mutant version of the gene to be present for an individual to be affected by the disorder. This is called autosomal recessive inheritance.

Some people have a copy of a mutant version of the gene, but are unaffected by the disorder. The mutant version of the gene can be passed on, and such people are called carriers.
WHY IS IT IMPORTANT TO UNDERSTAND GENETIC CAUSES OF DISEASE?

- Help with diagnosis
- Understand disease biology
- Target for treatments

ALS/MND GENETICS

WHY IS GENETICS RELEVANT TO ALS/MND?

- Most people with ALS/MND develop the condition for unknown reasons.
- Some people with ALS/MND have a family history of the condition, or related disorders.
- Historically, the above have been referred to as sporadic and familial ALS/MND, respectively.
- Genetic causes have not been identified in all people with familial ALS/MND.
- In some cases of sporadic ALS/MND, genetic causes have been identified.

Familial/hereditary

Ambiguous family history

Sporadic with genetic mutation

Sporadic

Our understanding of the role genetics plays in ALS/MND has advanced considerably.

The field is moving away from a clear distinction between familial and sporadic ALS/MND, recognizing that ALS/MND exhibits a spectrum of inheritance patterns and genetic involvement.

More than 40 genes have been identified as being associated with either causing or increasing the risk of developing ALS/MND.

Incidence of these genetic mutations varies geographically.
ALS/MND GENETICS

IF I CARRY AN ALS GENE MUTATION, WILL I DEFINITELY DEVELOP ALS/MND?

- This is called gene penetrance.
- Penetrance is the risk that you will develop ALS/MND if you carry an associated gene mutation.
- Most ALS/MND gene mutations have incomplete penetrance, meaning there is a chance that symptoms may never develop.

Both genetic and other factors (environment, lifestyle, ageing) contribute to the development of ALS/MND symptoms.

**Individuals who all carry the same ALS/MND gene mutation**

**Complete penetrance**

**Incomplete penetrance**

CAN GENES AFFECT THE TYPE OF ALS/MND?

- ALS/MND varies between individuals:
  - Site of onset of symptoms
  - Age of onset
  - Progression rate
  - Impact on cognition

- Some gene mutations directly cause ALS/MND, and influence the type of symptoms present, while other mutations increase the risk of developing ALS/MND, and modify the symptoms present.

- Some gene mutations are associated with increased risk of developing other diseases as well, such as frontotemporal dementia (FTD) or ataxia. This is called pleiotropy.
Therapies are being developed that specifically target ALS/MND-associated genetic mutations.

Therapeutic strategies can include: antisense oligonucleotides, antibody therapy, and gene therapy

**Antisense Oligonucleotide Therapy**

- Normal gene → correctly formed protein
- Mutated gene → misfolded protein → Accumulation of misfolded protein leads to ALS
- Mutated gene treated with ASO → Blocks formation of toxic protein

**Antisense oligonucleotide (ASO)**
a small piece of synthetic DNA or RNA, designed to bind to a specific gene

**Antibody Therapy**

- Mutated gene → misfolded protein
- Antibody targeting misfolded protein

**Gene Therapy**

- Healthy gene + Viral vector with healthy gene → Gene therapy