



## Glossary of scientific expressions

For the 8<sup>th</sup> Annual Symposium on *ATP1A3* in Disease

*Moving towards the light*

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*This glossary aims to cover some key terms that will come up in the symposium, including both scientific and medical terms.*

*If there are some terms mentioned during the symposium, which you are missing in this glossary, please highlight these to the organising committee, so we can make sure these are covered during the question and answer sessions.*

*The glossary is split up in sections to make following lectures around these topics easier.*

### Cell structure (general cells)

**Cell (plasma) membrane** – the lipid layer surrounding a cell, which separates the inside from the outside. The membrane contains many lipids and enzymes, which control the movement of substances into and out of the cell.

**Endoplasmic reticulum (ER)** – a structure inside a cell. This is where membrane proteins are synthesized, and protein molecules folded. It is a confined part of the cell, surrounded by a membrane.

**Nucleus** – centre of the cell that contains almost all the genetic material. It is a confined part of the cell, surrounded by a membrane.

**Mitochondria** – part of the cell that produces energy (it is regarded the energy factory inside a cell). It generates most of the cell's supply of ATP. It is a confined part of the cell, surrounded by a membrane.

**Transmembrane** – crossing of the plasma membrane, so from inside to outside the cell, or the other way around.

**Pluripotent stem cell (PSC)** - a sub-type of stem cell which can differentiate into any specialised cell and is found naturally early in development.

[see below] **iPSC-derived** – induced pluripotent stem cells. Produced in laboratories from specialised cells e.g. skin cells. These cells have the ability to differentiate into any specialised cell and potentially replace diseased cells.

**Stem cell** – a cell with a unique ability to differentiate into many types of cells. When the word pluripotent is added, this indicates that the stem cell can differentiate into any of the 200 plus specialised cell types within the body. Multipotent stem cells,

however, can differentiate into a limited number of specialised cell types. Early embryos have the highest ability to differentiate into any cell.

**Isogenic cell lines** – cells from a single donor that are engineered and used in research to model a disease.

**HEK293** – a basic human cell line derived from human embryonic kidney.

**UPR** – **u**nfolded **p**rotein **r**esponse is a set of programmes that a cell can use to protect itself from mutation-caused misfolding.

**PERK, eIF2 $\alpha$**  - a pathway that reduces normal protein translation but increases defensive proteins.

**Cation** – positively charged ion (molecule)

**Anion** – negatively charged ion (molecule)

**Intrinsic** – internal factor

**Extrinsic** – external factor

**Exogenous** – external cause, something originating from outside the cell or human body.

**Endogenous** – internal cause, something originating from within the cell or human body.

## Nerve cells

**Neuron/nerve cell** – a cell of the nervous system and consists of several parts (axon, dendrites) and conducts nerve impulses through synapses.

**Cortical** - pertaining to the outer layer of the brain, the cerebral cortex. It plays a role in perception, thought and consciousness.

**Myelin** – protective sheath/cover around the axon. Like insulation around an electric wire, it ensures that the electrical signals pass quickly.

**Dendrites** – short branch-like extensions of a neuron that connects to other neurons.

**Axon** – the long extension of a neuron. It conducts an electrical signal (action potential) to the synapse at the end, where it triggers the release of a neurotransmitter. The longest axons in the human body can be over a metre long.

**Synapse** – gap or space between brain cells. Chemical signals (neurotransmitters) are released from one neuron and cross this gap to get to the next cell/neuron to pass on the message/action.

**Pre-synaptic** – before the gap (some drugs work on this site).

**Post-synaptic** – after the gap (some drugs work on this site).

**GABAergic neuron** – neurons that make GABA (neurotransmitter)

**Glutamatergic neuron** – neurons that make glutamate (neurotransmitter)

**Neurotransmitters** – *these are a variety of chemicals that are produced in the body to transmit signals within the nervous system*

**GABA** – gamma-aminobutyric acid, is a main neurotransmitter. One of the main roles is reducing nerve cell excitability.

**Ach (Acetylcholine)** – a neurotransmitter released by nerve cells and transmits signals to muscle cells.

**Glutamate** – main neurotransmitter for exciting neurons.

**Adrenaline (epinephrine)** – hormone (and medication) that acts as a neurotransmitter to increase blood pressure, heart rate and other changes.

**Noradrenaline (norepinephrine)** – hormone and neurotransmitter that is involved like adrenaline in increasing blood pressure and heart rate. It is released continuously.

**Serotonin** – neurotransmitter, sometimes called the happy chemical. In addition to affecting mood, it has a complex biological function including affecting cognition, reward, learning, memory.

**Dopamine** – a neurotransmitter sending signals to other cells and is important for reward-motivation and movements (motor control). It is reduced in Parkinson's disease.

## Genetic structures

**DNA – deoxyribonucleic acid (DNA)** is a molecule consisting of two chains that are coiled together and form a double helix (“twisted ladder” structure). It carries the genetic material. It is essential for life.

**RNA – ribonucleic acid**, a single chain of nucleotides (rather than the double chain like DNA). RNA is made by copying a piece of DNA and is the produce when a gene is expressed.

**Nucleotides** –These are the building block of DNA and RNA. There are four kinds, and they are connected together in a specific order to form long chains of DNA/RNA, which can be read as a manuscript written with four letters. When the RNA is decoded to make a protein, a row of three nucleotides specify one amino acid.

**Base pairs** – the four nucleotides fit together in two sets of base pairs. Guanine (G) is always paired with Cytosine (C), Adenine (A) is always paired with Thymine (T) (Uracil (U) in RNA). These bases pair together as building blocks and form the backbone of DNA as part of the double stranded helix of DNA.

**Amino acid (a.a)** –They are building blocks of proteins and involved in many other processes. There are 20 types of amino acids, which can be connected together in a specific order. When a specific sequence of amino acids is formed, the chain folds up into a protein. If one specific amino acid is changed to another, it may alter how the protein functions, or destroy the protein completely. Amino acids have a three-letter code and a one-letter code (e.g. Asp and D both refer to the amino acid called Aspartic acid).

**Protein** – a large molecule made up of amino acids and can have many different roles in the body. They are the ‘functional units’ in the cell – the machines, the building blocks etc. They have many different functions e.g. muscle contraction; cell structures; sending signals; transporting other chemicals.

**Gene** – an essential unit that is inherited and is made up of DNA. It is a sequence in the DNA that codes for a molecule with a function, e.g. a protein. There are ~20,000 protein-coding genes in the human genome. For each gene, there are two copies, one inherited from the father and one from the mother. (In men, genes on the X chromosome are only inherited from the mother.)

**Gene therapy** – term that encompasses several different types of therapy using genes to improve genetic conditions. Genetic material is delivered into a patient's cells for treatment of a disease.

**AAV** – Adeno-associated virus. A virus (not pathogenic) that is used as a vector (biological transporter or carrier) to carry a gene in gene therapy.

**Vector** – this can be considered a ‘transporter’ and is used in gene therapy to carry the good copy of the gene from outside to inside the human cells.

**Wildtype (WT)** – refers to the ‘normal’ gene

**Knock-out** – where a gene is removed (e.g. in a mouse) so that it is then missing e.g. a specific protein.

**Knock-in** – where a gene is altered (e.g. in a mouse) to reflect a genetic mutation by making the ‘mouse-model’ of the genetic condition seen in humans.

## ATP1A3 and cell signalling

**Na<sup>+</sup>**- sodium ion (molecule).

**K<sup>+</sup>**- potassium ion (molecule).

**ATP**- adenosine tri-phosphate, the universal fuel of cells.

**ADP**- adenosine di-phosphate, a product formed when ATP is consumed.

**ATP1A3 gene** – this is the gene that codes for the sodium/potassium transporting ATPase enzyme. It encodes the alpha ( $\alpha$ ) 3 subunit that is the cause of most AHC/RDP patients.

**ATP1A3** – sodium/potassium transporting ATPase subunit alpha 3 is an enzyme.

**ATPase** – a group of enzymes that break down (hydrolyses) ATP to ADP and uses the energy from this for another process.

**Sodium/potassium ATPase (sodium/potassium pump)** – cell membrane enzyme responsible for maintaining electrochemical gradients across the cell membrane. It is composed of two subunits (alpha and beta). For every ATP molecule that the pump uses, 3 sodium (Na<sup>+</sup>) ions are pumped out of the cell and 2 potassium (K<sup>+</sup>) are pumped into the cell. Nerve cells depend on the pump to transmit signals. It is found in practically all cells in animals, where it maintains the cell volume, resting potential and many other functions of the cell.

**De novo** – this means ‘of new’ and refers to a new mutation in the child that is not inherited from either parent but happened by chance in the egg or sperm.

**Mutation** – this refers to the abnormal gene.

**Heterozygous (Het)** – where one copy of the gene is normal, and one copy of the gene is abnormal (mutated) in a medical genetic condition.

**Homozygous** – where both copies of the gene are abnormal (mutations) in a medical genetic condition.

**Autosomal dominant** – Inheriting one abnormal copy of the gene which causes the disease.

**Autosomal recessive** – Inheriting one abnormal copy of the gene does not cause the disease, but two abnormal copies (one from each parent) does cause the disease.

**Subunits** – when two or more individual amino acid chains (subunits) are together in a complex to form a protein.

**Alpha subunit** – the catalytically active subunit in the sodium/potassium ATPase. It is the subunit involved in ATP1A3 gene conditions.

**D801N** – the commonest disease-causing mutation within the ATP1A3 gene. This mutation causes the amino acid aspartic acid (abbreviated to D or Asp), at position 801 within the ATP1A3 gene to be changed to a different amino acid, asparagine (abbreviated to N or Asn). D is the one letter code for Aspartic acid (an amino acid).

**Asp801Asn** – this is the same as above (D801N) but written in three letter amino acid code.

**E815K** – second commonest disease-causing mutation within the ATP1A3 gene. E, or Glutamic acid, is the amino acid at position 815 which has been changed to a different amino acid, lysine (abbreviated to K or Lys).

**Genotype** – genetic make-up of a cell (the genes).

**Phenotype** – how the symptoms of a condition present in a person.

**Ion channel** – a protein in the membrane that can open and close to allow specific ions to flow into or out of the cell. E.g. when a sodium channel opens, sodium flows into the cell because of the difference in sodium concentrations across the membrane created by the sodium/potassium ATPase.

**Ion channel blocker** – a drug that binds to an ion channel and hinders ions from flowing through it.

**Resting potential** – resting voltage of a cell. The voltage at which a cell rests and is not active. There is a difference across the cell membrane with the cell being negative on the inside versus the outside.

**Action potential** – in a nerve cell, an electrical impulse that travels down the axon and changes the membrane electrochemical gradient (potential). This results in the activation of neurotransmitters which are released across the synapse.

### Laboratory tests/terms

***In vitro*** – this means within ‘*the glass*’, and refers to an artificial environment, not in a living organism.

***In vivo*** – in the living organism.

**Multielectrode array** – device which connects neurones to an electronic measuring system

**Patch clamp recording** – a technique in electrophysiology to study the currents of ions in cells.

**Current clamp method** – detects the transmembrane voltage that results from the movement of ions.

**Whole exome sequencing (WGS)** – process of determining the complete DNA sequence of a person.

**Molecular dynamics simulations** – a computer simulation method. It is used to study the movements of molecules.

## **Brain Anatomy**

**Hemisphere** – the brain is divided into two halves (left and right) and 4 lobes (parts). Hemisphere refers to one half of the brain. Right side of the brain controls left side of body and vice versa.

**Cerebrum** – biggest part of the brain made up of two halves. Responsible for motor function (body movement); thinking; behaviour; emotions; and sensory input e.g. hearing, seeing, touch, smell and taste.

**Cerebral** – referring to cerebrum.

**Cerebellum** – smaller part of the brain at the back of the head and top of neck. Helps to coordinate movement and balance.

**Corpus callosum** – this is a membrane separating the two halves of the brain.

**Caudate nucleus** – structure in the midbrain (and part of basal ganglia).

**Putamen** – round structure in the forebrain. It has many functions including regulating movements.

**Thalamus** – part of the brain that is involved with sensory and motor signals. It is also involved with sleep and awake/alertness.

**Brainstem** – is at the back (posterior) part of the brain and is connected to the spinal cord (the cord that leaves the brain and travels down the back. It includes the midbrain and other structures of the brain.

**Basal ganglia** – a collection of parts within the brain that are located in the midbrain. One of the function is regulation of movements.

**Substantia nigra** – part of the midbrain and source of the neurotransmitter dopamine.

**Hippocampus** – part of the brain that is involved in memory predominantly.

**Occipital** – a lobe (part) of the brain at the back. Where sight is based.

**Temporal** – a lobe (part) of the brain at the side. Where hearing is based. A type of epilepsy starts from here.

**Parietal** – a lobe (part) of the brain at the top towards the back. It has many roles including sensory and spatial awareness.

**Frontal** – the lobe (part) of the brain at the front of the head. Responsible for many functions including speech expression and emotions.

**Fronto-parietal** – part of the brain including both frontal and parietal lobes.

**Ventricles** – fluid-filled pockets inside the brain.

**Subarachnoid spaces** – space between different layers surrounding the brain.

**White matter** – part of the central nervous system that are made up of axons and tracts.

**Grey matter** – major part of the central nervous system made up of neurones/cell bodies.

**Glial cells** - these cells surround neurons and provide support/insulation

**Atrophy** – wasting of a part of the body/brain

**Sclerosis** – replacement of normal tissue with scar like tissue

**Polymicrogyria** – a condition that affects multiple (poly) parts of the brain.

**Spinal cord** – nervous tissue that starts at base of brain and travels down the spine/vertebra

**CSF or Cerebral spinal fluid** – fluid in the ventricles, around the brain, and around the spinal cord. Samples can be taken from the bottom of the spine.

**BBB** - Blood brain barrier that separates the brain from the rest of the body.

**Intrathecal injection** - Injection into the spinal canal or rarely into the brain.

## Seizures

**Focal** – seizures that affect one hemisphere of the brain (previously referred to as partial).

**Generalised** – this affects both hemispheres of the brain. A common type of seizure is a generalised tonic clonic seizure (*grand mal*).

**Absence** – period of vacantness/absence associated with a seizure. The symptoms will vary between people. It is a type of generalised seizure.

**Todd's paresis** – focal weakness in part/parts of the body after a seizure. It typically affects one side of the body (hemiplegia) and resolves commonly 48 hours after the seizure.

## Clinical terms – conditions all caused by ATP1A3 mutations

**AHC** – Alternating Hemiplegia of Childhood (in 70-80% of patients disease is caused by a mutation in the *ATP1A3* gene. In the remaining patients the clinical diagnosis may be different or further genes are still to be found)

**CAPOS** – Cerebellar ataxia (incoordination), Areflexia (no reflexes), Pes cavus (inward sloping chest wall), Optic atrophy (vision loss) and Sensorineural hearing (hearing loss due to neurological condition) loss.

**RDP** – Rapid onset Dystonia of Parkinsonism.

**EEIE** – Early Epileptic Infantile Encephalopathy.

**FIPWE** – Fever-Induced Paroxysmal Weakness and Encephalopathy.

**RECA** – Recurrent Episodes of Cerebellar Ataxia.

## Clinical Symptoms

**Orphan diseases** - a rare disease that has not been adopted by the pharmaceutical industry because it provides negligible financial incentive to invest in research and therapeutic developments.

**Clinical response** – the change that can be seen by a doctor (clinician) in response to a treatment or event

**Generalised** – used in relation to symptoms happening all over the body/area

**Episode** – a range of neurological symptoms referred to within AHC event.

**Paroxysmal** – sudden recurrence of symptoms.

**Hemiplegia/Hemiparesis** – paralysis of one side (one half left or right) of the body

**Unilateral** – one side of body (left or right).

**Bilateral** – both sides (e.g. both arms or both legs).

**Quadraplegia/Quadraparesis** – paralysis of all four limbs.

**Paroxysmal movement disorders** – Involuntary abnormal movements that only occur during an episode, seizure or attack.

**Dystonia** – rigidity of one or many muscles (often extremely painful).

**Bradykinesia** – slowness of movement

**Ataxia** – a type of movement associated with incoordination.

**Gait** – medical term for walking and way a person walks.

**Motor symptoms** – movement symptoms

**Encephalopathy** – an altered mental state/confusion due to the brain.

**Nystagmus** - flickering of the eye (normally from side to side). There are many causes for this and can be abnormal (pathological) or normal (physiological).

**Monocular** – one eye.

**Biocular** – both eyes.

**Choreathetosis** – involuntary movements that involve chorea (irregular contractions) and athetosis (twisting and writhing).

**Chorea** – involuntary movements that are ‘jerky’ in nature.

**Clonus** – involuntary rhythmic muscular contractions. It is present in several neurological conditions.

**Myoclonus** – involuntary spasmodic contractions of the muscles that can be described as rhythmic or jerky.

**Dyskinesia** – group of movement disorders that cause involuntary muscle movements.

**Action tremor** – tremor that develops on doing something (action).

**Resting tremor** – tremor that is evident at rest.

**Pill rolling tremor** – a fine rolling subtle tremor (named as like rolling a pill in-between fingers).

**Intention tremor** – a tremor that is most obvious when trying to touch an object (on intention). It is normally due to damage in the cerebellum.

**Apnoea** – temporary stopping of breathing, often during sleep.

**Sleep study** – several different type of sleep studies but they ultimately study during sleep that looks at breathing, apnoea, heart rate, brain activity.

**Respiratory arrest** – when a person stops breathing or is breathing ineffectively.

**Sudden infant death syndrome (SIDS)** – is the unexplained death of a child less than one year old.

**Sudden Unexplained Death in Epilepsy (SUDEP)** – a fatal complication of epilepsy.

**ECG/EKG** – electrocardiogram (measures the heart rhythm).

**Cardiac arrhythmia** – a disturbance of normal heart rhythm.

**Tachyarrhythmia** – a fast abnormal heart rhythm.

**Bradycardia** – a slow abnormal heart rhythm.

**Tachycardia** – a fast heartbeat.

**Bradycardia** – a slow heartbeat.

**Syncope** – a loss of consciousness/collapse due to a cardiac (heart) cause such as an abnormal heart rhythm.

**Pauses** – when the heart rhythm stops for a certain time and starts again.

**Heart Block** – where the heart rhythm is abnormal and has stops intermittently. (several different types of heart block and some need a pacemaker to correct).

**QT interval** – part of the ECG that relates to the contraction of part of the heart. muscle and is displayed on the ECG as an electrical movement called QT

**QTc** – this is the QT interval but ‘c’ stands for corrected (so it is corrected for the heart rate and is more accurate).

**BP** – blood pressure.

**Sats** – refers to oxygen saturations (sats).

**Pulse oximeter** – used to measure oxygen saturations (also referred to as a ‘sats monitor’) and normally attached to finger or foot.



## Drugs

*These are listed below with their generic, non-trade names, but some common trade names are included also. These will vary by country.*

**Flunarizine** – a calcium channel blocker (calcium antagonist) used in AHC which blocks the calcium channels in the cell membrane reducing the calcium that comes into the cell, but it is unclear how it works in AHC. It is sometimes referred to as an ion channel blocker (calcium is an ion, molecule).

**Diphenylpiperazine** – a drug that enhances the serotonin receptor.

**Benzodiazepine** – several different types of drugs within this category. They are used for their sedating properties (for seizures and also AHC episodes). These include:

**Midazolam, Diazepam, Clobazam, Clonazepam, Lorazepam**

**Acetaminophen/paracetamol** – pain relief

**Acetazolamide** – carbonic anhydrase (found in red blood cells) inhibitor, which works in the first part of the kidney and results in bicarbonate, sodium and chloride being excreted from the kidney into urine.

**Trihexiphenidyl (artane)** – is an anti-Parkinson drug and antimuscarinic (relaxes the muscles) and is used for dystonia.

**Chloral hydrate** – a sedative drug.

**Gabapentin** – is a gabapentinoid, which is an anti-seizure drug that also has properties for pain (neuropathic) relief and other symptoms including helping with sleep.

**Cannabidiol** – from the cannabis plant

**THC** – stands for tetrahydrocannabinol. This is the psychoactive part of the cannabis plant.

**Epidiolex** – cannabidiol medication licensed in some countries.

**Sativex** – cannabis-based medication licensed in some countries, contains THC and cannabidiol.

**Lipophilic** – combines/mixes with fats (used in relation to drugs as well as other mechanisms at the cell level)

## Organisations/Abbreviations

**IAHCRC** – International Consortium for the Research on Alternating Hemiplegia of Childhood

**OBSERV-AHC** – Worldwide research study that has just started to collect information on the children and adults with AHC

**Eurodis** - European Organisation for Rare Diseases

## Acknowledgement

*This glossary was prepared by:*

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