GRI DISORDER GLOSSARY

This Glossary developed in partnership with colleagues in the Institute for Neuroscience and Cardiovascular Research and the Simons Initiative for the Developing Brain at the University of Edinburgh and GRI-UK. With special thanks to Jess Lonsdale for co-ordinating the glossary and to Hailey Fazio, Daniel Fong and other anonymous contributors for their edits to various drafts of the glossary.

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CLINICAL AND TREATMENT TERMS

NDD/NDC

Neurodevelopmental Disorder/Conditions are conditions that affect people throughout brain development and are generally lifelong.

Monogenic NDD/NDC

A neurodevelopmental condition caused by a mutation in a single gene

Phenotype

Phenotype is a term used to describe the symptoms of someone with a specific health condition.

Deleterious Impacts

Harmful impacts

Small Molecule Treatment

Small molecule treatments are medicines with small molecular weights (in other words, they're not made from many big or heavy atoms), made to work on specific biological targets that are altered in a condition. This means that they may interact with a specific enzyme (proteins that help in chemical reactions like breaking down food), receptor, protein or even RNA in order to help reduce the symptoms of a condition or illness. The effects of a small molecule treatment aren't generally permanent and thus the medication may need to be taken often and over many years.

AAV

Adeno-associated vectors (AAVs) are small packages of DNA derived from viruses. These are able to correct genetic mutations within a cell, depending on the type of cell the viruses affect, treatment may only be needed once. The viruses do not reproduce and so cannot be spread from person to person.

ASO

Antisense oligonucleotides (ASOs) are strands of man-made DNA. They can bind to messenger RNA and modify the message it brings to the ribosomes, essentially protein construction sites. This allows them to change the final protein that is produced, reducing symptoms of a genetic condition without directly changing the gene.

iPSC

Induced pluripotent stem cells (iPSCs) are cells taken from a person or animal which have been reverted back to an early state where they can become any type of cell. This is done by re-expressing (turning on) genes and proteins that are made during early development but stop being expressed (are turned off) when they have performed their function.

Gene therapy

Treatments that directly modify a gene within a patient's cells in order to treat a condition.

Gene editing

The process of changing a gene and by extension the protein it produces.

Stimulant

A type of medicine that makes people more active. Caffeine is a type of stimulant, but stronger stimulants are sometimes used to help with traits of some neurodevelopmental conditions, such as ADHD.

Pharmacogenetics

Understanding how an individual's genes might change how a medicine affects them.

ECG

An electrocardiogram (ECG) is a test that records the electrical activity of the heart (NHS definition)

EEG

An electroencephalogram (EEG) is a test that records electrical activity of the brain (NHS definition)

GENETICS TERMS

Genotype

Genotype is a term used to describe the specific genetic mutation someone has. This might alter the symptoms of a condition that they have.

DNA

DNA (deoxyribonucleic acid) exists within cells to provide the blueprints of what to make. It carries the genetic instructions for development, functioning, growth, and reproduction. DNA

is organised into units called “genes”, which are packaged into structures called “chromosomes”. DNA is passed on from parents to offspring, carrying hereditary information. There are 4 letters in the DNA (A, C, G, T). If those change (mutate), this can cause a condition or a disease.

RNA

RNA (ribonucleic acid) exists within cells to help build and regulate proteins.

mRNA

mRNA (messenger ribonucleic acid) is a type of RNA that copies information in DNA so it can be read and can instruct the production of proteins.

Chromosome

Chromosomes are large bundles of DNA. Most people have 23 pairs of chromosomes.

Gene

A gene is a section of DNA that holds instructions for a specific protein.

Protein

Proteins are materials with set roles within or outside a cell. Genes in the DNA hold instructions on how to make these proteins.

Protein Synthesis

The making of proteins.

Mutation

A mutation is a change in a gene. Sometimes called a ‘variant’.

Allele

An allele is a variation of a gene found in a chromosome. Most people have two copies of a given gene in their body. Sometimes, one copy of the gene is different to the other. This might not make any difference, or it might cause a condition depending on the gene affected and how. For example, for some genes, you only need one allele that works while for others you need two.

Heterozygosity

Heterozygous means that the two alleles someone has are different. This might cause harmless changes such as changes in hair colour, or it might cause disabilities if one of the alleles isn’t able to make a healthy protein.

Homozygosity

Homozygous means that both alleles are the same. This might be harmless if both alleles are able to make a healthy protein, but it can cause major problems or even cause death if neither of the alleles is able to make a healthy protein.

Dominant Inheritance

Dominant inheritance means that only one parent has to carry the mutation to pass it onto their children. Often parents are also affected by the mutation.

Recessive Inheritance

Recessive inheritance means that both parents have to carry the mutation to pass it onto their children. Parents often aren't affected by the mutation in these cases and are known as 'carriers'.

Null Variant

Null variants cause complete loss of function of a gene.

Missense variant

A small change in a gene that somewhat changes what it does. This might result in less or more of a protein being produced, or it might change the shape of the protein that's produced which might affect its ability to function.

Nonsense variant

A change in a gene that stops it from being able to perform its normal function.

Pathogenic variant

A change that is known to cause disease or disability.

Benign variant

A change that has no effect on the individual.

Unknown Significance

A mutation of unknown significance may or may not be causing difficulties for an individual. To ascertain the significance of a variant in patients, clinical researchers need to compare the symptoms of different people who share the same variant to see if they have a specific symptom (or group of symptoms) in common.

Atypical Presentation

Someone affected by a condition who has different traits to the usual patient.

Gain of Function

A gene variant / mutation that causes a protein to have an additional or different function to standard or one that makes a protein 'more efficient' at its job. This isn't always beneficial as it may disrupt balances between other proteins.

Loss of Function

A gene variant / mutation that causes a protein to not work as intended.

Haploinsufficiency

Having half the amount of a protein necessary, due to a loss of function in one gene.

X-Linked

A mutation that is carried on the X chromosome. These are generally more severe in people with only one X chromosome (e.g., the majority of males)

Autosomal

On one of the non-sex-linked chromosomes (i.e., chromosomes 1-22).

RESEARCH METHOD TERMS

Basic Science

Research to understand how a specific gene or protein works or to prove the concept of something without necessarily thinking about how it might translate to people.

Translational Research

Research that builds on basic science by considering factors such as how a condition affects humans and how we might make someone feel better.

Clinical Trial

Research done in humans to see if a therapy has a positive effect.

In silico

Research done using computers.

In vitro

Research done outside of a living being such as in test tubes or petri dishes.

In vivo

Research done inside a living being, e.g., rats.

N of 1

A clinical trial in with only one participant.

Longitudinal Study

Research that looks at how something changes over time.

PhD

Someone who has a doctorate in researching things. In the context of genetic conditions, they study how these conditions work but they probably don't treat them in people.

MD

An MD (medical doctor) is someone who treats people with illnesses, injuries, or long-term conditions. Some medical doctors are also medical researchers.

ANIMAL TERMS

Model Systems

Something designed to look like a condition. This could be a computer program that predicts what might happen in a condition, cells grown into organ like structures, or animals which have been modified in some way to have similar symptoms or changes to someone with a condition.

Animal Models

Animals used to understand the way a disease or condition works. Common animal models include mice, rats, chickens, zebrafish, fruit flies and worms.

Wild Type

An animal that has not been genetically modified

Knock In

The insertion of a gene in an animal model (a genetic modification)

Knock Down

The reduction of production of a protein in an animal model (by a genetic modification)

Knock Out

The removal of a gene in an animal model (by genetic modification)

Heterozygous

A person or animal with two different copies of a specific gene; i.e. one standard, one with a mutation / variant

Homozygous

A person or animal with two identical copies of a specific gene (either both standard, or both with the same mutation / variant)

NEURONAL STRUCTURE TERMS

Neurons

Nerve cells, they fire electrical signals around the nervous system. These are what allow us to perceive and react to the world around us.

Synapse

A structure between neurons that allows for communication between them through chemical or electrical signals

Potentiation

Nerve impulses increasing in strength when pathways are used more often

RECEPTOR TERMS

Receptor

A protein-based structure that is able to receive signals such as neurotransmitters

Neurotransmitters

Compounds that are exchanged between neurons and to other cells to allow them to communicate

Binding Site

The point on a protein where something is able to bind with it. This might be another protein, a fat, a neurotransmitter, or an ion (a type of atom or collection of atoms). The protein then

responds to the item binding to it. It might do this by opening to let other things through it, it might release something in response, it might break down the thing that's bound to it (Not in the case of ions), it might go on to bind with a protein itself.

Excitatory

Excitatory signals and neurotransmitters encourage a neuron to fire and thus send a signal to another cell.

Inhibitory

Inhibitory signals and neurotransmitters discourage a neuron from firing and thus prevent it from sending a signal to another cell.

Glutamate

A type of neurotransmitter that is excitatory. It is very common throughout the brain

AMPAR

A type of receptor that mediates excitatory transmission. It regulates potentiation.

NMDAR

Another excitatory receptor on neurons that opens during neuron firing and helps the brain learn and form memories.

KAR

Kainate receptors, also known as kainate acid receptors, are involved in both excitatory and inhibitory neuronal firing.

Delta Glutamate Receptors

Receptors that bind to amino acids without opening. They play roles in the formation of synapses, synaptic potentiation, and motor coordination.

Subunit

A single protein that works with others to make a receptor

GluN1 / GluN2A-D / GluN3A-B

NMDAR subunits that come in different subtypes (flavours), with different properties.

GRIN genes: GRIN1 / GRIN2A-D / GRIN3A-B

Genes that hold instructions for corresponding NMDAR subunits. Mutations in these genes disrupt NMDAR function and lead to phenotypes we see in GRIN conditions

GRIA genes: GRIA1 / GRIA2 / GRIA3 / GRIA4

Genes that hold instructions for different subunits of an AMPA receptor. Mutations in these disrupt AMPAR function and lead to the phenotypes we see in GRIA conditions.

GluA1 / GluA2 / GluA3 / GluA4

AMPAR subunits with different subtypes and properties.

GRID genes: GRID1 / GRID2

Genes that hold instructions for subunits of delta glutamate receptors. Mutations in these genes disrupt delta glutamate receptor functions and lead to the phenotypes we see in GRID conditions.

GluD1/GluD2

Delta glutamate receptor subunits with different subtypes and properties.

GRIK genes: GRIK1 / GRIK2 / GRIK3 / GRIK4 / GRIK5

Genes that hold instructions for different subunits of the kainate receptor. Mutations in these disrupt kainate receptor functions and lead to the phenotypes we see in GRIK conditions.

GluK1/GluK2/GluK3/GluK4/GluK5

KAR subunits with different subtypes and properties, changes in these cause the symptoms of GRIK related conditions.

Agonist

An agonist binds to and activates a receptor

Antagonist

An antagonist binds to a receptor but does not activate it

PAMs

Positive allosteric modulators (PAMs) increase how well an agonist is able to bind to and activate a receptor

NAMs

Negative allosteric modulators (NAMs) decrease how well an agonist is able to bind to and activate a receptor

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