What is CDG?

CDG stands for Congenital Disorders of Glycosylation

A *congenital disorder* is a condition that is present at birth, and these disorders can be divided into two main types: structural disorders, where there are problems with the shape of the body and functional disorders, where there are problems with how a body part works[1]. CDG is a functional disorder, because there are problems with how the metabolic system in the body works. The metabolic system is comprised of the chemical reactions in our bodies, which enable us to do three main things[2]:

a) Convert food and fuel into energy;
b) Build important molecules likes proteins, fats and nucleic acids (for our DNA, for example), and;
c) Remove nitrogen waste from our bodies.

In CDG, we are concerned with the second main purpose of the metabolic system - the process that builds molecules, because part of this process includes glycosylation.

Glycosylation

Glycosylation is the process of building and joining up important molecules in the body, i.e. building glycans (sugar chains) and attaching them to proteins or lipids[3]. Once the glycan is attached to the protein or lipid, it can help them function. There are many functions for glycosylated proteins and lipids (glycoproteins/glycolipids) in the body, such as supporting larger molecular structure, supporting the protection and lubrication of molecules, helping form transport molecules and disease fighting molecules, supporting hormones and drug action, facilitating cell to cell communication, regulating development, and assisting with blood clotting [4].

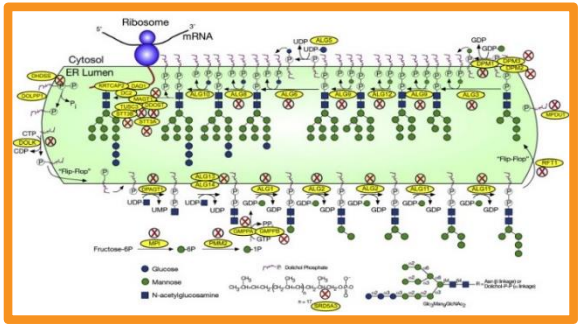
Because glycoproteins and glycolipids have many different roles in the body, and are present in all of our organs including the brain, it is easy to see that a problem with the process can lead to many health problems in a CDG patient.

However, not all symptoms in CDG patients are the same, and the health problems can vary in severity. In fact, at the time of writing, there are over 100 subtypes of CDG and more are being identified every year[5]. Some diseases, such as Wrinkly Skin Syndrome, have now been found to be caused by CDG[6]. Subtypes exist, because building glycans and attaching them to proteins and lipids happens in stages, and the subtype is used to refer to the stage where the error in the process is found.

Types of CDG

In the past, CDGs have been divided into two types, CDG type I and CDG type II, depending on the actual site in the cell in which the error occurs, i.e. type I for assembly defects outside a part of the cell called the endoplasmic reticulum (ER) and type II for processing defects inside the ER. More recently, CDGs have been named by the faulty gene which codes for the specific enzyme (a builder) needed for each stage of the process[7]. For example, the most common type of CDG used to be known as CDG 1a, but is now referred to as PMM2-CDG (where PMM2 refers to the phosphomannomutase 2 gene on chromosome 16, which codes for the phosphomannomutase enzyme, which is the only enzyme in the body that can convert mannose-6-phosphate to mannose-1-phosphate)[8]. An example of a type II CDG is SLC35A2-CDG, and at the time of writing, there are two identified patients in the UK. As there are over 100 enzymes involved in glycosylation, it is understandable that there are so many subtypes of CDG, all named by the gene-CDG, i.e. PMM2-CDG. The image below shows how the enzymes build the sugar chains in the ER[9]. For example, ALG6 adds an extra molecule of glucose sugar onto the growing tree, and if this is faulty the result is ALG6-CDG.

Location of defects in type I congenital disorders of glycosylation (CDG-I)



To add more complexity to the matter, two patients with the subtype PMM2-CDG may present quite differently, usually because of an error in the genetic code of a gene. Think of genes as words in a book that describe how someone is built. There are about 20,000 human genes, and we have two copies of each; one from the mother and one from the father. For example, The PMM2 gene has 2313 bases (letters of code)[10], any of which could mutate to cause an error in function. In addition, most CDGs are recessive[11], which means that the child with CDG carries two faulty copies of the gene, one from each parent. The combination of faulty genes passed to a child may define how severely the disorder affects them. The most common combination of mutations is p.R141H from one parent with p.F119L from another, both caused by a single change in a base (letter of DNA code), and is responsible for 27% of 249 patients from 23 countries[12].

There are only approximately 1,000 cases of CDG diagnosed worldwide, with around 100 in the UK[13]. Through the determined effort of geneticists, researchers, clinicians and parents, our understanding of CDG has expanded greatly since it was first medically recognized in the 1980s. Greater awareness of the disease has, and is still, creating opportunities for earlier and more accurate diagnosis as well as the proper categorisation of the existing CDG sub-types. However, despite increased understanding and awareness, CDG is a very rare disease and the diagnosis of CDG can remain elusive. It is our belief that many children with CDG remain undiagnosed or have been misdiagnosed, and as a result the true number of cases remains unknown. CDG UK aims to support patients and families affected by CDG, to raise awareness about CDG in the medical, professional and research communities, and raise funds for additional research into the disease.

References:

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Photo Credit, Barbara Asboth http://www.1in17.uk/2018/06/finn-congenital-disorders-of.html

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