Published in final edited form as:

J Inherit Metab Dis. 2018 May ; 41(3): 541–553. doi:10.1007/s10545-018-0156-5.

Recognizable phenotypes in CDG

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Abstract

Pattern recognition, using a group of characteristic, or discriminating features, is a powerful tool in metabolic diagnostic. A classic example of this approach is used in biochemical analysis of urine organic acid analysis, where the reporting depends more on the correlation of pertinent positive and negative findings, rather than on the absolute values of specific markers. Similar uses of pattern recognition in the field of biochemical genetics include the interpretation of data obtained by metabolomics, like glycomics, where a recognizable pattern or the presence of a specific glycan sub-fraction can lead to the direct diagnosis of certain types of congenital disorders of glycosylation. Another indispensable tool is the use of clinical pattern recognition—or syndromology—relying on careful phenotyping. While genomics might uncover variants not essential in the final clinical expression of disease, and metabolomics could point to a mixture of primary but also secondary changes in biochemical pathways, phenomics describes the clinically relevant manifestations and the full expression of the disease. In the current review we apply

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Compliance with ethical standards

Contribution

Carlos Ferreira and Eva Morava: study design, data collection, composing manuscript

Ruqaiyah Altassan: study design and data collection

Rita Francisco, Dorinda Marquez-Da-Silva: data collection

Jaak Jaeken: study design, revision of manuscript

Conflicts of interest

Carlos R. Ferreira, Ruqaiyah Altassan, Rita Francisco, Dorinda Marquez-Da-Silva, Jaak Jaeken and Eva Morava declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participant were in accordance with the ethical standards of the institutional and national research committee.

phenomics to the field of congenital disorders of glycosylation, focusing on recognizable differentiating findings in glycosylation disorders, characteristic dysmorphic features and malformations in PMM2-CDG, and overlapping patterns among the currently known glycosylation disorders based on their pathophysiological basis.

Keywords

Congenital disorders of glycosylation; syndrome; diagnosis; phenomics; serum transferrin; O-linked hypoglycosylation; therapy

Introduction

A phenotype is the set of all observable characteristics of an organism. The etymology of the word stems from the Greek word “phainein”, (to show) and “typos” (type), or “visible type”. Phenotyping is the oldest practice used by physicians to diagnose disease. Syndromology is a specific way of phenotyping, using a group of signs and symptoms that occur together to characterize a particular abnormality or condition. Patients born with an inborn error of metabolism can present with a genetic syndrome, showing a set of concurrent findings that form an identifiable pattern, even if the symptoms vary in severity. Congenital disorders of glycosylation (CDG) belong to a rapidly expanding group of metabolic disorders, frequently present as “syndromes” (Jaeken and Peanne, 2017). In fact, they were initially discovered as a novel disease group based on careful phenotyping of the most frequent form, now known as PMM2-CDG, where patients show dysmorphic facial features—strabismus, inverted nipples, abnormal fat distribution—and a variable combination of endocrine abnormalities and coagulation defects, making the disorder recognizable. Since the description of PMM2-CDG there have been more than 130 CDG subtypes described, and the number of disorders is rapidly growing. A few of these disorders are treatable, therefore early diagnosis is very important (Dorre et al., 2015, Riley et al., 2017). Some subtypes are detectable by transferrin isoform screening or other forms of glycosylation analysis, helping the diagnostic crusade (Buczowska et al., 2015, Bengston et al., 2016). But is there a specific clinical pattern in CDGs, which could point the clinician towards the correct diagnosis? In the current era of next-generation sequencing, is there a role for the clinician, or will the art of phenotyping succumb to molecular techniques in the –omics era? In this mini-review we structured all subtypes of CDGs described to date according to their biochemical nosology, and then attempt to establish a correspondence between certain subtypes with overlapping phenotypes and their biochemical basis. Finally, we review the existing literature on the phenotypic features associated with PMM2-CDG, and present data on computer-aided phenotyping by means of facial recognition analysis. We propose that the art of phenomics, either as performed by clinicians or with the help of currently-available technologies, continues to be very much alive, and rather than being supplanted by other –omics, it’s complementary to these.

Methods

A literature review was performed for each individual disorder of glycosylation, and a table was created with all subtypes of glycosylation disorders described to date (see Table 1). Each subtype of CDG was individually evaluated, and a concise summary was performed on those disorders that were felt to have clinical, imaging or laboratory findings that allow recognition and distinction from other disorders.

Next, a literature review was performed on congenital malformations in PMM2-CDG, using a PubMed search. PubMed database search was performed using the following terms: Congenital disorder(s) of glycosylation, type Ia OR PMM2 OR PMM2-CDG OR phosphomannomutase 2 deficiency OR Jaeken syndrome OR CDG-Ia OR carbohydrate deficient glycoprotein syndrome plus Anomaly OR malformation OR Malformation OR dysmorphic. All the publications were included in the search from the time of the disorder discovery, i.e. 1980. Only patients with confirmed *PMM2* mutations or enzymatically-confirmed phosphomannomutase 2 deficiency were included.

A total of 165 papers were reviewed. Reported cases were collected and summarized in an Excel table (Supplementary Table 1). In total, 561 patients were reported in the literature with confirmed PMM2-CDG.

Finally, we performed facial recognition analysis using the Facial Dysmorphology Novel Analysis (FDNA, Boston MA, USA) technology, which allows for assessment of subtle craniofacial dysmorphic features and facial pattern recognition. The input consisted of 53 facial frontal photos from 50 unaffected controls, as well as photos 18 patients with confirmed PMM2-CDG. A binary comparison was then performed between groups, and the capacity to distinguish them was assessed by measuring the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curve, which plots the true positive rate as function of the true negative rate. An AUC of 1 indicates perfect accuracy, while an AUC of 0.5 is the performance obtained by a totally random system (as for example a coin toss). Cross validation was performed by recurrently and randomly splitting the data into training sets, each set contained half of the photos. This random split was repeated 10 times (Lumaka et al. 2017).

Results

Recognizable phenotypes in congenital disorders of glycosylation

(Type 1 serum transferrin N-hypoglycosylation pattern: *, type 2 N-hypoglycosylation pattern: **, O-linked hypoglycosylation#, GPI-anchoring deficiency ##)

MPI-CDG*—MPI-CDG presents with liver disease (hepatomegaly and hepatopathy, cirrhosis), coagulopathy (increased bleeding tendency and risk for thrombotic episodes), hyperinsulinemic hypoglycemia, and gastrointestinal symptoms (chronic diarrhea, protein-losing enteropathy). It is treatable by mannose (200 mg/kg 4–6 times a day). Some patients need liver transplantation. There is normal intellectual development.

PMM2-CDG*—PMM2-CDG is the most common N-glycosylation abnormality. Strabismus, large ears, thin upper lip, inverted nipples, abnormal fat distribution and developmental delay (intellectual disability in most cases) are characteristic. Coagulation abnormalities, thrombotic events, stroke-like episodes, hepatopathy, endocrine abnormalities are not detectable in all patients, although hypogonadism is prevalent. Cerebellar hypoplasia can be present as early as the neonatal period.

GFPT1-CDG, DPAGT1-CDG*, ALG14-CDG, ALG2-CDG *—All of these subtypes can present with disordered neurotransmission in the form of myasthenia. In addition, DPAGT1-CDG and ALG2-CDG can present with a multisystemic disorder.

RFT1-CDG*, ALG11-CDG*—Both subtypes are associated with developmental delay, seizures and intellectual disability, all rather non-specific findings, but unlike other CDG subtypes, they are frequently accompanied by sensorineural hearing loss.

ALG6-CDG* and ALG8-CDG*—Patients with ALG6-CDG have developmental disability, proximal muscle weakness, seizures and in most cases ataxia. Brachydactyly and finger malformations have been described in several patients. ALG8-CDG is also accompanied by brachydactyly, as well as intellectual disability and dysmorphic features including low-set ears, hypertelorism and macroglossia.

ALG3-CDG*, ALG9-CDG* and ALG12-CDG*—The severe form of ALG9-CDG (Gillesen-Kaesbach-Nishimura syndrome) is accompanied by polycystic kidneys, hepatic fibrosis, congenital heart disease, and characteristic skeletal changes including mesomelia, a round pelvis, shortened sacrosciatic notch and ovoid ischia, hypomineralization of skull, cervical vertebral bodies, and pubic rami, and thick occipital bone. Similar skeletal anomalies were described in ALG3-CDG and ALG12-CDG.

MGAT2-CDG**—MGAT2-CDG is a disorder with recognizable facial features (long eyelashes, prominent nasal bridge, underdeveloped alae nasi, low-hanging columella, thin vermilion of the upper lip, thick vermilion of the lower lip). This disease is also characterized by severe growth delay, mental disability with absent speech and in some patients, radio-ulnar synostosis.

MAN1B1-CDG***—MAN1B1-CDG is a Golgi CDG with intellectual disability and, in most patients, facial dysmorphism (widely spaced eyes with down-slanting palpebral fissures, long ears, underdeveloped naso-labial fold, thin vermilion of the upper lip) and truncal obesity.

SRD5A3-CDG*—SRD5A3-CDG is a syndromal form of a dolicholphosphate synthesis defect; patients have eye malformations (cataract, retinal anomalies, glaucoma, visual loss), cerebellar ataxia and in about one third of the cases ichthyosiform skin anomalies. Developmental disability is mostly severe.

DOLK-CDG*—DOLK-CDG is usually associated with a multisystem phenotype, with neurologic, endocrine and coagulation abnormalities. A discriminative feature is dilated cardiomyopathy. Milder cases benefit from early cardiac transplantation.

DPM1-CDG*, DPM2-CDG* and DPM3-CDG*—All of these subtypes lead to alpha-dystroglycan hypoglycosylation, elevated creatine kinase levels and muscle dystrophy. Unlike other phenotypes of alpha-dystroglycanopathies, patients with either of these three forms of CDG also show abnormal transferrin glycosylation in serum.

COG1-CDG**—COG1-CDG patients show variable phenotypic features and variable severity. Some patients have been described with a costo-cerebro-mandibular-like syndrome.

COG7-CDG**—COG7-CDG is recognizable in most patients based on microcephaly, growth impairment, adducted thumbs, ventricular septal defect and episodes of hyperthermia.

SLC35C1-CDG**—SLC35C1-CDG is a disorder with frequent infections, neutrophilia and distinct facial features including brachycephaly, low insertion of the anterior hairline, coarse features, puffy eyelids, flat nasal bridge, large tongue, long upper lip with everted lower lips. Patients also have a rare blood type, the Bombay blood group. The immune phenotype improves with oral fucose supplementation.

ATP6V0A2-CDG#**—ATP6V0A2-CDG is also called autosomal recessive cutis laxa type 2A (ARCL2A). Generalized congenital sagging skin, cutis laxa, abnormal fat distribution, motor developmental disability, skeletal abnormalities, short stature, and joint luxation are characteristic. Intellectual development can be normal. Cutis laxa improves with age. Some patients have cobblestone-like brain dysgenesis and seizures.

ATP6V1A-CDG and ATP6V1E1-CDG#**—ATP6V1A-CDG and ATP6V1E1-CDG patients are very similar to those diagnosed with ATP6V0A2-CDG. They have generalized cutis laxa, motor and intellectual developmental disability, cardiac involvement and hypercholesterolemia. Cutis laxa improves with age.

ATP6AP1-CDG and ATP6AP2-CDG#**—ATP6AP1-CDG and ATP6AP2-CDG both present with early liver disease (cholestasis, fibrosis, cirrhosis). Frequent infections are mostly associated with hypogammaglobulinemia. Early symptoms include cutis laxa, which disappears with age.

TMEM199-CDG and CCDC115-CDG#**—TMEM199-CDG and CCDC115-CDG also present with early liver disease (cholestasis, fibrosis, cirrhosis) as well as hypercholesterolemia, low serum ceruloplasmin and developmental disability. These conditions can mimic Wilson disease, given the liver disease with hypoceruloplasminemia. Liver transplantation is a therapeutic option.

TMEM165-CDG#**—TMEM165-CDG is a recognizable spondyloepimetaphyseal skeletal dysplasia with extreme osteopenia, short stature, hyperinsulinism, growth hormone

deficiency and variable intellectual disability. Galactose treatment (1g/kg/day) showed biochemical improvement of glycosylated proteins in blood.

SLC39A8-CDG#**—SLC39A-CDG is a multisystem disorder with seizures. Several patients show a skeletal dysplasia with rhizomelic shortening and dwarfism. Not all patients have abnormal transferrin isoform analysis. Laboratory examinations, however, reveal low blood manganese and zinc concentrations, with increased urinary concentration from renal wasting. Patients show clinical and biochemical improvement on galactose (1g/kg/day) and individually dosed oral manganese therapy.

PGM1-CDG*/**—PGM1-CDG is a disorder with midline malformations (Pierre-Robin sequence, bifid uvula, cleft palate), hepatopathy, muscle weakness, cardiomyopathy and hypoglycaemia. This is an unusual CDG in that the type 2 transferrin pattern hides a combined type 1/type 2 defect. Galactose treatment (1g/kg/day) showed biochemical improvement of blood glycoproteins and liver function tests.

GMPPA-CDG—GMPPA-CDG is accompanied by alacrima, achalasia, and intellectual disability. Although NGLY1 deficiency can have alacrima and intellectual disability, patients don't have achalasia. Triple A syndrome can present alacrima and achalasia, but patients also have adrenal insufficiency, not seen in GMPPA-CDG.

PIGL-CDG##—PIGL-CDG is also known as CHIME syndrome, an acronym that describes its salient features of ocular Colobomas, congenital Heart disease, early-onset Ichthyosis, Mental retardation and Ear anomalies (conductive hearing loss).

PIGM-CDG##—PIGM-CDG is characterized by portal vein thrombosis and seizures. The seizures can improve with sodium butyrate, which increases transcription.

Phenotype of PMM2-CDG

The following congenital anomalies were reported in patients with confirmed PMM2-CDG.

Strabismus—Strabismus was described in 290 of 395 patients (73 %). In the available case series of 10 or more patients, the frequency of strabismus has been variably reported as 36 of 56 patients, or 64 % (Erlandson et al. 2001), 8 of 10 patients (Thompson et al. 2013) and 16 of 20 (de Lonlay et al. 2001), or 80 %, 25 of 28 patients, or 89 % (Monin et al. 2014), 12 of 13, or 92 % (Serrano et al. 2015), and 17 of 17 (Honzík et al. 2012), 23 of 23 (Kjaergaard et al. 2001), or 33 of 33 patients (Grünwald et al. 2001).

Inverted nipples—Inverted nipples were seen in 183 of 343 patients (53%). In the available case series of 10 or more patients, the frequency of inverted nipples has been variably reported as 5 of 20 patients, or 25 % (Barone et al. 2015), 3 of 11 adult patients, or 27 % (Monin et al. 2014), 9 of 26, or 35 % (Briones et al. 2002), 36 % out of 66 patients (Pérez et al. 2011), 10 of 26, or 38 % (Grünwald et al. 2001), 7 of 10 patients (Thompson et al. 2013), 10 of 13, or 77 % (Imtiaz et al. 2000), 16 of 17 patients, or 94 % (Honzík et al. 2012)—although it disappeared over time in 6 of those 16 patients—and in 23 of 23 patients

(Kjaergaard et al. 2001), although it disappeared over time in 2 of them. It can sometimes be unilateral (van de Kamp et al. 2007; Léticée et al. 2010).

Abnormal fat distribution—Abnormal fat distribution was reported in 168 out of 357 patients (47 %). In the available case series of 10 or more patients, the frequency of abnormal fat distribution has been variably reported as 5 of 20 patients, or 25 % (Barone et al. 2015), 27 % of 66 patients (Pérez et al. 2011), 7 of 19 adult patients, or 37 % (Monin et al. 2014), 10 of 26, or 38 % of patients (Grünewald et al. 2001), 4 of 10 (Thompson et al. 2013), and 21 of 23, or 91 % (Kjaergaard et al. 2001), but it disappeared over time in 9 of those 21 patients. A specific review of abnormal fat distribution found it in 24 of 32 patients, or 75 % (Wolthuis et al. 2013).

Dysmorphic facial features—Dysmorphic features have been described in large series in 29 % of 66 patients (Pérez et al. 2011), 11 of 20, or 55 % (de Lonlay et al. 2001), and 24 of 37, or 65 % of patients (Barone et al. 2015), including a prominent forehead, large ears and ear lobules, thin upper lip, prominent jaw, and long and slender fingers and toes. The prominent jaw develops over time, as the mandible can start as retrognathic (Al-Maawali et al. 2014). Almond-shaped eyes have also been frequently described, including in 7 of a series of 13 patients (Serrano et al. 2015). Other features reported in more than single patients include skin/peau d'orange in 7 (Clayton et al. 1992; Vabres et al. 1998; de Michelena et al. 1999; Stark et al. 2000; Noelle et al. 2005; van de Kamp et al. 2007), dysplastic ears (cupped, anteverted or crumpled) in 7 patients (Clayton et al. 1992; Garel et al. 1998; Tayebi et al. 2002; Rudaks et al. 2012; Resende et al. 2014; Serrano et al. 2015), low-set ears in 6 (Clayton et al. 1992; Imtiaz et al. 2000; Al-Maawali et al. 2014; Serrano et al. 2015), long philtrum in 6 (Harding et al. 1988; Pavone et al. 1996; Morava et al. 2004; van de Kamp et al. 2007; Kasapkara et al. 2017), high-arched palate in 5 (Tayebi et al. 2002; Bubel et al. 2002; I ikay et al. 2014; Kasapkara et al. 2017), long face in 3 (de Michelena et al. 1999; Tayebi et al. 2002), narrow/short palpebral fissures in 3 (Truin et al. 2008; I ikay et al. 2014), epicanthal folds in 2 (Tayebi et al. 2002; Enns et al. 2002), prominent nose in 2 (Barone et al. 2008; Thong et al. 2009), and anteverted nares in 2 (Tayebi et al. 2002; Morava et al. 2004). Other features variably reported included hypertelorism in 2 (Edwards et al. 2006; Kasapkara et al. 2017), but hypotelorism in 2 (Pavone et al. 1996); downslanted palpebral fissures in 3 (Clayton et al. 1992; Bubel et al. 2002), while others had upslanted palpebral fissures (Kjaergaard et al. 2001; Brum et al. 2008); flat nasal bridge in 5 (Harding et al. 1988; Tayebi et al. 2002; Thong et al. 2009; Al-Maawali et al. 2014; Kasapkara et al. 2017) but high nasal bridge in 4 (Artigas et al. 1998; Antoun et al. 1999; Laplace et al. 2003). A coarse face has been described in older adults (Bortot et al. 2013; Barone et al. 2015).

Congenital cardiac malformations—Conotruncal heart defects were described in a few patients, including tetralogy of Fallot in 3 patients (Vermeer et al. 2007; Romano et al. 2009; Al Teneiji et al. 2017), while common arterial trunk (also known as truncus arteriosus) was reported in 2 (Romano et al. 2009; Serrano et al. 2015; Marques-da-Silva et al. 2017).

Congenital airway and lung malformations—No malformations have been reported so far in PMM2-CDG patients.

Congenital liver and bile duct malformations—No liver and bile duct malformations have been reported so far in PMM2-CDG patients. Fibrotic changes and bile duct dilatation described in a few cases appeared later during the course of disease compared to other CDGs, like MPI-CDG (Marques-da-Silva et al. 2017)

Congenital urogenital malformations—Hydrocele, inguinal hernia and/or cryptorchidism was seen in 10 of 12 boys in one series (Kjaergaard et al. 2001), while cryptorchidism was described in 4 other patients (Veneselli et al. 1998; Garel et al. 1998; Truin et al. 2008; Resende et al. 2014). The most commonly reported malformations were multicystic kidneys, reported in seventeen patients (thirteen detected by ultrasound, three by renal biopsy and one by autopsy) followed by enlarged kidney size in four patients, and hydronephrosis in one patient (Schiff et al. 2017, van de Kamp et al. 2007, Hertz-Pannier et al. 2006, De Lonlay et al. 2001).

Facial recognition analysis of PMM2-CDG

For the facial phenotypic analysis of patients with PMM2-CDG, a composite image of unaffected controls vs that of patients can be found in figures 2A–B. Facial recognition analysis allowed for the discrimination of patients with PMM2-CDG vs controls, with an AUC of 0.84 (p value 0.014, see figures 2C–D).

Discussion

Here we define the PMM2-CDG phenotype, which is recognizable in at least 50% of the patients based on the presence of strabismus and inverted nipples and abnormal fat distribution. However, not only the inverted nipples and abnormal fat distribution, but also the facial phenotype seems to be recognizable among patients with PMM2-CDG. In particular, commonly reported facial dysmorphic features included almond-shaped eyes, large ears in relation to the (variably) decreased head circumference, a thin vermilion of the upper lip, short nose with long, smooth philtrum, and over time also prognathism. Although not reported in the literature, deep-set eyes and high-arched eyebrows are also often found in the authors' experience. Another dysmorphic finding frequently reported in the literature is arachnodactyly.

It is easy to understand why patients with mutations in genes involved in similar pathways would have similar symptoms. For example, it is understandable that mutations in 12 genes involved in the O-glycosylation of alpha-dystroglycan would all lead to a similar phenotype of muscular dystrophy, since glycosylation is essential for the anchoring function of dystroglycan (Endo 2015). However, by the same token it is hard to explain how mutations in certain genes involved in N-glycosylation could lead to such discrepant phenotypes. Since the transfer of the lipid-linked oligosaccharide (LLO) from the dolichol carrier to the nascent protein in the ER happens en bloc, in theory a deficiency of any of the 14 enzymes involved in the synthesis of the LLO would lead to a similar clinical presentation, as all would lead to the same deficient N-glycosylation of the nascent protein. However, this is not the case, and

the phenotypes appear to be clustered instead. For example, a defect in the synthesis of UDP-GlcNAc (as in GFPT1-CDG) or proteins participating in the addition of the first or second GlcNAc to the LLO (DPAGT1- and ALG14-CDG, respectively) all cause a similar phenotype of congenital myasthenic syndrome (Wu et al. 2003; Senderek et al. 2011; Cossins et al. 2013). A defect in the addition of the fourth and fifth mannoses (ALG11-CDG) and of the immediate next step of flipping the LLO from the cytoplasmic to the luminal side of the ER (RFT1-CDG) both lead to sensorineural hearing loss, a finding that is otherwise quite rare in other types of CDG (Vleugels et al. 2009a; Rind et al. 2010; Regal et al. 2015). Defects in the addition of the last four mannoses in the luminal side of the ER (ALG3-CDG, ALG9-CDG and ALG12-CDG) are associated with very characteristic skeletal changes, defined by mesomelic brachymelia, round pelvis, shortened sacrosciatic notch and ovoid ischia, hypomineralization of the skull, cervical vertebral bodies, and pubic rami, and a thick occipital bone (Tham et al. 2016). These skeletal findings are not similar to those seen in any of the other CDGs. Finally, defects in the next two steps in the synthesis of the LLO, meaning the addition of the first (ALG6-CDG) and second (ALG8-CDG) Glc lead to brachydactyly (Höck et al. 2015; Morava et al. 2016), while the most common type of CDG is associated with the opposite phenotype of long and slender fingers and toes. See figure 2 for a diagram depicting the aforementioned enzymatic steps.

This clustering of phenotypes is puzzling, since again all of these steps occur prior to the en bloc transfer of the glycan chain to the protein. The explanation for this phenotype clustering can thus not solely be related to protein hypoglycosylation. One possibility is that the accumulated LLOs themselves, or modifications of these, could in some way be toxic. For example, the cytosolic accumulation of Man3GlcNAc2-PP-Dol or Man4GlcNAc2-PP-Dol could lead to damage of the inner ear cells, while ER accumulation of Man5GlcNAc2-PP-Dol to Man8GlcNAc2-PP-Dol could lead to a reproducible skeletal dysplasia, and ER accumulation of Man9GlcNAc2-PP-Dol or GlcMan9GlcNAc2-PP-Dol would lead to brachydactyly as opposed to arachnodactyly. Alternatively, it is possible that the pathogenesis of these disorders is not only related to protein hypoglycosylation, but also to protein misglycosylation, with truncated LLOs, since it is known that truncated LLOs can indeed be transferred to the nascent protein, either with decreased efficiency (Krasnewich et al. 1995, Panneerselvam & Freeze 1996; Vleugels et al. 2009b). Even in the latter scenario, proteins that are misglycosylated with specific truncated LLOs as above could lead to the clustered phenotypes described.

It is clear that our understanding of the pathophysiologic mechanisms leading to the different phenotypes seen in CDG patients is still poor. However, the rapid scientific advances that ushered in the next-generation sequencing should not deter us from careful patient phenotyping, the oldest tool in the physician's armamentarium. Next-generation sequencing should lead to next-generation phenotyping, and the different -omics should be complementary with the process of phenomics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study is supported by the 1805218N FWO subsidie, in part by the Hayward Foundation and by 1 U54 GM104940 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds the Louisiana Clinical and Translational Science Center. Additionally this work was supported by the European Union's Horizon 2020 research and innovation program under the ERA-NET Cofund action N° 643578 – EURO-CDG-2

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Figure 1.

Facial recognition analysis of patients with PMM2-CDG.

A: Composite photo created by averaging the extracted mathematical information of the photos in the control cohort. B: Composite photo obtained from images of patients with PMM2-CDG. C: Score distribution of the binary comparison between unaffected controls and patients with PMM2-CDG. D: ROC curve with pertinent statistics obtained after conducting 10 random splits (true positive rate on the ordinate, true negative rate on abscissa).

Figure 2.
Diagram on the different steps in lipid-linked oligosaccharide assembly.

Table 1

Current list of subtypes of congenital disorders of glycosylation

Disease	Defective gene	Gene locus OMIM#	Defective protein	Localization of defect	Inheritance	Paper with initial molecular characterization (PMID)
N-linked glycosylation (effects)						
Interconversion of monosaccharides)						
PMM2-CDG	<i>PMM2</i>	601785	Phosphomannomutase	Cytosol	AR	9140401
MPI-CDG	<i>MPI</i>	154550	Phosphomannose isomerase	Cytosol	AR	9525984
N-glycan lipid-linked oligosaccharide assembly						
DPAGT1-CDG; CMS13	<i>DPAGT1</i>	191350	GlcNAc-1-P transferase	ER (cytosolic side)	AR	12872255
ALG13-CDG in males; EEIE36 in females	<i>ALG13</i>	300776	UDP-GlcNAc transferase	ER (cytosolic side)	XL	22492991
CMS15	<i>ALG14</i>	612866	UDP-GlcNAc transferase	ER (cytosolic side)	AR	23404334
ALG1-CDG	<i>ALG1</i>	605907	β 1-4 Man-transferase	ER (cytosolic side)	AR	14709599, 14973778, 14973782
ALG2-CDG; CMS14	<i>ALG2</i>	607905	α 1-3/6 Man-transferase	ER (cytosolic side)	AR	12684507
ALG11-CDG	<i>ALG11</i>	613666	α 1-2 Man-transferase	ER (cytosolic side)	AR	20080937
RFT1-CDG	<i>RFT1</i>	611908	Man5GlcNAc2-PP-Dol flippase	ER	AR	18313027
ALG3-CDG	<i>ALG3</i>	608750	α 1-3 Man-transferase	ER (luminal side)	AR	10581255
ALG9-CDG	<i>ALG9</i>	606941	α 1-2 Man-transferase	ER (luminal side)	AR	15148656
ALG12-CDG	<i>ALG12</i>	607144	α 1-6 Man-transferase	ER (luminal side)	AR	11983712
ALG6-CDG	<i>ALG6</i>	604566	α 1-3 Glc-transferase	ER (luminal side)	AR	10359825
ALG8-CDG	<i>ALG8</i>	608103	α 1-3 Glc-transferase	ER (luminal side)	AR	12480927
Glycan transfer to nascent protein						
TUSC3-CDG (MRT7/MRT22)	<i>TUSC3</i>	601385	OST subunit	ER	AR	18455129, 18452889
DDOST-CDG	<i>DDOST</i>	614507	OST subunit	ER	AR	22305527
SST3A-CDG	<i>SST3A</i>	601134	OST subunit	ER	AR	23842455
SST3B-CDG	<i>SST3B</i>	608605	OST subunit	ER	AR	23842455
SSR4-CDG	<i>SSR4</i>	300090	Translocon-associated protein, delta subunit	ER	AR	24218363
N-glycan processing						
MOGS-CDG	<i>MOGS</i>	601336	α 1-2 glucosidase I	ER	AR	10788335
Polycystic kidney disease 3	<i>GANAB</i>	104160	α 1-3 glucosidaseII subunit alpha	ER	AD	27259053

Disease	Defective gene		Gene locus OMIM#	Defective protein	Localization of defect	Inheritance	Paper with initial molecular characterization (PMID)
Polycystic liver disease 1		<i>PRKCSH</i>	177060	α 1-3 glucosidase II subunit beta	ER	AD	12529853, 12577059
MAN1B1-CDG (MKT15)		<i>MAN1B1</i>	604346	α 1-2 mannosidase I	ER	AR	21763484
MGAT2-CDG		<i>MGAT2</i>	602616	β 1-2 GlcNAc-transferase II	Medial-Golgi	AR	8808595
B4GALT1-CDG		<i>B4GALT1</i>	137060	β 1-4 Gal-transferase	Trans-Golgi	AR	11901181
O-linked glycosylation defects							
O-Man glycosylation							
MDDGA1, MDDGB1, MDDGC1	<i>POMT1</i>		607423	Protein O-Man-transferase	ER	AR	12369018
MDDGA2, MDDGB2, MDDGC2	<i>POMT2</i>		607439	Protein O-Man-transferase	ER	AR	15894594
MDDGA3, MDDGB3, MDDGC3, RP76	<i>POMGNT1</i>		606822	β 1-2 GlcNAc-transferase	Golgi	AR	11709191
MDDGA8	<i>POMGNT2</i>		614828	β 1-4 GlcNAc-transferase	ER	AR	22958903
MDDGA11	<i>B3GALNT2</i>		610194	β 1-3 GalNAc-transferase II	ER	AR	23453667
MDDGA12, MDDGC12	<i>POMK</i>		615247	Protein O-mannose kinase	ER	AR	23519211
MDDGA7, MDDGC7	<i>ISPD</i>		614631	Methyl erythritol 4-phosphate cytidyltransferase	Cytosol	AR	22522420, 22522421
MDDGA4, MDDGB4, MDDGC4	<i>FKTN</i>		607440	Fukutin	Golgi	AR	9690476
MDDGA5, MDDGB5, MDDGC5	<i>FKRP</i>		606596	Fukutin-related protein	Golgi	AR	11592034
MDDGA10	<i>TMEM5</i>		605862	β 1-4 xylosyltransferase	Golgi	AR	23217329
MDDGA13	<i>B4GAT1</i>		605581	β -1,3 glucuronyltransferase I	Golgi	AR	23359570
MDDGA6, MDDGB6	<i>LARGE1</i>		603590	β 1-3 GlcA-transferase/ α 1-3 Xyl-transferase	Golgi	AR	12966029
O-Xyl glycosylation							
Desbuquois dysplasia 2	<i>XYLT1</i>		608124	Xyl-transferase 1	Golgi	AR	23982343
Spondyloocular syndrome	<i>XYLT2</i>			Xyl-transferase 2	Golgi	AR	26027496
Progeroid EDS 1 (Larsen of Reunion Island syndrome)	<i>B4GALT7</i>		604327	β 1-4 Gal-transferase I	Golgi	AR	10473568, 10506123
SEMDIL Beighton type (progeroid EDS 2)	<i>B3GALT6</i>		615291	β 1-3 Gal-transferase II	Golgi	AR	23664117
Larsen-like syndrome	<i>B3GAT3</i>		606374	β 1-3 GlcA-transferase I	Golgi	AR	21763480
MHE type 1	<i>EXT1</i>		608177	β 1-4 GlcA-transferase II/ α 1-4 GlcNAc-transferase II	Golgi	AD	7550340

Disease	Defective gene	Gene locus OMIM#	Defective protein	Localization of defect	Inheritance	Paper with initial molecular characterization (PMID)
MHE type 2; Seizures, scoliosis and macrocephaly syndrome	<i>EXT2</i>	608210	β 1–4 GlcA-transferase II/ α 1–4 GlcNAc-transferase II	Golgi	AD; AR	8782816; 26246518
Immunoskeletal dysplasia with neurodevelopmental abnormalities	<i>EXTL3</i>		α 1–4 GlcNAc-transferase I and II	Golgi	AR	28132690; 28148688
Temitamy preaxial brachydactyly syndrome	<i>CHSY1</i>	608183	β 1–3 GlcA-transferase/ β 1–4 GalNAc-transferase	Golgi	AR	21129728
SED with congenital joint dislocations (AR Larsen syndrome, SED Omani type, humerospinal dysostosis)	<i>CHST3</i>	603799	GalNAc-6-O-sulfotransferase	Golgi	AR	15215498
EDS musculocontractural type 1	<i>CHST14</i>	608429	GalNAc-4-O-sulfotransferase	Golgi	AR	20004762
EDS musculocontractural type 2	<i>DSE</i>	605942	Dermatan sulfate epimerase	Golgi	AR	23704329
Desbuquois dysplasia	<i>CSGALNACT1</i>	616615	β 1–4 GalNAc-transferase I	Golgi	AR	27599773
Macular corneal dystrophy	<i>CHST6</i>	605294	GalNAc-6-O-sulfotransferase	Golgi	AR	11017086
Desbuquois dysplasia 1	<i>CANTI</i>	613165	UDP-Gal-nucleotidase	ER and Golgi	AR	19853239
O-GalNAc glycosylation						
Hyperphosphatemic familial tumoral calcinosis	<i>GALNT3</i>	601756	Polypeptide GalNAc-transferase	Golgi	AR	15133511
Tn polyagglutination syndrome	<i>C1GALT1C1</i>	300611	Core 1 β 1–3 galactosyltransferase chaperone	ER	Somatic	16251947
O-GlcNAc glycosylation						
MIRX106	<i>OGT</i>	300255	O-GlcNAc transferase	Nucleus and cytosol	XL	28302723; 28584052
Adams-Oliver syndrome 4	<i>EOGT</i>	614789	EGF-domain O-GlcNAc transferase	ER	AR	23522784
MIRT12; EIEE15	<i>ST3GAL3</i>	606494	α 2–3 Sia-transferase	Golgi	AR	21907012; 23252400
O-Glc glycosylation						
Dowling-Degos disease 4; LGMD2Z	<i>POGLUT1</i>	615618	Protein O-glucosyltransferase	ER	AD; AR	24387993; 27807076
O-Fuc glycosylation						
Dowling-Degos disease 2	<i>POFUT1</i>	607491	Protein O-fucosyltransferase	ER	AD	23684010
Spondylocostal dysostosis type 3	<i>LFNG</i>	602576	β 1–3 GlcNAc-transferase	Golgi	AR	16385447
Peters-Plus syndrome	<i>B3GALT1</i>	610308	β 1–3 Glc-transferase	ER	AR	16909395
GPI biosynthesis defects						

Disease	Defective gene	Gene locus OMIM#	Defective protein	Localization of defect	Inheritance	Paper with initial molecular characterization (PMID)
MCAHS2 (GPIBD4, EEIE20)	<i>PIGA</i>	311770	GlcNAc-transferase complex, catalytic subunit	ER (cytosolic side)	XL	22305531
MRT62 (GPIBD16)	<i>PIGC</i>	601730	GlcNAc-transferase complex	ER (cytosolic side)	AR	27694521
PIGQ-CDG	<i>PIGQ</i>	605754	GlcNAc-transferase complex	ER (cytosolic side)	AR	24463883
EEIE55 (GPIBD14)	<i>PIGP</i>	605938	GlcNAc-transferase complex	ER (cytosolic side)	AR	28334793
HPMRS6 (GPIBD12)	<i>PIGY</i>	610662	GlcNAc-transferase complex	ER (cytosolic side)	AR	26293662
CHIME syndrome (GPIBD5)	<i>PIGL</i>	605947	GlcNAc-PI de-N-acetylase	ER (cytosolic side)	AR	22444671
HPMRS5 (GPIBD11)	<i>PIGW</i>	610275	Inositol acyltransferase	ER (luminal side)	AR	24367057
GPIBD1	<i>PIGM</i>	610273	Man-transferase 1	ER (luminal side)	AR	16767100
HPMRS1 (GPIBD2)	<i>PIGV</i>	610274	Man-transferase 2	ER (luminal side)	AR	20802478
MCAHS1 (GPIBD3)	<i>PIGN</i>	606097	EnNP-transferase 1	ER (luminal side)	AR	21493957
HPMRS2 (GPIBD6)	<i>PIGO</i>	614730	EnNP-transferase 3	ER (luminal side)	AR	22683086
MRT53 (GPIBD13)	<i>PIGG</i>	616918	EnNP-transferase 2	ER (luminal side)	AR	26996948
MCAHS3 (GPIBD7)	<i>PIGT</i>	610272	GPI transamidase	ER (luminal side)	AR	23636107
GPIBD15	<i>GPAAI</i>	603048	GPI anchor attachment protein 1	ER (luminal side)	AR	29100095
MRT42 (GPIBD9)	<i>PGAPI</i>	611655	Inositol deacylase	ER (luminal side)	AR	24784135
HPMRS4 (GPIBD10)	<i>PGAP3</i>	611801	Phospholipase A2	Golgi	AR	24439110
HPMRS3 (GPIBD8)	<i>PGAP2</i>	615187	GPI-anchor remodeling protein	Golgi	AR	23561846, 23561847
Glycolipid glycosylation						
Amish infantile epilepsy syndrome (salt and pepper syndrome)	<i>ST3GAL5</i>	604402	α 2-3 Sia-transferase	Golgi	AR	15502825
SPG26	<i>B4GALNT1</i>	601873	β 1-4 GalNAc-transferase	Golgi	AR	23746551

Disease	Defective gene	Gene locus OMIM#	Defective protein	Localization of defect	Inheritance	Paper with initial molecular characterization (PMID)
NOR polyagglutination syndrome	<i>A4GALT</i>	607922	α 1–4 Gal transferase	Golgi	AD	22965229
Disorders of multiple pathways						
Monosaccharide synthesis						
CMS12	<i>GFPT1</i>	138292	Glutamine:F6P amidotransferase	Cytosol	AR	21310273
GENE myopathy; sialuria	<i>GENE</i>	603824	UDP-GlcNAc 2-epimerase/ManNAc kinase	Cytosol	AR; AD	11528398; 10330343
SEMD, Camera-Genevieve type	<i>NANS</i>	605202	N-acetylneuraminic acid-9-phosphate synthase	Cytosol	AR	27213289
Monosaccharide interconversion						
PGM1-CDG	<i>PGM1</i>	612934	Phosphoglucomutase	Cytosol	AR	19625727
Immunodeficiency 23	<i>PGM3</i>	172100	GlcNAc phosphate mutase	Cytosol	AR	24589341; 24698316; 24931394
Severe congenital neutropenia 4	<i>G6PC3</i>	611045	Glucose-6-phosphatase	ER	AR	19118303
Dolichol biosynthesis						
RP59	<i>DHDDS</i>	608172	Cis-isoprenyl transferase	ER (cytosolic side)	AR	21295283
NUS1-CDG	<i>NUS1</i>	610463	Cis-isoprenyl transferase subunit	ER	AR	25066056
SRD5A3-CDG	<i>SRD5A3</i>	611715	Polyprenol reductase	ER	AR	20637498
DOLK-CDG	<i>DOLK</i>	610746	Dolichol kinase	ER	AR	17273964
Dolichol-P-sugar biosynthesis and utilization						
DPM1-CDG	<i>DPM1</i>	603503	Dol-P-Man synthase	ER (cytosolic side)	AR	10642597; 10642602
DPM2-CDG	<i>DPM2</i>	603564	Dol-P-Man synthase	ER	AR	23109149
DPM3-CDG	<i>DPM3</i>	605951	Dol-P-Man synthase	ER	AR	19576565
MPDU1-CDG	<i>MPDU1</i>	604041	Dol-P-Man flippase	ER	AR	11733564
Nucleotide-sugar synthesis						
CAD-CDG (EIEE50)	<i>CAD</i>	114010	Carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase	Cytosol	AR	25678555
Alacrima, achalasia, and mental retardation syndrome	<i>GMPPA</i>	615495	<i>GDP-mannose pyrophosphorylase</i> α subunit	Cytosol	AR	24035193
MDDGA14, MDDGB14, MDDGC14	<i>GMPPB</i>	615320	<i>GDP-mannose pyrophosphorylase</i> β subunit	Cytosol	AR	23768512
Transporters						
SLC35A1-CDG	<i>SLC35A1</i>	605634	CMP-Sia transport	Golgi	AR	15576474
SLC35A2-CDG (EIEE22)	<i>SLC35A2</i>	314375	UDP-Galactose transport	Golgi	AR	23561849

Disease	Defective gene	Gene locus OMIM#	Defective protein	Localization of defect	Inheritance	Paper with initial molecular characterization (PMID)
SLC35A3-CDG	SLC35A3	605632	UDP-GlcNAc transport	Golgi	AR	24031089
SLC35C1-CDG	SLC35C1	605881	GDP-Fuc transport	Golgi	AR	11326279, 11326280
Schneckenbecken dysplasia	SLC35D1	610804	UDP-GlcA/UDP-GalNAc transporter	Golgi	AR	17952091
SLC39A8-CDG	SLC39A8	608732	Cation transporter	Plasma membrane	AR	26637978, 26637979
Vesicular trafficking						
COG1-CDG	COG1	606973	Conserved oligomeric Golgi complex subunit 1	Vesicular membrane/cytosol	AR	16537452
COG2-CDG	COG2	606974	Conserved oligomeric Golgi complex subunit 2	Vesicular membrane/cytosol	AR	24784932
COG4-CDG	COG4	606976	Conserved oligomeric Golgi complex subunit 4	Vesicular membrane/cytosol	AR	19494034
COG5-CDG	COG5	606821	Conserved oligomeric Golgi complex subunit 5	Vesicular membrane/cytosol	AR	19690088
COG6-CDG (Shaheen syndrome)	COG6	606977	Conserved oligomeric Golgi complex subunit 6	Vesicular membrane/cytosol	AR	20605848
COG7-CDG	COG7	606978	Conserved oligomeric Golgi complex subunit 7	Vesicular membrane/cytosol	AR	15107842
COG8-CDG	COG8	606979	Conserved oligomeric Golgi complex subunit 8	Vesicular membrane/cytosol	AR	17220172
Autoimmune interstitial lung, joint, and kidney disease	COPA	601924	COP-I subunit alpha	Vesicular membrane/cytosol	AD	25894502
Primary microcephaly	COPB2	606990	COP-I subunit beta-2	Vesicular membrane/cytosol	AR	29036432
Rhizomelic short stature with microcephaly, micrognathia, and developmental disability	ARCNI	600820	COP-I subunit delta	Vesicular membrane/cytosol	AD	27476655
Craniofacial dysmaturational dysplasia (Boyadjev-Jabs syndrome)	SEC23A	61051	COPII	Vesicular membrane/cytosol	AR	16980979
Congenital dyserythropoietic anemia type II; Cowden syndrome 7	SEC23B	610512	COPII component	Vesicular membrane/cytosol	AR; AD	19561605, 19621418, 26522472
Cole-Carpenter syndrome 2	SEC24D	607186	COPII component	Vesicular membrane/cytosol	AR	25683121
Chylomicron retention disease	SAR1B	607690	COPII GTPase	Vesicular membrane/cytosol	AR	12692552
Achondrogenesis IA	TRIP11	604505	Golgi microtubule-associated protein 210	cis-Golgi	AR	20089971
SED tarda	TRAPPC2	300202	Subunit of TRAPP tethering complex	Vesicular membrane/cytosol	AD	10431248
TRAPPC6B-CDG	TRAPPC6B	610397	Subunit of TRAPP tethering complex	Vesicular membrane/cytosol	AR	28626029
MRT13	TRAPPC9	611966	Subunit of TRAPP tethering complex	Vesicular membrane/cytosol	AR	20004763, 20004764, 20004765
LGMD2S	TRAPPC11	614138	Subunit of TRAPP tethering complex	Vesicular membrane/cytosol	AR	23830518
TRAPPC12-CDG	TRAPPC12	614139	Subunit of TRAPP tethering complex	Vesicular membrane/cytosol	AR	28777934

Disease	Defective gene	Gene locus OMIM#	Defective protein	Localization of defect	Inheritance	Paper with initial molecular characterization (PMID)
Golgi homeostasis						
Autosomal recessive cutis laxa type IIA (wrinkly skin syndrome)	<i>ATP6V0A2</i>	611716	Subunit of vacuolar ATPase	Vacuolar membrane	AR	18157129
Immunodeficiency 47	<i>ATP6API</i>	300197	Subunit of vacuolar ATPase	Vacuolar membrane	XL	27231034
X-linked mental retardation, Hedera type; X-linked parkinsonism with spasticity	<i>ATP6AP2</i>	300556	Subunit of vacuolar ATPase	Vacuolar membrane	XL	15746149
Autosomal recessive cutis laxa type IID	<i>ATP6V1A</i>	607027	Subunit of vacuolar ATPase	Vacuolar membrane	AR	28065471
Autosomal recessive cutis laxa type IIC	<i>ATP6V1E1</i>	108746	Subunit of vacuolar ATPase	Vacuolar membrane	AR	28065471
TMEM199-CDG	<i>TMEM199</i>	616815	Assembly factor for vacuolar ATPase	Vacuolar membrane	AR	26833330
CCDC115-CDG	<i>CCDC115</i>	613734	Assembly factor for vacuolar ATPase	Vacuolar membrane	AR	26833332
X-linked myopathy with excessive autophagy	<i>VMA21</i>	300913	Assembly factor for vacuolar ATPase	Vacuolar membrane	XL	23315026
TMEM165-CDG	<i>TMEM165</i>	614726	Ca ²⁺ /H ⁺ antiporter	Golgi	AR	22683087
Unknown						
Catel-Manzke syndrome	<i>TGDS</i>	616146	TDP-Glc 4,6-dehydratase	Unknown	AR	25480037

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CMS, congenital myasthenic syndrome; CS, chondroitin sulfate; DS, dermatan sulfate; EDS, Ehlers-Danlos syndrome; EGF, epidermal growth factor-like; EIEE, early infantile epileptic encephalopathy; EtNP, ethanolamine phosphate; F6P, fructose 6-phosphate; GPIBD, glycosylphosphatidylinositol biosynthesis defect; HPMRS, hyperphosphatasia with mental retardation syndrome; HS, heparin sulfate; KS, keratan sulfate; LGMD, limb-girdle muscular dystrophy; MCAHS, multiple congenital anomalies-hypotonia-seizures syndrome MDDG, muscular dystrophy-dystroglycanopathy; MHE, multiple hereditary exostoses; MRT, mental retardation; Neu5Ac, N-acetylneuraminic acid; PI, phosphatidylinositol; OST, oligosaccharyltransferase; RP, retinitis pigmentosa; SED, spondyloepiphyseal dysplasia; SEMDJL, spondyloepimetaphyseal dysplasia with joint laxity; SPG, spastic paraplegia; TSR, thrombospondin type repeats; XL, X-linked.