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Clinical and Biochemical Footprints of Congenital Disorders of Glycosylation: Proposed Nosology

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Abstract

We have identified 200 congenital disorders of glycosylation (CDG) caused by 189 different gene defects and have proposed a classification system for CDG based on the mode of action. This classification includes 8 categories: 1. Disorders of monosaccharide synthesis and interconversion, 2. Disorders of nucleotide sugar synthesis and transport, 3. Disorders of N-linked protein glycosylation, 4. Disorders of O-linked protein glycosylation, 5. Disorders of lipid glycosylation, 6. Disorders of vesicular trafficking, 7. Disorders of multiple glycosylation pathways and 8. Disorders of glycoprotein/glycan degradation. Additionally, using information from IEMbase, we have described the clinical involvement of 19 organs and systems, as well as essential laboratory investigations for each type of CDG. Neurological, dysmorphic, skeletal, and ocular manifestations were the most prevalent, occurring in 81%, 56%, 53%, and 46% of CDG, respectively. This was followed by digestive, cardiovascular, dermatological, endocrine, and hematological symptoms (17–34%). Immunological, genitourinary, respiratory, psychiatric, and renal symptoms were less frequently reported (8–12%), with hair and dental abnormalities present in only 4–7% of CDG. The information provided in this study, including our proposed classification system for CDG, may be beneficial for healthcare providers caring for individuals with metabolic conditions associated with CDG.

Keywords

CDG; glycoproteins; glycans; IEMbase; glycosaminoglycans; glycosphingolipids; glycosylphosphatidylinositol

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COI

None of the authors have any COIs.

Introduction

Due to the rapid advancement of modern genomic and metabolomic techniques, congenital disorders of glycosylation (CDG) [1] have emerged as a rapidly expanding category of inherited metabolic disorders (IMD), often characterized by multiorgan involvement, and overlapping clinical symptoms [2]. Since the initial description of twins in 1980 by Jaak Jaeken [3], the number of newly described CDG has increased exponentially, with currently 189 genes associated with 200 disorder phenotypes (Figure 1). In 2009 Jaeken and colleagues proposed a new nomenclature for CDG [4] using (only) the official gene symbol followed by '-CDG'. 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, since it is both clear and sufficient for all stakeholders including practicing physicians, clinical and biomedical basic researchers, patients, parents, and families. In this article we define glycosylation, CDG, and the criteria for their inclusion in the growing list.

Definitions

- Glycosylation is the cellular process of linking glycans (sugar chains) to other molecules, primarily proteins and lipids. This includes the genesis, addition, and modification of sugars prior to or after their addition to acceptors.
- CDG are human pathological conditions caused by genetic variants in any pathway that alters normal glycosylation in human subjects or in accepted cellular/animal models.

Inclusion Criteria

- Genes and pathological variants that demonstrate altered glycosylation in human subjects.
- Comparable variants in genes that alter glycosylation in eukaryotic cellular or multicellular model systems.
- Variants in proven glycosylation genes that are highly conserved throughout evolution and for which no other human homolog exists.
- Inclusion does not imply that these same disorders are not also previously classified into other groups, nor should families or support groups be confused by being included in the CDG roster.

We decided to add descriptors to CDG-related genes leading to disorders with different modes of inheritance, either autosomal recessive (ar) or autosomal dominant (ad). This was done not only because of the different mode of inheritance, but also because in many cases the phenotype of the disorders is markedly different. As an example, COG4-CDG(ar) is characterized by intellectual disability, seizures and elevated liver transaminases [5], while COG4-CDG(ad), also known as Saul-Wilson syndrome, is characterized by skeletal dysplasia with profound short stature, cataracts, retinal degeneration, and characteristic facial features [6]. Similarly, ALG8-CDG(ar) and ALG9-CDG(ar) lead to multisystemic disorders, while ALG8-CDG9(ad) and ALG9-CDG(ad) lead to polycystic liver disease. Not only the clinical manifestations but also the mechanism of disease can vary depending

on the mode of inheritance; as an example, SLC37A4-CDG(ar) leads to deficiency of glucose-6-phosphate transporter (and glycogen storage disease type 1b), while variants leading to SLC37A4-CDG(ad) cause a loss of the ER retention signal and mislocalization of the transporter (with liver disease and coagulopathy) [7].

We should note the remarkable growth of CDG numbers in recent years. A recent review submitted in 2021 [8] mentioned over 160 CDG, while our current count of 200 represents a 25% increase in the span of just 3 years. There are several reasons for this discrepancy. First, there were 16 novel CDG reported since 2021, as can be seen in figure 1. Second, we split some CDG caused by variants in the same gene into different entries due to discrepant clinical manifestations, mode of inheritance, or disease mechanism, as explained above, leading to 13 additional entries. Third, we included disorders that, although described in some cases decades ago, have not been routinely considered CDG. Examples include galactosemia (4 entries), hereditary fructose intolerance (1 entry), and mucolipidosis (two entries). We feel justified in this approach, as these disorders fulfill our inclusion criteria. Galactosemia leads to defective glycosylation of serum transferrin [9], IgG [10], and whole serum glycans; hereditary fructose intolerance leads to hypoglycosylation of transferrin [11], while mucolipidosis is caused by a deficiency of the machinery necessary to tag enzymes with a mannose-6-phosphate glycan for transport to the lysosome. Thus, all these entities fulfill our criteria of genes associated with disorders leading to demonstrable altered glycosylation in human subjects. Fourth, our understanding of pathomechanisms continues to increase over time; thus, we now know that disruption of the GARP complex needed for vesicular trafficking leads to N- and O-glycosylation abnormalities in cells [12], and a patient with a deficiency of VPS51, a subunit of the GARP complex, showed hypoglycosylation on serum transferrin isoelectric focusing, abnormal N-glycan and O-glycan profiles [13]. VPS51 deficiency thus fulfilled our criteria of demonstrable glycosylation abnormalities, while a deficiency of VPS53, another GARP subunit, fulfilled our criteria of comparable deficiency in genes that alter glycosylation in eukaryotic cellular models, in this case in human cell lines [12]. We expect that this trend of growth in the number of known CDG will continue as our understanding of disease mechanisms expands.

Due to the variety of glycosylation pathways and targeted proteins, congenital disorders of glycosylation exhibit a wide range of phenotypic presentations.

Materials and Methods

The information was sourced from IEMbase, a knowledgebase of inherited metabolic disorders (IMDs) available at http://www.iembase.org [14]. As of January 2024, IEMbase contains data on 1,907 IMDs and 4,342 corresponding clinical and biochemical signs and symptoms, which have been categorized into 22 organ systems and conditions (Autonomic system, Cardiovascular, Dental, Dermatological, Digestive, Dysmorphic, Ear, Endocrine, Eye, Genitourinary, Hair, Hematological, Immunological, Metabolic, Muscular, Neurologic, Psychiatric, Kidney, Respiratory, Skeletal, Tumoral and Other). The classification of IMDs [15] has been updated according to the International Classification of Inherited Metabolic Disorders (ICIMD) [16].

Results

Table 1 summarizes the proposed nosology of CDG, clinical involvement of 19 organs and systems, as well as essential laboratory investigations for each CDG.

A total of 200 CDG, resulting from 189 distinct gene defects, were organized into 8 categories: 1. Disorders of monosaccharide synthesis and interconversion, 2. Disorders of nucleotide sugar synthesis and transport, 3. Disorders of N-linked protein glycosylation, 4. Disorders of O-linked protein glycosylation, 5. Disorders of lipid glycosylation, 6. Disorders of vesicular trafficking, 7. Disorders of multiple glycosylation pathways and 8. Disorders of glycoprotein/glycan degradation. Disorders of O-linked protein glycosylation were further broken down into: Disorders of O-mannosylation, Disorders of O-GalNAcylation, Disorders of O-GlcNAcylation, Disorders of O-glucosylation, Disorders of O-galactosylation, Disorders of O-fucosylation and Disorders of glycosaminoglycan synthesis and O-xylosylation, while Disorders of lipid glycosylation were further divided into: Disorders of glycosylphosphatidylinositol biosynthesis and Disorders of glycosphingolipid synthesis.

Disorders of other glycosylation pathways were further categorized as: Disorders of dolichol metabolism and Disorders of Golgi homeostasis. Four disorders (MAN2B2-CDG, MPI-CDG, PMM2-CDG and SLC37A4-CDG(ad)) were listed in more than one category. This classification system delineates the various CDG based on their genetic origins and specific pathways involved and includes genes affecting glycosylation substrates (sugars) shortage.

The overall clinical profile can vary widely depending on the specific CDG, but some features include neurological involvement (developmental/intellectual disability, epilepsy, hypotonia, ataxia), failure to thrive, poor growth, facial dysmorphism, liver, cardiac, gastrointestinal and endocrine involvement, and coagulation abnormalities.

We utilized data from IEMbase to compile clinical symptoms for the 200 CDG listed in Table 1. The most prevalent symptoms were neurological (80.5%), followed by dysmorphisms (55.6%), skeletal abnormalities (52.7%), ocular problems (46.3%), digestive issues (34.1%), cardiovascular abnormalities (22.0%), muscular problems (20.0%), short stature (18.5%), dermatological issues (17.6%), hematological abnormalities (16.6%), endocrine issues (16.1%), immunological problems (11.7%), ear-related symptoms (11.2%), respiratory issues (10.2%), genitourinary problems (9.8%), psychiatric symptoms (9.8%), renal complications (8.3%), hair-related issues (6.8%) and dental problems (4.4%) as shown in Table1 and Figure 2.

Among the neurological symptoms, hypotonia, developmental/intellectual disability were the most common, with rates of 50.5%, 42.0%, and 35.5%, respectively. The most frequently reported dysmorphisms included facial dysmorphism, such as widely spaced eyes, and micrognathia at rates of 21.5%, 11.0%, and 8.5%, respectively. Common skeletal abnormalities included kyphoscoliosis at a rate of 20.0% and joint laxity and retrognathia each at 6.0%.

In the ocular group, prevalent abnormalities were strabismus at a rate of 15.0%, cataract at a rate of 10.5%, and nystagmus at a rate of 6.0%. Within the gastrointestinal group, feeding difficulties were reported at a rate of 12.0%, hepatomegaly at a rate of 9.5%, and hepatopathy at a rate of 4.5%. In the cardiovascular group, common symptoms included cardiomyopathy at a rate of 5.5% and congenital heart defects at a rate, including ventricular septal defect, at a rate of 4.5%.

The ten most common symptoms reported in the aforementioned groups are summarized in Table 2 for easy reference.

Discussion

Glycosylation is an ancient process; it occurs in all organisms [17]. An estimated 2% of the expressed genome encodes proteins that produce, regulate, or bind to glycans. It is not surprising that pathological genetic variants in these genes would disrupt normal development or physiology. Each cell uses exogenous, endogenous, and salvaged building materials (sugars and modifiers) and its variable set of transferases, multiprotein complexes, and glycosidases to construct and modify thousands of glycans spanning at least 10 separate pathways. Unlike nucleic acid and protein synthesis, glycosylation is not template-driven. With few exceptions [18], there is no universal glycan code for physiological functions. Many environmental factors interact with the glycosylation machinery to assemble and present these variably-sized, flexible molecules. Unlike the robust technologies available for analysis of other macromolecules, analysis of glycans (glycomics) and the range/types of glycans present at an individual position (glycoproteomics) is lagging but improving [19]. A recent discussion of CDG inclusion criteria was more conservative than those presented here, generating a “grey zone” for interpretation and debate [8]. The definition of glycosylation and CDG as presented here casts a wide net for human disorders that disrupt one or more of these pathways as demonstrated in one or more molecules. Since we don’t know every glycan in every cell, our current analysis covers a narrow band of biomarkers and physiologically important molecules. This visible glyco-spectrum is hardly complete. Witness the very recent and surprising discovery of glycosylated t-RNA molecules [20, 21] at the cell surface which have now been shown to control neutrophil recruitment [22] other functions will certainly emerge for this novel class of molecules.

We expect that others may have reservations about including some of these disorders as CDG, especially when we cannot show that impaired glycosylation is the basis of an individual’s pathology. In that case, we have provided glycosylation biomarkers that may be useful for natural history or therapy studies.

Few studies show that salvaged monosaccharides are reused for glycan synthesis [23]. Although the extent is unknown, it is conceivable that failure to recycle some sugars would compromise glycosylation. In fact, recent studies show that glycogen-derived monosaccharides contribute to N-glycan synthesis [24, 25]. Such discoveries may blur the bright line between disorders of glycan synthesis and glycan degradation. The IEMbase offers detailed information on all CDG and the currently proposed nosology will be regularly curated and updated in the GAMUTS section (http://www.iembase.org/gamuts/).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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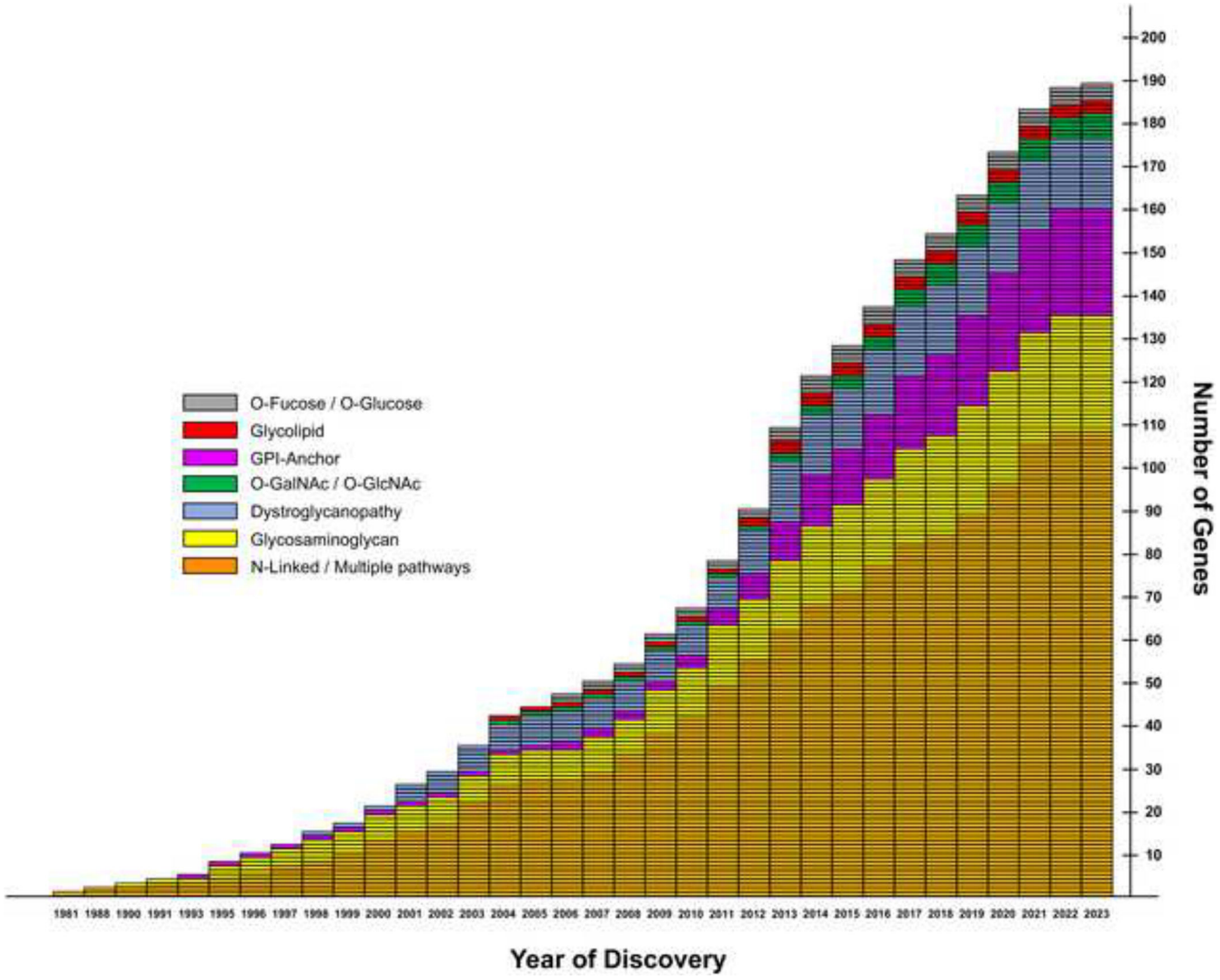

Figure 1.

Identification of CDG genes. The cumulative growth of disorders that affect glycosylation of multiple pathways is shown based on the year of their discovery. In many early cases, strong biochemical evidence preceded identification of the human gene.

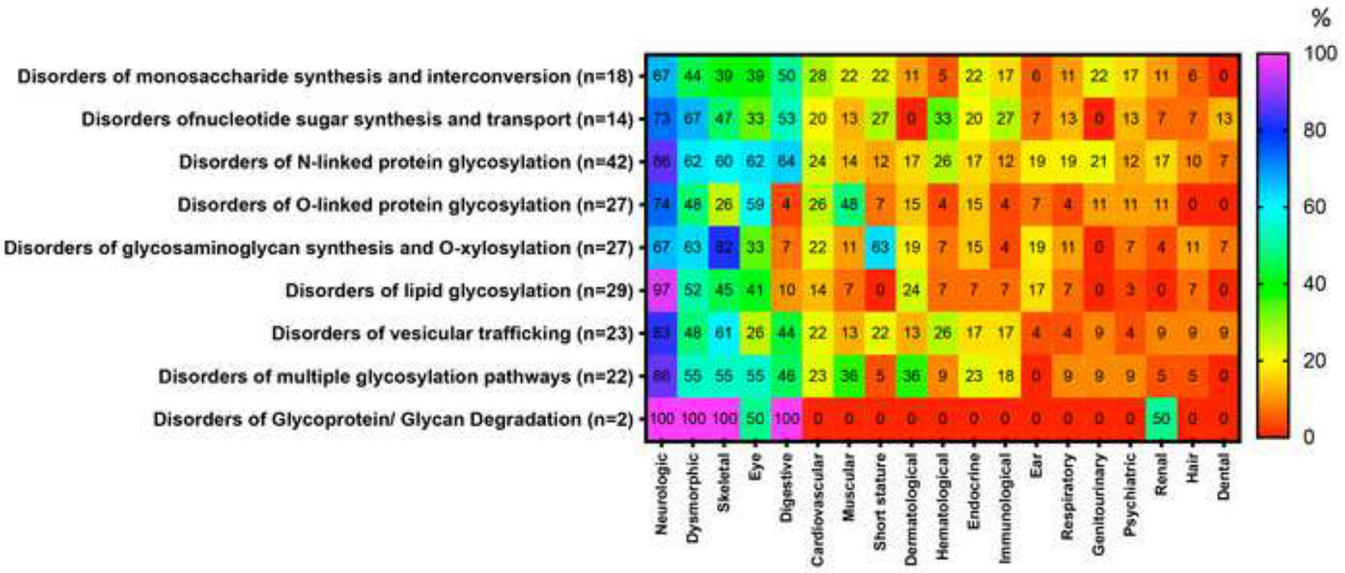

Figure 2.

The frequency (%) of 19 organ/systems involvements reported in 9 categories of congenital disorders of glycosylation (CDG) is presented. The percentages of organ/system involvement were calculated using the total number of CDG in each category with any organ/system involvement as the denominator. The heat scale ranges from red (0%) for disorders with no specific reported symptoms to violet (100%) for disorders with particular symptoms occurring more frequently within the disorders group. For details see the Table 1. For an explanation of the color references in this figure legend, readers are directed to the web version of this article.

	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
	X	X		X	X	X					X	X	X		X	
	X	X		X				X			X					
	X	X			X	X		X	X		X			X	X	
											X					
	X	X				X		X			X				X	
					X					X	X					
										X				X		
	X	X									X				X	X
		X									X				X	X
		X	X							X					X	
		X		X				X	X		X				X	X
		X									X				X	X

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...gical	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
	X												X			
	X				X							X				
					X											
					X											
	X			X	X	X		X	X		X	X				
								X			X					
	X	X	X	X	X						X					
					X					X	X					
	X										X					X
	X	X					X			X	X					
		X			X				X		X					
								X			X	X				
	X	X			X				X		X				X	
		X									X	X			X	

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
		X						X	X		X					X
	X	X													X	
	X	X		X				X	X				X	X	X	X
	X							X						X	X	X
		X													X	X
X	X	X		X	X	X					X	X	X		X	
X	X	X		X				X			X					
X	X	X			X					X	X					
X	X	X			X			X		X	X					
X					X					X	X			X		
X	X	X			X			X		X	X		X		X	
					X						X					

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
	X	X	X		X			X			X			X	X	
	X	X	X		X			X			X					
	X	X			X						X				X	
	X	X			X						X					
	X															
	X	X	X	X	X	X		X			X	X	X		X	
													X			
	X	X									X				X	
	X	X						X			X		X			

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
	X		X		X						X				X	
		X			X						X				X	X
	X										X				X	
		X			X					X	X				X	X
					X	X		X			X			X		
		X			X						X				X	
					X				X		X					
	X	X	X		X	X			X		X			X	X	
	X	X			X	X					X				X	
		X					X		X		X	X		X		
	X										X					
	X	X			X	X	X		X		X			X	X	
	X												X			
	X												X			

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
		X			X						X				X	
		X			X						X	X				
	X	X			X	X		X	X		X			X	X	
	X	X	X	X	X	X	X	X	X	X	X			X	X	X
	X	X			X			X			X					
	X	X		X	X		X			X	X			X	X	
		X	X		X			X			X	X			X	X	
		X			X					X	X					X
		X			X					X	X					X
		X			X					X	X					X

…ical	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
		X			X					X	X					
		X			X					X	X	X				
					X					X	X					
		X		X	X					X	X					X
		X			X					X	X			X		X
		X			X					X	X					
				X	X					X	X					
					X	X				X	X		X			
					X					X	X				X	
			X								X		X			
		X			X						X	X				
								X	X							
		X		X							X	X				

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
															X	
					X											
											X				X	
		X									X				X	
		X			X	X					X				X	
										X						
											X					
															X	
					X											
				X		X					X					
	X		X	X			X				X		X		X	X
		X			X										X	X
			X		X						X					X

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
		X			X						X				X	X
		X		X							X			X	X	X
		X			X						X				X	X
		X									X				X	X
	X	X							X		X				X	X
											X			X	X	
		X									X					
	X	X					X				X	X				X
		X									X		X			
		X		X						X	X					X
		X			X						X					X
		X	X					X			X					X
			X		X			X		X	X				X	X
		X													X	X

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
					X											
		X			X						X				X	X
		X	X								X			X	X	X
				X			X								X	X
		X														X
		X		X						X	X				X	
	X	X									X					
		X									X					
					X		X				X					
											X	X				
											X					
		X									X				X	

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
			X		X						X					
											X					
								X			X					
					X					X	X					
	X		X								X				X	
		X	X								X			X	X	
		X	X		X						X				X	
		X									X				X	
		X									X				X	
		X			X			X	X		X				X	
		X			X					X	X				X	
		X			X						X				X	
		X		X	X		X				X					

gical	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
					X						X				X	
		X									X			X	X	
		X									X					
			X								X					
			X		X						X					
				X	X						X				X	
											X					
									X							
	X	X						X			X					X
	X	X		X				X			X					
	X	X			X						X					
											X					
		X			X						X				X	X
	X		X		X	X					X				X	X
	X	X		X				X	X		X				X	
	X	X				X			X		X		X		X	

Cardiological	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
					X				X		X				X	X
	X			X							X		X		X	
							X			X	X					
	X										X			X		
		X					X	X	X							
	X	X		X							X				X	
					X			X								
		X					X			X	X					
											X	X			X	
																X

…ical	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal	Short stature
					X	X					X		X			
											X	X				
					X						X				X	
											X					
		X		X	X					X	X				X	
		X		X	X		X				X					
	X				X						X					
	X	X			X				X	X	X			X	X	
		X								X	X				X	
	X	X		X	X						X				X	
		X		X	X						X				X	
		X			X					X	X				X	
		X			X					X	X				X	

Neurological	Psychiatric	Renal	Respiratory	Skeletal	Short stature	Digestive	Dysmorphic	Ear disorders	Endocrine	Eye disorders	Genitourinary	Hair disorders	Hematological	Immunological	Muscular
X						X							X	X	
X						X	X				X				
						X	X								
X	X					X	X			X					
															X
X				X	X				X	X				X	
X				X		X	X		X	X				X	X
X				X											X
X			X	X		X	X		X				X	X	
X	X			X											
X	X			X											

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; MU: muscle; P: plasma; PLT: platelets; RBC: red blood cells; S: serum; U:

Table 2.

Clinical manifestations and symptoms observed in CDGs, based on the six most frequently affected systems.

Neurological	**%**	**Dysmorphisms**	**%**	**Skeletal**	**%**
Hypotonia	50.5	Facial dysmorphism	21.5	Kyphoscoliosis	20.0
Developmental delay	42.0	Widely spaced eyes	11.0	Joint laxity	6.0
Intellectual disability	35.5	Micrognathia	8.5	Retrognathia	6.0
Microcephaly	22.5	Cleft palate	6.5	Brachydactyly	5.0
Epilepsy	21.0	Inverted nipples	6.0	Clubfoot	5.0
Seizures	16.0	Low-set ears	6.0	Brachycephaly	3.5
Cerebellar atrophy	12.0	Long philtrum	5.0	Short neck	3.5
Cerebral atrophy	11.0	Coarse face	4.0	Skeletal dysplasia	3.5
Ataxia	10.0	Microphthalmia	4.0	Clinodactyly	3.5
Cobblestone lissencephaly	5.5	Prominent forehead	4.0	Osteopenia	3.0
Ocular	**%**	**Digestive**	**%**	**Cardiovascular**	**%**
Strabismus	15.0	Feeding difficulties	12.0	Cardiomyopathy	7.5
Cataract	10.5	Hepatomegaly	9.5	Congenital heart defects	5.5
Nystagmus	6.0	Hepatopathy	4.5	Ventricular septal defect	4.5
Glaucoma	4.5	Hepatosplenomegaly	3.0	Cardiovascular abnormality	2.0
Myopia	4.5	Diarrhea	3.0	Atrial septal defect	1.5
Optic atrophy	4.5	Gastrointestinal dysmotility	2.5	Cardiac anomalies, malformations	1.5
Coloboma	3.0	Liver failure	2.5	Aortic insufficiency	1.0
Corneal clouding	3.0	Gastroesophageal reflux	2.0	Cardiac failure	1.0
Optic nerve hypoplasia	2.0	Liver cirrhosis	2.0	Digital necrosis (distal phalanges)	0.5
Pigmentary retinopathy	2.0	Vomiting	2.0	Heart valve dysplasia	0.5