The Evolving Genetic Landscape of Congenital Disorders of Glycosylation

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Highlights:

- Alternate phenotypes in monogenic CDG
- The emergence of autosomal dominant forms of CDG
- The future of the genetic diagnosis of CDG

Abstract:
Congenital Disorders of Glycosylation (CDG) are an expanding and complex group of rare genetic disorders caused by defects in the glycosylation of proteins and lipids. The genetic spectrum of CDG is extremely broad with mutations in over 140 genes leading to a wide variety of symptoms ranging from mild to severe and life-threatening. There has been an expansion in the genetic complexity of CDG in recent years. There are several examples of alternate phenotypes in recessive forms of CDG and new types of CDG following an autosomal dominant inheritance pattern have been identified. In addition, novel genetic mechanisms such as expansion repeats have been identified and several already known disorders have been classified as CDG as their pathophysiology was better elucidated. We also consider the future and outlook of CDG genetics, with a focus on exploration of the non-coding genome using whole genome sequencing, RNA-seq and multi-omics technology.

Keywords:
Glycosylation, congenital disorders of glycosylation, next generation sequencing, autosomal dominant

1 Introduction

Glycosylation is the process by which carbohydrate chains, known as glycans, are linked covalently to proteins or lipids. There are several types of glycosylation including the addition of N-linked glycans, O-linked glycans, glycosaminoglycans and glycosylphosphatidylinositol (GPI) anchors to proteins or the formation of glycosphingolipids through the attachment of sugars to lipids. [1,2] There are a vast number of naturally occurring sugars that can be combined in many ways to produce unique and specific glycan structures. In proteins, glycan addition occurs at specific sites in the peptide backbone and affects stability, trafficking and folding of the glycoprotein. [3] In humans, approximately 50% of proteins are glycosylated, making it among the most important post-translational modifications. [4]

Congenital Disorders of Glycosylation (CDG) are genetic disorders affecting the synthesis, processing or attachment of glycans linked to glycoproteins or glycolipids. [5] The first CDG was described clinically in 1980 [6], biochemically in 1995 [7], and mutations in *PMM2* were found to be the cause of the most frequent type of the disorder in 1997 [8]: PMM2-CDG, then termed CDG1A. PMM2-CDG was among the few early CDG that were identified by linkage analysis and more classical genetic techniques. In the early 2000s, the biochemical analysis of glycosylation abnormalities, largely using analysis of lipid-linked-oligosaccharides (LLO) by HPLC and glycan analysis by mass spectrometry, allowed the targeted search for the genetic cause of defects identified in patients. By 2007, approximately 25 forms of CDG had been identified. [9] After this, an important moment in the identification of new CDG was the arrival of Whole Exome Sequencing (WES), allowing the untargeted analysis of affected patients, beginning with the identification of PIGV-CDG in late 2010. [10] This opened the floodgates; as of 2021, more than 140 genetic loci for CDG have been identified and most hospitals use WES for the genetic diagnosis of a patient with a suspected CDG. [11]

Initially, most forms of CDG identified were clearly relevant to known glycosylation pathways such as deficiencies of glycosyltransferases [12], glycosidases [13], and sugar nucleotide transporters. [14] These were initially related mostly to the best understood aspect of glycosylation, N-linked glycosylation and biosynthesis of the LLO within the endoplasmic reticulum. However, in 2004, mutations in *COG7,* a subunit of the Conserved Oligomeric Golgi (COG) complex were found to cause a combined N- and O- glycosylation defect due to abnormal Golgi protein trafficking. [15] Since then, an increasing number of CDG have been identified that are caused by mutations in genes important for processes such as trafficking proteins [16] and channels implicated in pH [17] or metal ion homeostasis. [18] These cause downstream abnormalities due to a secondary effect on proteins directly involved in glycosylation.

Accordingly, researchers within the field of CDG and glycosylation tend to place genetic defects into certain groups according to the aspect of glycosylation that is affected. These include broad groups such as O-linked, GPI anchor defects, CDG-I (those affecting the N-linked attachment of the LLO to recipient glycoproteins) and CDG-II (those affecting the downstream processing of N-linked glycans). In addition, within CDG-I there are CDG that disrupt the processing of the immature LLO, some affecting oligosaccharyltransferase (OST) complex function, and those leading to abnormal dolichol biosynthesis. Within CDG-II, there are trafficking defects affecting anterograde or retrograde transport, and transporter defects affecting the Golgi microenvironment, as well as others. In this review we will keep to these same systems of categorization within each respective section, following the N-glycan as it is assembled and attached to the recipient glycoprotein in the ER, then trimmed and processed in the Golgi and cytoplasm, where it is joined by other glycans formed by, for example, O-glycosylation.

Despite our advances in the diagnosis of CDG, a significant number of patients with biochemical markers and/or clinical pictures suggestive of a CDG that have travelled through the standard clinical diagnostic procedure have not yet received a diagnosis. These 'unsolved' patients are assumed to have either; i) a defect in a gene not yet known to cause a glycosylation defect; ii) an unusual, complex or novel type of genetic rearrangement or other molecular mechanism in a known CDG gene; iii) an oligogenic CDG, meaning variants in two or several genes that individually may not lead to disease but when combined can cause a clinical presentation of CDG.

In addition, a current theme is the reclassification of known inherited disorders to CDG, as their pathophysiology is expanded to include an underlying glycosylation defect (e.g. Saul-Wilson syndrome (*COG7*), Hedera type X-linked developmental delay (*ATP6AP2*), X-linked myopathy with excessive autophagy (*VMA21*) and Cowden syndrome 7 (*SEC23B*)). These are linked to numerous recent examples of the discovery of 'unexpected CDG'; namely, individual patients or disorders that do not appear to have a classical CDG phenotype but, upon investigation, are found to have a pathophysiology associated with disordered glycosylation. This is a major outcome of WES. Indeed, in these patients a CDG is not suspected at all prior to WES analysis, such is the advantage of an untargeted diagnostic technique. One example of this is polycystic liver disease which can be caused by hypoglycosylation of the glycoprotein polycystin due to heterozygous mutations in *ALG8* or *ALG9*. [19]

This review will discuss the recent developments in CDG from a genetics standpoint. New discoveries allowing us to 'fill the gaps' in known glycosylation pathways will be mentioned. This underlines how research into CDG has identified novel glycosylation genes and pathways. Another intriguing novelty is the identification of heterozygous and thus dominant mutations in genes that were previously associated with recessive (autosomal and X-linked) forms of CDG. We list the known examples in this review. Several CDG result in multiple distinct clinical presentations from mutations within the same gene; important examples of these will be explored. Finally, novel and future techniques including the full exploitation of WGS and its potential integration with other omics technologies will be discussed.

2 Unexpected and novel genetic findings in CDG

The aim of this review is not to discuss all identified CDG in detail, comprehensive summaries of these can be found elsewhere: Jaeken and Morava 2016 [20], Jaeken and Péanne 2017 [21], Péanne *et al.* 2018 [2], Ng and Freeze 2018 [22] and Ondruskova *et al.* 2020 [11]. However, within this section the most intriguing recent developments in the genetic landscape of CDG will be discussed, grouped by the aspect of glycosylation that is affected. There are thus several themes that run through this topic: i) the reclassification of existing disorders to include CDG as part of their pathophysiology; ii) the discovery of novel disorders in unexpected cohorts; iii) the identification of autosomal dominant forms of existing CDG, often leading to a different phenotype.

2.1 Reclassification of existing disorders as CDG

2.1.1 CDG directly affecting the oligosaccharyltransferase complex

Multiple CDG have been described that cause a deficiency of subunits of the oligosaccharyltransferase (OST) complex that transfers the precursor glycan ($Glc_3Man_9GlcNAc_2$) to asparagine residues of target

proteins. These include STT3A-CDG, STT3B-CDG [23] and OSTC-CDG [24]. They are examples of novel CDG within important glycosylation pathways. Indeed, the OST has long been known as important for N-glycosylation but it was only in 2013 that the first CDG were identified caused by mutations in genes encoding OST subunits.

One disorder related to OST function has recently been reclassified as CDG due to an improved understanding of its pathophysiology. A deficiency of MAGT1 was identified in patients with a CDG causing primarily intellectual disability, which was therefore termed MAGT1-CDG. [25] However, mutations in *MAGT1* are also known to lead to 'X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection and neoplasia' or XMEN disorder. [26] *MAGT1* encodes a protein previously described as either a Mg^{2+} transporter [27] or a subunit required for N-glycosylation by the OST complex when STT3B is the catalytic subunit. [28] Prior to recent years, the pathophysiology of XMEN was ascribed to a defect in Mg^{2+} homeostasis. [26] However, Blommaert *et al.* [25] showed that deficiency of MAGT1 leads in fact primarily to an N-glycosylation disorder and any Mg^{2+} transport defect is likely secondary to aberrant glycosylation of relevant glycoproteins, as was later confirmed by Ravell *et al.* [29]

Accordingly, MAGT1 deficiency can display two phenotypes, one with intellectual disability and another with primary immunodeficiency. These do not segregate according to the type of pathogenic variant (missense or nonsense) or the presence or absence of aberrant glycosylation. Blommaert *et al*. suggested that the presence of a mutually exclusive protein of homologous function, TUSC3, in the STT3B OST complex, could be implicated in these divergent phenotypes. They showed that TUSC3 was upregulated in MAGT1-CDG patient fibroblasts, in an apparent compensatory mechanism.[25]

Another more extreme example of variable phenotypes resulting from mutations in the same gene is mutations in *TREX1*. When mutations truncate the C-terminus of TREX1 but leave intact exonuclease activity, a phenotype of retinal vasculopathy with cerebral leukodystrophy is present. [30] This is thought to be due to an interaction of the TREX1 C-terminus with the OST complex. The absence of this interaction increases LLO hydrolysis, leading to aberrant glycosylation and a CDG (TREX1-CDG). [31–33] However, damaging missense or nonsense variants in *TREX1* can lead to either autosomal dominant or recessive Aicardi-Goutieres syndrome 1 [MIM: 225750]. This is an encephalopathy mimicking an *in utero* viral infection that seems to be caused by a lack of 3'-5' exonuclease activity, the classical function of the TREX1 protein. This pathophysiology is unrelated to glycosylation. [34,35]

Since the OST complex contains at least 11 subunits, additional defects can be expected in the future, possibly with complex and varying phenotypes as in those already identified.

2.1.2 Golgi homeostasis defects

Further down the path of N-glycosylation assembly and modifications are defects within the Golgi. In particular, several CDG have been described caused by dysfunction of the V-ATPase complex including ATP6V0A2-CDG and ATP6V1A-CDG, both leading to autosomal recessive cutis laxa. [17] Another disorder caused by mutations in a V-ATPase subunit has been reclassified as a CDG in recent years. This is the X-linked disorder, ATP6AP2 deficiency. Exon-skipping mutations in *ATP6AP2* had previously been linked to an encephalopathy comprising epilepsy, intellectual disability and parkinsonism. [36] The ATP6AP2 protein was at this time tentatively suggested to be a (pro)renin receptor. However, in 2017, Rujano *et al.* identified missense mutations in *ATP6AP2* causing liver disease, psychomotor impairment, cutis laxa and immunodeficiency, as well as defective glycosylation detected by tIEF. [37] They showed that ATP6AP2 was a crucial constituent of the V-ATPase complex and plays an important role in autophagy and mTOR

signaling. Deficiency likely leads to aberrant homeostasis of the Golgi and ER, and thus defective glycosylation. ATP6AP2-CDG shows a strong genotype-phenotype correlation: the aforementioned exon-skipping mutations do not seem to cause a glycosylation defect and are limited to neurological involvement. [36,38] Rujano *et al.* suggested that this was indicative of less severe mutations, shown by the partial penetrance of these variants. [37]

Similarly, mutations in *VMA21*, encoding another V-ATPase complex subunit, have recently been associated with aberrant glycosylation. Previously, pathogenic *VMA21* variants were known to lead to X-linked myopathy with excessive autophagy [XMEA; MIM: 310440]. However, Serio *et al.* in 2020 reported a subset of patients that presented primarily with liver disease, consisting of cholestasis, raised transaminases, raised LDL cholesterol and hepatocytic steatosis as well as hypoglycosylation of liver-derived glycoproteins. [39] The reason that XMEA and VMA21-CDG patients present with two distinct phenotypes has yet to be elucidated.

2.1.3 Glycosylphosphatidylinositol anchor biosynthesis defects

Defects in the glycosylphosphatidylinositol (GPI) anchor synthesis pathway, termed inherited GPI deficiencies (IGD), are a rapidly growing group of CDG. In the last 3 years, 7 have been identified [40–46] Common features are intellectual/developmental disability, seizures, musculoskeletal abnormalities and in several increased or decreased serum alkaline phosphatases. These patients were identified and diagnosed largely by the investigation of intellectual disability and developmental delay (DDD) cohorts [47], as well as international coordination using tools such as Genematcher. [48] The story of IGDs indicates the importance of worldwide cooperation and the sharing of whole exome or genome datasets.

2.2 Autosomal dominant CDG

Like most metabolic disorders, CDG were historically considered mostly autosomal recessive disorders, with some X-linked forms. However, more recently several autosomal dominant forms have been described in genes that were previously associated with recessive forms of CDG. Often these disorders have two distinct phenotypes linked to differences in pathomechanism which stem from their underlying genetic cause.

2.2.1 N-Glycan assembly

The first dominant CDG caused specifically by defective N-glycan assembly identified, in 2012, was a *de novo* form of the X-linked ALG13-CDG. [49] This was particularly novel as it showed a combination of recessive and dominant disorders caused by mutations in the same gene. In this case, hemizygous *de* novo males and heterozygous *de novo* females. Both forms of ALG13-CDG lead to early-onset seizures but are clinically recognized as CDG. Most patients with X-linked dominant ALG13-CDG are females and have the same *de novo* c.320A>G (p.N107S) mutation (**Figure 1**). The exact pathomechanism for dominant ALG13-CDG in males, and exactly how this relates to the hemizygous form of the disorder, has yet to be elucidated. The pathology of ALG13-CDG is complicated due to the proposed dual role of ALG13 as both a glycosyltransferase and deubiquitinase enzyme. [50]

One CDG displaying two explicitly different phenotypes according to inheritance pattern is ALG8-CDG. It was first described as an autosomal recessive CDG in 2003 in a patient with a predominant hepatic presentation [51] but soon expanded to include a more severe phenotype characterised by severe life-

threatening multi-organ failure. [52] Recently however, autosomal dominant mutations in *ALG8* have been found to cause polycystic liver disease and associated kidney cysts. [53] Similarly, ALG9-CDG caused by autosomal recessive missense mutations, presumably maintaining some residual function, leads to a primarily neurological and hepatic phenotype. [54] A more severe presentation consisting of an *in utero* lethal skeletal dysplasia with polycystic kidneys, first reported in 1993, was shown to have a homozygous mutation at the splice donor site of exon 10 in *ALG9* (c.1173+2T>A). [55] Most recently, in addition, *ALG9* mutation carriers have also been shown to develop kidney and liver cysts. [19]

By conclusion, in addition to *ALG8* and *ALG9*, there are several other genes encoding proteins involved in protein biogenesis and/or glycosylation in the ER that cause autosomal dominant polycystic liver disease (*PRKCSH, SEC63, GANAB, SEC61B*), suggesting a common disease mechanism. Indeed, aberrant biogenesis, trafficking and/or glycosylation of polycystin-1 has recently been proposed as the pathophysiological mechanism in these patients.

2.2.2 Dolichol synthesis and utilisation

Moving back to the earliest steps of glycosylation, we come to the biosynthesis of the dolichol pyrophosphate upon which the N-glycan is first built in the ER, forming the lipid-linked oligosaccharide required for N-glycosylation of nascent glycoproteins. Several CDG have been identified that disrupt the formation or metabolism of dolichol or its polyprenol derivative. One of these is DHDDS-CDG, caused by a deficiency of dehydrodolichyl diphosphate synthase. Autosomal recessive mutations in *DHDDS* can lead to a more 'classical' multisystem CDG. [56], a recurrent point mutation (c.124A>G; p.Lys42Glu) in the Ashkenazi Jewish population is associated with autosomal recessive retinitis pigmentosa [57], and *de novo* mutations cause developmental/intellectual disability and epilepsy. [58]

NUS1-CDG, also affecting the biosynthesis of dolichol, can be caused by both autosomal recessive and heterozygous *de novo* mutations. The autosomal recessive p.R290H mutation appears to lead to skeletal abnormalities, developmental/intellectual disability, epilepsy and retinitis pigmentosa. [59] However, three different *de novo* mutations have been reported to cause a phenotype more limited to intellectual disability with seizures. [58] Interestingly, five novel pathogenic *de novo* variants in *DHDDS* and *NUS1* were recently identified in a cohort of 84 individuals with progressive myoclonus epilepsies. [60] This is an example of finding CDG in 'unexpected' places and shows the potential of casting a wider net in the search for novel CDG. *NUS1* encodes the NogoB receptor (NgBR) and for the *de novo* forms of the NUS1 deficiency, a haploinsufficiency has been put forward [58], whereby lysosomal cholesterol accumulation contributes to the pathophysiology. [61]

Based on these examples, it seems that genes encoding proteins involved in the biosynthesis of dolichol and the N-glycan are prime candidates for having dominant as well as recessive forms.

Table 1: Congenital Disorders of Glycosylation with dominant inheritance

Glycosylation pathway	CDG	Dominant inheritance phenotypes	Recessive inheritance phenotypes	(Proposed) mechanisms of dominant pathogenicity
N-Glycan assembly	ALG8-CDG	Polycystic liver disease and associated kidney cysts [53]	Multisystem disorder (neurological, hepatic, dysmorphic, skin, gastrointestinal features) [52]	Haploinsufficiency leading to abnormal polycystin-1 biogenesis [53]
	ALG9-CDG	Polycystic liver disease and associated kidney cysts [19]	Multisystem disorder (neurological, hepatic, dysmorphic, skin, gastrointestinal features) [54]	Haploinsufficiency leading to abnormal polycystin-1 biogenesis [53]
	ALG13-CDG	Developmental and epileptic encephalopathy-36 [49]	Developmental and epileptic encephalopathy-36 (X-linked) [50]	Unknown
N-Glycan processing	GANAB-CDG	Polycystic liver disease and associated kidney cysts [62]	-	Haploinsufficiency leading to abnormal polycystin-1 biogenesis [53]
	PRKCSH-CDG	Polycystic liver disease and associated kidney cysts [62]	-	Haploinsufficiency leading to abnormal polycystin-1 biogenesis [53]
Dolichol synthesis and utilisation	DHDDS-CDG	Intellectual disability with seizures [58]	Multisystem disorder [56] or retinitis pigmentosa (RP only in cases with c.124A>G; p.Lys42Glu) [57]	Unknown (likely dominant-negative) [58]
	NUS1-CDG	Intellectual disability with seizures [58]	Intellectual disability, seizures, retinitis pigmentosa, skeletal abnormalities [59]	Likely haploinsufficiency [58]
Golgi homeostasis	SLC37A4-CDG	Liver disease [63], skeletal abnormalities, membranoproliferative glomerulonephritis [64]	Glycogen storage disease type 1b [MIM: 232220]	Mislocalisation of SLC37A4 protein truncated by the p.R423* variant [63]

Vesicular trafficking	SEC23B-CDG	Cowden Syndrome [MIM: 616858]	Congenital dyserythropoietic anemia type II [MIM: 224100]	Dominant 'change-of-function' leading to ER stress [65]
	COG4-CDG	Saul-Wilson syndrome [MIM: 618150]	Multisystem disorder (neurological, hepatic, dysmorphic, skin, gastrointestinal features) [16]	Dominant effect, Golgi volume changes due to the p.G516R substitution [66]
Nucleotide sugar transport	SLC35A2-CDG	Neurological (epilepsy, severe intellectual disability) [67]	-	X-linked dominant; Somatic X-inactivation and/or mosaicism [68]
GAG biosynthesis	EXT1-CDG	Multiple cartilaginous exostoses	-	Haploinsufficiency leading to disrupted heparan sulphate synthesis [69]
	EXT2-CDG	Multiple cartilaginous exostoses	Seizures-scoliosis-macrocephaly syndrome [MIM: 616682] [70]	Haploinsufficiency leading to disrupted heparan sulphate synthesis [69]
O-linked glycosylation	POFUT1-CDG	Dowling-Degos disease 2 [MIM: 615327]	-	Haploinsufficiency leading to Notch signalling disruption
	POGLUT1-CDG	Dowling-Degos disease 4 [MIM: 615696]	Limb-girdle muscular dystrophy [MIM: 617232]	Haploinsufficiency leading to Notch signalling disruption

2.2.4 Golgi trafficking

As for CDG Type II in this series of examples, we begin with COG4-CDG, caused by autosomal recessive mutations. COG4-CDG is characterised by a variable and multisystem disorder. [16] *COG4* encodes a subunit of the conserved oligomeric Golgi (COG) complex, responsible for both anterograde and retrograde vesicular protein trafficking. In 2018, the cause of Saul-Wilson syndrome [MIM: 618150] was found to be a recurrent heterozygous *de novo* missense variant (p.Gly516Arg) in *COG4*, classifying it as a CDG (**Figure 1**). [66] It is phenotypically distinct from the previously recognized syndrome. The pathogenic mechanism behind *de novo* p.G516R mutation was attributed by Ferreira *et al.* [66] to be a gain-of-function of this particular mutation and protein variant. This is supported by an increase in the rate of retrograde Golgi to ER transport, as opposed to a decrease seen in recessive COG4-CDG. In addition, the protein levels of COG4 and other COG proteins appeared to be normal, as well as the glycosylation in serum and fibroblasts. The pathology of Saul-Wilson syndrome was instead attributed to altered glycosaminoglycan (GAG) modelling or metabolism due to aberrant inter-compartmental Golgi transport.

Another example of different inheritance patterns leading to alternate phenotypes, are mutations in *SEC23B*. This gene encodes a subunit of the coat protein complex II (COPII) responsible for ER to Golgi transport. The first identified mutations caused autosomal recessive congenital dyserythropoietic anemia type II (CDAN2; [MIM: 224100]). [71] Later, inherited autosomal dominant missense mutations were found to be linked to Cowden Syndrome [MIM: 616858], a disorder characterised by a high lifetime risk of epithelial cancer. [65]

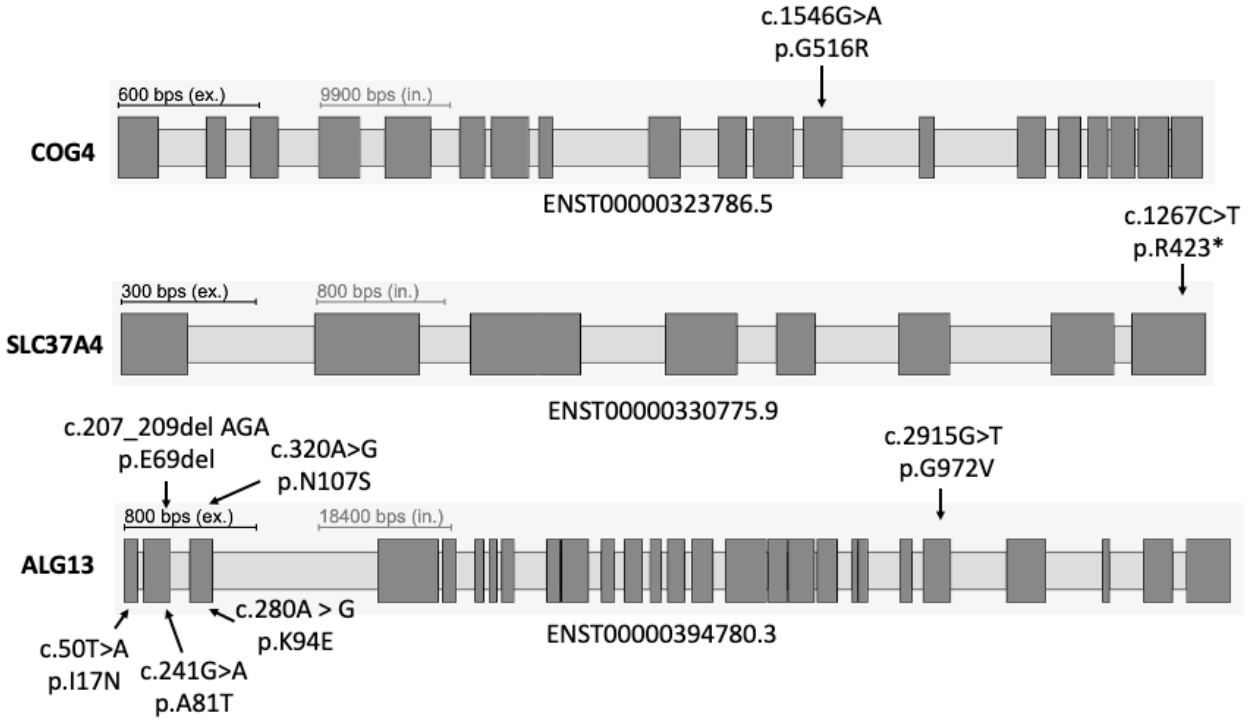

Figure 1: Examples of CDG caused by location-specific *de novo* variants
COG4-CDG: The recurrent p.G516R substitution leads to Saul-Wilson syndrome [MIM: 618150] due to the disruption of a hook-like feature in the 3D structure of COG4. [66] **SLC37A4-CDG:** Truncation of SLC37A4 by the p.R423* variant leads to mislocalisation of the transporter and disrupted Golgi homeostasis, causing a CDG characterised mainly by liver disease. [63,64] **ALG13-CDG:** Deleterious *de novo* in the X-linked gene *ALG1*3 lead to Developmental and epileptic encephalopathy-36. [50] All but one (p.G972V) is located within the glycosyltransferase domain of ALG13. Gene schematics created using Webscipio 2.0. [72]

2.2.3 Nucleotide sugar transport and Golgi homeostasis

First described in 2013 [73], SLC35A2-CDG is caused by *de novo* missense or nonsense mutations in the X-linked *SLC35A2* gene, a locus encoding the primary human UDP-galactose transporter and extremely intolerant to damaging variants. For this reason, the hemizygous deficiency is highly detrimental and almost all known individuals are female (29/30; [67]) and carry mosaicism due to X-chromosome inactivation randomly silencing one of their two allele, throughout the body. It is likely that hemizygous damaging *SLC35A2* mutations are lethal *in utero*, providing an explanation for the lack of male patients. Affected SLC35A2-CDG patients present with a primarily neurological phenotype consisting of epilepsy, developmental/intellectual disability. As well as germ line *de novo* mutations, in 2018 Winawer *et al.* identified somatic *SLC35A2* mutations in 5/56 brain samples from epilepsy surgery specimens. [68] Remarkably, even most non-mosaic patients have normal glycosylation biomarkers, perhaps due to tissue-specific positive selection of cells expressing the wild-type SLC35A2 allele or redundancy with another

related SLC35A transporter. [73] A specific biochemical test for SLC35A2-CDG has recently been developed by Ng *et al.* [67], consisting of the measurement of SLC35A2-dependent UDP-galactose transport into the Golgi of fibroblasts. SLC35A2-CDG has recently been shown to be (partially) treatable with galactose supplementation. [74] This is a good example of a specific biochemical therapy for a CDG.

In 2020, the heterozygous *de novo* c.1267C>T (p.R423*) variant in *SLC37A4* was reported in two patients with liver disease and a type 1 tIEF pattern. One patient also suffered from diabetes, scoliosis and membranoproliferative glomerulonephritis (**Figure 1**). [63,64] Biallelic autosomal recessive mutations in *SLC37A4* cause glycogen storage disease 1b (GSD 1b) [75], so the identification of a CDG caused by this *de novo* variant was unexpected. However, It was recently identified that the mechanism involved disruption of the Golgi due to mislocalisation of the functional but truncated SLC37A4 protein to the Golgi, instead of its canonical position at the ER membrane. [63] The normal allele, however, was able to perform its normal function, explaining the absence of typical features of GSD 1b. This remarkable mechanism shows again how specific genetic variants, even in the same gene, can cause widely disparate phenotypes. This example in particular exemplifies that biochemical phenotyping still remains important in the genomic era.

2.2.5 Dominant CDG with no recessive form

In addition to those discussed here, there are other autosomal dominant CDG described in the literature (e.g. for N-linked glycosylation: GANAB-CDG, PRKCSH-CDG; O-linked: EXT1/EXT2-CDG, POFUT1-CDG, POGLUT1-CDG). [5] Intriguingly, several of these disorders do not have recessive forms, such as EXT1-CDG. Possible reasons could be: i) an extremely different phenotype in the homozygous form, so that their pathology has not yet been linked to CDG; ii) non-viable homozygous damaging mutations, leading to *in utero* lethality; iii) a pathophysiology functionally linked to a specific dominant effect of the pathogenic variants identified, whereby absence of the functional protein in itself is not pathogenic.

3 Novel genetic mechanisms

3.1 Lack of expression in SLC10A7-CDG

Among the recently discovered CDG, SLC10A7-CDG is particularly interesting. Affected patients were first identified in a cohort of 99 individuals with aberrant Golgi glycosylation using a combination of hierarchical glycomics profiling and whole exome sequencing. This allowed the identification of a subset of 4 patients with a unique glycomics signature, linked to *SLC10A7* mutations or dysfunction. [76] This is an excellent example of integrated omics for rare disease diagnosis within CDG. Patient phenotypes included amelogenesis imperfecta, skeletal dysplasia and decreased bone mineral density. [77,78] SLC10A7 function is important in intracellular Ca^{2+} signaling and GAG biosynthesis. In two of the four original patients reported by Ashikov *et al.*, as well as those identified since, inheritance fits an autosomal recessive pattern. However, in the other two patients originally described, no mutations were identified using whole exome sequencing. Instead, a complete loss of *SLC10A7* mRNA was identified, including when primary skin fibroblasts were cultured with cycloheximide to inhibit nonsense-mediated decay. This indicates, still unexplained, aberrant *SLC10A7* regulation at a transcriptional level, either through deep intronic variants or epigenetic changes.

3.2 XYLT1-CDG caused by a repeat expansion

It is clear that we must now begin to investigate the non-coding genome for the diagnosis of 'unsolved' CDG. One recent success with regards to this is a study by LaCroix *et al.* [79] The authors have shown that a pathogenic GGC repeat expansion in the promoter region of the *XYLT1* gene is a cause of Baratela-Scott Syndrome (XYLT1-CDG; Desbuquois dysplasia 2; [MIM: 615777]), making up 50% of disease alleles in a cohort of 12 individuals. XYLT1-CDG is an autosomal recessive disorder characterized by facial dysmorphism, short stature, skeletal dysplasia and developmental disability. [80] *XYLT1* encodes XT1, a xylosyltransferase responsible for catalysis of the initial step of the biosynthesis of the glycosaminoglycans chondroitin and dermatan sulphate. [81] The GCC repeat expansion identified leads to hypermethylation of the first exon of the canonical *XYLT1* transcript, resulting in reduced expression of *XYLT1*. The authors were able to confirm this using bisulfite sequence analysis and proved that, in patients heterozygous for the GCC repeat expansion, the hypermethylated alleles were not transcribed, providing a satisfying interface between genetics and epigenetics. Remarkably, the 238 bp sequence of the promoter region of *XYLT1* in which this repeat expansion is found, is not present in the human reference genome (GRCh37/hg19, GRCh38/hg38) but was found in all individuals tested in this study. This shows the limitations of reference genomes currently used for diagnostic pipelines.

Lacroix *et al.* used a combination of genomic and transcriptomic techniques in order to identify the causative repeat expansion, study the effect this had upon methylation of the promoter region and the resulting impact upon expression. The study is therefore a good example of complementation of several layers of biochemistry in order to elucidate disease etiology as well as an example of success with regards to the investigation of the non-coding genome with regards to CDG.

This brings us to an area of great potential within the diagnostics of inherited disease, the epigenome. It can be considered to consist of either the individual chemical modification of DNA and histones known as 'chromatin marks' or more complex 'chromatin features'. Both lead to alterations in chromatin structure and therefore function of the genome. [82] There is a large amount of literature focused on the regulation of glycosylation by the epigenome, this is however largely limited to modulation of glycosylation in cancer. One example is the hypomethylation of the *XYLT1*, *B3GALT6* and *B3GAT3* genes, encoding enzymes involved in heparan sulphate biosynthesis, in multi-drug resistant A549 lung cancer cells. [83] Other examples, in various cancers, include the aberrant expression of various *GALNT* family members and *FUT8* due to modulation by miRNA, as well as *MGAT3*, due to aberrant methylation of its promoter region. [84] On a gross level, the N-glycome profile shows dramatic changes in a model of ovarian cancer in the presence of epigenetic inhibitors. [85] The field of epigenetic CDG seems to be a very promising one.

4 The genetics of CDG – where do we go from here?

4.1 Oligogenic inheritance

At one end of the spectrum, monogenic disorders are caused by highly pathogenic alleles, where the typical transmission model is that of mendelian, monogenic inheritance. These include the more rare and severe genetic disorders such as CDG. At the other end of the spectrum are the multifactorial (and usually more common) conditions, with aspects of heritability that can only be explained by an interaction with the environment and between variants in many genes or 'risk-alleles'. [86,87] Between monogenic and polygenic conditions, however, are a group of digenic or oligogenic disorders that result from two or several alleles of variable pathogenicity at separate genetic loci. [88] As yet there are very few examples, but these include forms of retinitis pigmentosa, identified as long ago as 1994 [89] and types of muscular dystrophy. [90] Indeed, a recent large gene-panel study of 4,656 limb-girdle muscular dystrophy (LGMD) patients identified at least 31 patients with heterozygous potentially pathogenic variants in more than one LGMD-related gene, making up 3% of all diagnosed patients. The authors show one pedigree in which severity of disease appears to correlate with the presence of three monoallelic variants, two in *ANO5*, and one in *COL6A2*. [91]

CDG as a group of disorders can be considered good candidates for oligogenic inheritance. Indeed, as we attempt to increase the diagnostic yield from exome and genome data, an oligogenic inheritance pattern must be considered in order to explain the pathology of 'unsolved' CDG patients. It is possible that the complexity of glycosylation pathways means that two or more individually non-pathogenic 'hits' in different genes could be pathogenic. This is particularly likely due to the 'assembly line' aspect of glycosylation and is particularly likely to be true for disorders of LLO and/or dolichol biosynthesis (**Section 2.2**): it is possible that the presence of one or more of these variants together in different genes in the LLO or dolichol metabolic pathway could create a complex and multigenic inheritance pattern. This is, however, unlikely to lead to the diagnosis of large groups of unsolved CDG patients. The numbers in question are currently too small for this to be applicable on more than a case-by-case basis. The same principal will almost certainly also affect the phenotype in the monogenic forms of CDG, whereby variants in other genes will act as modifiers. For example, it is notable that several defects leading to aberrant LLO formation or attachment (causing a CDG-I) lead to a variable phenotype according to the type of mutation, sometimes manifesting as an alternate dominant form of the disease.

Accordingly, the first digenic CDG has been proposed by Gupta *et al.* [92], with homozygous mutations in both *MAN1B1* (p.Met400Ile) and *SEC23A* (p.Arg334Cys). Both genes encode proteins involved in Golgi glycan remodeling or ER to Golgi vesicular trafficking, respectively. MAN1B1-CDG is already a known CDG, whereas mutations in *SEC23A* cause craniolenticosultura dysplasia [MIM: 607812]. The two brothers identified shared a combined clinical picture of both disorders (carbohydrate-deficient transferrin, tall stature, obesity, macrocephaly, and malocclusion teeth). In a cell model the authors also reported some interaction between MAN1B1 and SEC23A, with Golgi abnormalities. With regards to this case though, it should be kept in mind that there exist patients with two separate disorders, and this is not, thus, always the same as digenic inheritance.

4.2 Exploration of the non-coding genome

WES has its limits, only able to interrogate the coding sequence and flanking splice sites. An example of this limitation was its inability to detect the GCC repeat identified in the non-coding promoter region of *XYLT1*. As hinted in the discussion of *XYLT1* in **Section 3.2**, the next step for investigation of undiagnosed patients lies in the analysis of the non-coding, intergenic and intronic regions of the genome. This leads us to whole genome sequencing (WGS) technology. WGS has recently been expanded beyond research application to use in the clinic, in part due to continued cost reductions. For example, in our hands WGS recently led to a diagnosis of ATP6V0A2-CDG caused by deletion of coding exon 16 (ENST00000330342.8:c.1936-159_c.2055+113del) and the rapid identification of the intronic breakpoints, something impossible using whole exome sequencing.

Outside CDG, WGS has been found to lead to an increase in diagnostic yield over WES, but not as high as was initially hoped. [88,93] This is in part due to the limitations of our knowledge of the non-coding genome and a resulting lack of clinically validated and suitable bioinformatics tools for its interrogation. This can lead to uncertainty as to the effect of non-exonic variants, which must be investigated further by other technologies. There are many success stories however. The first major example was the study of Gilissen *et al.* [94] who show the value of WGS over WES and arrays for the diagnosis of intellectual disabilities (ID). The authors give the example of detection of a *de novo* duplication–insertion event inserting the last six exons of *TENM3* into the known ID gene, *IQSEC2*.

4.3 Transcriptomics (RNA-seq) to aid the interpretation of whole genome data analysis

As mentioned above, a major limitation of WGS technology is our current lack of understanding of the intricate relationship between intronic or intergenic genetic variation and gene expression. In combining genomic (WGS) and transcriptomic (RNA-seq) analysis, we have a powerful and exciting new method for the diagnosis of patients. If both techniques are carried out simultaneously, RNA-seq data can be used to study the deleterious effect of a variant of unknown significance upon splicing, leading to aberrant transcripts or reduced gene expression.

As another example, if altered expression of a candidate gene is identified via RNA-seq but no clear pathogenic candidate variant found using WGS, genome data can be further investigated for deep intronic or intergenic variants that could lead to a pathogenic alteration of gene expression. [95,96] However, due to the cost and technical limitations, combined WGS/RNA-seq analysis is only beginning to be explored.

The first examples of the systematic use of transcriptomics to aid rare disease diagnosis were described by Cummings *et al.* [97] and Kremer *et al.* [98] and detail the investigation of muscular and mitochrondrial disease cohorts, respectively. The success rate for these studies was 10-35% and subsequent studies agree with these outcomes. The consensus for most efficient strategy appears to be the comparison of a patient cohort with RNA-seq data from the general population, for example from the Genotype Expression (GTEx) database. [99] This allows the detection of abnormal transcripts that can indicate pathogenic splice-altering variants.

The systematic combination of WGS and transcriptomics analysis has not yet been used for a cohort of CDG patients. The major question regarding this will be the suitability of fibroblasts for transcriptomics analysis, as these have long been the most prevalent sample type used for the study of CDG. However, since a pathology characterized by defective glycosylation can be observed in fibroblasts for many or most CDG, the outlook is positive.

5 Concluding remarks

For some patients and families, their diagnostic odyssey has been long, up to several decades. Thanks to WES, we have now been able to solve cases that have remained elusive for many years. For those that still remain 'negative', we will have to consider the novel molecular mechanisms of disease, as outlined and exemplified here. It is estimated that 2 % of the 20,000 genes in the human genome encode proteins involved in glycosylation (± 400 genes). Even with over 140 genetically defined CDG currently identified, we are still far from reaching a complete knowledge of the genetic landscape of disorders resulting from defects in glycosylation.

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