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CDG or not CDG

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To the Editor

Congenital Disorders of Glycosylation (CDG) are an exponentially growing group of genetic diseases. The first patients were reported in 1980 by Jaak Jaeken, and subsequently found to have PMM2-CDG.[1,2] The actual number of CDG is over 160 and several others are in the pipeline.[3] It is not always clear whether a certain disease belongs to this group. Therefore, one of us (Hudson H. Freeze) took the initiative for a discussion about this matter on occasion of the Scientific CDG symposium 2021 (virtual symposium 23–24 June 2021) organized by Gert Matthijs. This discussion was attended by some 45 clinicians, biochemists, geneticists, researchers, and representatives of patient organizations. The discussion was moderated by Gert Matthijs and introduced by Hudson H. Freeze. Jaak Jaeken presented a brief history of the CDG nomenclature.

The first point of discussion was the cornerstone of the CDG house: what is glycosylation? This seems to be a very simple question but it is not. A consensus could be reached about the following definition: Glycosylation is the synthesis of fully functional glycans, and their covalent enzymatic attachment to other molecules including proteins, lipids, and small RNA[4]. Factors necessary for these functions are various enzymes, donor and acceptor substrates, proper pH, metal ions and other features needed to maintain homeostasis. (Congenital) glycosylation disorders are caused by (inborn) pathogenic variants in the genes encoding proteins involved anywhere in the different glycosylation pathways. These are mostly disorders of assembly and modification of bound glycans, but may include their disassembly when it also affects their assembly.

The next question was whether the actual ‘CDG’ conform to this definition. For example, what about ‘CDG’ that are ‘broader’ than just defects in the glycosylation machinery, such as defects in the conserved oligomeric Golgi (COG) complex? The ‘virtual audience’ was generally in favor of inclusion rather than exclusion. One, not scientific, argument was that patient advocacy groups would not be happy with ‘dropping’ defects that are already settled as CDG. Anyway, defects in soluble or membrane-associated trafficking molecules

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(alone or in complexes) can only be considered as CDG if they have a proven effect on glycosylation. Another puzzle is *ALG13*. In yeast, it is essential for the synthesis of the lipid bound N-glycan precursor. Humans have a single X-linked *ALG13* gene, and recurrent *de novo* mutations in the catalytic domain cause a neurological phenotype. Homologous patient mutations impair N-glycosylation in yeast, but they do not impair N-glycosylation of serum glycoproteins in patients[5]. Evolution and phylogenetics would say that defective ALG13 indeed causes a CDG.

What about defects in glycan modifying enzymes/transporters and modifications with sulfate, phosphate, amino acids, fatty acids? Some were in favor of inclusion, others against. A convincing argument in favor is that PMM2-CDG and MPI-CDG are actually defects in phosphate modifications of a monosaccharide. Nobody could imagine removing these from the CDG list! Also, including all defects in glycosylphosphatidylinositol (GPI) anchor synthesis defects as CDG provokes some controversy because not all defects in this pathway are pure glycosylation defects. Here too, the general tendency of the discussants was to be inclusive mainly because this pathway comprises the incorporation of glucosamine, inositol (a sugar alcohol), three mannose residues and their phosphate and fatty acid modifications.

Summarizing, CDG are inherited (recessive, dominant or X-linked) or *de novo* disorders that cause ‘substantial’ hypoglycosylation in one or more cell types.

Altogether, over 160 known CDG encompass some 220 different phenotypes or diseases. One defect can cause more than one disease depending on the molecular effects of the genetic variant(s). A recent example are COG4 defects. A recurrent *de novo* heterozygous p.Gly516Arg COG4 variant is responsible for the Saul-Wilson syndrome, a rare recognizable skeletal dysplasia with normal cognition.

This phenotype is different from that of the few COG4-CDG individuals with a neurological syndrome including intellectual disability, and biallelic loss-of-function variants.[6] Saul-Wilson syndrome was first reported as a clinical entity in 1990, and even though protein glycosylation in sera and fibroblasts of affected individuals was normal, the syndrome should be classified as a CDG because at least one protein, namely decorin, presents an altered Golgi-dependent glycosylation[6]. The more (*de novo*) dominant variants will be found in genes that were logically linked to recessive disorders, the more it will become complicated.

The fact that different variants of the same gene can cause a CDG or another disease has also been demonstrated regarding *SLC37A4*. Biallelic pathogenic variants in this gene cause glycogen storage disorder 1b (GSD1b), a recessive disorder, while the recurrent loss-of-function variant p.Arg423* causes the dominant SLC37A4-CDG, showing only modest coagulopathy and liver dysfunction.[7] A knock-out of SLC37A4 (as in GSD1b) leads to a glycosylation defect in neutrophils. However, calling GSD1b a CDG would be confusing: the disease is best known as (and should remain) a glycogen storage disorder. Thus, a (re-)classification of ‘single cell type’ glycosylation defect as a CDG could be disputed. Similar examples should be decided case-by-case.

Hemizygous variants in the X-linked *MAGT1* gene can cause a CDG or a combined immunodeficiency with “magnesium defect”, Epstein-Barr virus infection, and neoplasia disease (XMEN).[8] The differential pathophysiology of loss-of-function variants in the same gene remains unexplained, but given that XMEN patients also present glycosylation defects, they shall thus both be classified as CDG.

Defects have been reported in the following glycosylation pathways: N-linked, O-linked (O-mannose, O-fucose, O-glucose, O-xylose, O-GlcNAc, O-galactose, O-GalNAc), GPI anchor synthesis, and lipid glycosylation. No human defects have yet been reported in small RNA glycosylation. Glycosylation is an impressive machinery and defects have been reported in a large number of different enzymes (glycosyltranferases, mutases, glycosidases, pyrophosphorylases, synthases, chaperones, deacylases, epimerases, flippases, isomerases, kinases, reductases, transaminases), in multiprotein subunits, in transporters, trafficking complexes and in receptors. Some CDG genes have been pinpointed thanks to their role as proteins interacting with known pipelines, e.g. VMA21-CDG[9]. Also regulatory defects have made their appearance in the CDG field[10]. No doubt that many CDG are still under the waterline such as defects in ER/Golgi mannosidases and in Golgi N-acetylglucosaminyltransferase I to name just a few.. We include a table summarizing our inclusion/exclusion criteria along with examples.

Gene, Function or Activity	Examples	CDG?
Gene known to be involved in any glycosylation pathway	*PMM2, ALG1, PIGA, EXT1/2, OGT, MOGS STT3A, MPI, DPM1, SLC35A2, PGM1, PIGL, POMT1, FKRP, PAPSS2, B3GLCT, B4GALT7, SRD5A3*	YES
Glycosylation Gene conserved in evolution	*ALG13*	YES
Gene in ER, Golgi, post-Golgi trafficking that alters glycan synthesis	*COG4, COG7, SEC23B, TRAPPC11, GET4*	YES
Gene involved in pH or metal ion homeostasis that alters glycan synthesis	*ATP6VOA2, TMEM199, ATP6AP2, SLC39A8*	YES
Subunit of a glycosylation-altering molecular complex, but lacking evidence of altered glycans	*TRAPPC12, TRAPP6B*	NO
Status debated without consensus	*GALT, GALE, ALDOB*	Yes/No?

In 2008, we proposed a nomenclature for CDG using (only) the official gene symbol followed by ‘-CDG’.[11,12] This combination has stood the test of time, and we trust that its use can be continued for the designation of novel types of CDG. The combination fits with the ‘GENE-related phenotype descriptor’ that was recently proposed for Mendelian genetic disorders by Biesecker and colleagues[13] and which has been presented as a dyadic approach to naming disorders. CDG, for congenital disorders of glycosylation, may be less specific (it actually stands for an entire (new) field of inborn errors of metabolism) than the examples given in the cited publication. Still, we believe that this designation is both clear and sufficient, for medical practitioners, clinical and basic researchers and, not in the least, for patients, parents and families, and shall thus remain. We hereby stress the importance for parents and patients to be able to associate themselves with a group of disorders, and be able to belong to a community.

Actually, we would like to designate some of the CDG and their (non-glycosylation) counterpart as ‘twin disorders’. Thus, using the dyad concept and diagnostic descriptors model, the following disorders would be ‘twins’: COG4-CDG and COG4-related Saul-Wilson syndrome; SLC37A4-CDG and SLC37A4-related glycogen storage disease; MAGT1-CDG and MAGT1-related XMEM.

According to the wishes of several discussants for a consultant group, the authors of this annotation are prepared to serve as advisors for ‘borderline’ CDG candidates. Additional input is also welcome from other appropriate individuals.

We look forward to comments and suggestions on this matter.

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