Congenital disorders of glycosylation (CDG): Quo vadis?

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\textbf{A B S T R A C T}

The survey summarizes in its first part the current status of knowledge on the Congenital Disorders of Glycosylation (CDG) with regard to their phenotypic spectrum, diagnostic and therapeutic strategies, and pathophysiology. It documents the clinical and basic research activities, and efforts to involve patients and their families. In the second part, it tries to look into the future of CDG. More specific biomarkers are needed for fast CDG diagnosis and treatment monitoring. Whole genome sequencing will play an increasingly important role in the molecular diagnosis of unsolved CDG. Epigenetic defects are expected to join the rapidly expanding genetic and allelic heterogeneity of the CDG family. Novel treatments are urgently needed particularly for PMM2-CDG, the most prevalent CDG. Patient services such as apps should be developed e.g. to document the natural history and monitor treatment. Networking (EURO-CDG, the European Reference Networks (MetaBERN)) is an efficient tool to disseminate knowledge and boost collaboration at all levels. The final goal is of course to improve the quality of life of the patients and their families.

\section{1. Introduction}

Approximately half of all proteins typically expressed in a cell undergo glycosylation to achieve their full functionality. There are mainly two categories of glycosylation: N-glycosylation and O-glycosylation. N-glycans are linked to the amide group of asparagine, while O-glycans are linked to the hydroxyl group of serine or threonine. The synthesis of N-glycans proceeds in three stages: formation of nucleotide-linked sugars, assembly (in cytosol and ER), and processing (in the Golgi). The synthesis of O-glycans does not involve processing, and occurs mainly in the Golgi. Besides, there is also lipid glycosylation and synthesis of glycosylphosphatidylinositol anchors. Congenital Disorders of Glycosylation (CDG) are genetic defects in the synthesis and attachment of glycoprotein and glycolipid glycans. Initially, mutations were found in genes encoding glycosyltransferases, remodelling glyciosidasises, and sugar nucleotide transporters, that are all known to have a direct role in glycosylation. However, new forms of CDG have recently been identified with defects in vesicular trafficking, pH homeostasis or Mn\textsuperscript{2+} homeostasis. Various approaches have been developed for the efficient diagnosis of these diverse types of CDG (see section 2.2 for more details). Since their first clinical description in 1980, 105 types of CDG have been identified, and that number keeps rising. Their clinical spectrum is extremely broad, covers nearly all known phenotypes, and comprises new phenotypes. Research into CDG received an enormous boost since 1999 thanks to the consecutive, collaborative initiatives of EUROLGCAN and EUROGLYCNET, that were originally funded by...
the European Commission’s Framework Programmes. In 2011, our group (Berlin, Brussels, Heidelberg, Leuven, Lille (Villeneuve d’Ascq), Madrid, Nijmegen, and Paris) has successfully replied to the E-Rare-2 Call for Proposals with the EURO-CDG project. Research in the context of EURO-CDG has yielded improved diagnostic methodologies resulting in the identification of an increasing number of CDG, shortening of the time to diagnosis, and CDG diagnosis in patients who remained ‘unsolved’ for many years. In addition, cellular models have been used to study the pathophysiology of disease and to identify molecular pathways that can be targeted for therapy. Within the network, more than 1300 CDG patients received a definite diagnosis (with PMM2-CDG representing 62% of the recorded patients, and 30 other CDG representing the remaining 38%).

Efforts are now guided towards the development of therapeutic approaches for PMM2-CDG, the most frequent CDG, but also for the more rare CDG. The functional characterization of disease-causing mutations in PMM2-CDG patients led to the identification of pharmacological chaperones to rescue the folding of the mutant PMM2 enzyme. In parallel, oral D-galactose therapy has been shown to be beneficial in CDG with hypogalactosylation. We initiated a multicentric clinical trial to characterize the effects of D-galactose supplementation in different genetic conditions affecting Golgi glycosylation, including PGMI-CDG, TMEM165-CDG and SLC35A2-CDG. The European network for research on CDG wants to build on its past achievements and is committed to explore different genetic conditions affecting Golgi glycosylation, including PMM2-CDG, TMEM165-CDG and SLC35A2-CDG. The European network for research on CDG wants to build on its past achievements and is committed to explore different possibilities to improve treatment and quality of life of the patients and their families. It will of course also share efforts to this aim with other researchers interested in CDG. Open, international meetings, often in parallel with patients and parents meetings, are meant to exchange experience and results, and to promote progress in CDG.

2. CDG at present

2.1. Phenotypic spectrum

Table 1 tabulates the known CDG (in alphabetical order) with the main associated organ involvement and symptomatology. For a recent review on CDG and a selection of reviews on organ/tissue-specific CDG and specific CDG/CDG groups see Jaeken and Morava 2016; Jaeken and Péanne 2017. The fact that five novel CDG have been reported in the first half of 2017 illustrates the rapid expansion of this disease family: ATP6V1A-CDG (Van Damme et al., 2017), ATP6V1E1-CDG (Van Damme et al., 2017), PIGC-CDG (Edvardson et al., 2017), TRAPPCL1-CDG (Matalonga et al., 2017), and OGT-CDG (Willems et al., 2017). Also, a novel regulatory mutation has been presented, with a defect in the PMM2 promoter (Cabezas et al., 2017). In recent years, it has become clear that some CDG can present totally different phenotypes depending on the types of mutation. Striking examples are PMM2-CDG (a dysmorphism-disability syndrome; polycystic kidney disease with hyperinsulinemic hypoglycaemia; isolated tendency to thrombosis), ALG9-CDG (a dysmorphism/neuro-hepato-renal syndrome; a skeletal phenotype with death in utero), ECT2-CDG (exostoses; seizures-scoliosis-macrocephaly syndrome), PIGA-CDG (intellectual disability and seizures without dysmorphism; ferro-cerebrocutaneous syndrome; Simpson-Golabi-Behmel syndrome type 2; early onset epileptic encephalopathy with severe muscular hypotonia, dysmorphism, multiple congenital anomalies and early death (MCAHS2)), and POGLUT1-CDG (skin disease; muscular dystrophy). No defects have yet been reported in many genes of the glycosylation machinery, as for instance in the Golgi mannosidases (except MAN1B1), in MGAT1, B4GAT1, ...which have been candidate genes, right from the beginning. We reckon that patients with defects in these genes are extremely rare and highly underestimated, or may not survive until birth.

There is an increasing number of reports on adult features of CDG such as PMM2-CDG (up to 67 years; Monin et al., 2014; Barone et al., 2015), SRD5A3-CDG (up to 45 years; Kahrizi et al., 2011; Kara et al., 2014; Wheeler et al., 2016), PGM3-CDG (up to 35 years; Sassì et al., 2014; Zhang et al., 2014). This helps in answering the often asked question of parents: what is the future of my child?

2.2. CDG frequency and registry

The standard test for the diagnosis of N-glycosylation disorders with sialic acid deficiency is still isoelectrofocusing of serum transferrin (TF IEF), which is only N-glycosylated. A type 1 pattern (decreased tetrasialotransferrin, increased disialo- and asialotransferrin) points to an assembly defect or a defect in the transfer to the peptide chain (CDG-I), whilst a type 2 pattern (increase also of threeasialo- and monosialotransferrin) suggests a remodelling defect (CDG-II). Note that in normal infants up to about 6 weeks, the serum transferrin bands are slightly more intense than later on (looking like a mild type 2 pattern).

In case of a typical MPI-CDG or PMM2-CDG presentation, enzymatic testing can be performed in leukocytes or fibroblasts although it is more cumbersome than direct mutation analysis of the MPI and PMM2 genes respectively. In addition, we have evidence that false negative PMM2 measurements in fibroblasts occur (G. Matthijs, E. Van Schaftingen and co-workers, unpublished). Hence, we propose to sequence the PMM2 gene first in all CDG type I cases. In the other cases with a type 1 pattern, there is a tendency to first perform a targeted CDG panel analysis, and when negative, whole genome/exome sequencing. Lipid-linked oligosaccharide analysis (LLO) in fibroblasts for type I is a cumbersome and expensive test that not always provides accurate results (see below). In patients with a type 2 pattern, mass spectrometry of transferrin glycans can first be performed but this rarely yields a specific pattern. Isoelectrofocusing of serum apolipoprotein C-III (which is only O-glycosylated) can detect some O-glycosylation disorders. A flowchart summarizing the approach to obtain molecular diagnosis in unsolved CDG is depicted in Fig. 1.

Since there is no worldwide CDG registry, information about frequency is lacking. In order to fill up this gap, in November 2016 the different laboratories in Europe offering CDG diagnosis were asked to fill an informal excel table with (i) the actual number of patients for each type of molecularly diagnosed CDG-I and CDG-II; (ii) and for the types with less than 4 patients, the initials and nationality of the patients, to avoid double counting of patients with a very rare CDG that could have been studied by more than one laboratory; and (iii) the number of ‘unsolved’ patients (indicating: positive screening for abnormal glycans, negative targeted sequencing or negative exome results). Thus only the CDG with an abnormal transferrin IEF were included in this study (for example not alpha-dystroglycanopathies).

The following laboratories accepted to share their data: Barcelona, Catania, Heidelberg, Leuven, Lille, Lyon, Madrid, Nijmegen, Paris, Porto, Prague and Tallinn. The number of molecularly diagnosed patients was 1350, distributed among 94% CDG-I and 6% CDG-II. Twenty-two different types of CDG-I and 15 of CDG-II were reported. Fig. 2 shows the distribution of the patients. As to CDG-I (Fig. 2A), PMM2-CDG, as expected, was by far the most frequent (62%; n: 834). ALG6-CDG was the second most frequent (8%; n: 101), followed by SRD5A3-CDG (n: 43), ALG1-CDG (n: 41) and MPI-CDG (n: 36). Regarding CDG-II (Fig. 2B), MANB1-CDG was the type with the largest number of patients (n: 18), followed by COG7-CDG (n: 10). The different COG deficiencies (COG1-CDG COG4-CDG to COG8-CDG) together comprised 33 patients. The distribution of some specific types was strikingly different within the different laboratories. For example, almost all of the TMEM165-CDG patients (n: 5/6) were reported by Leuven, the SRD5A3-CDG patients mainly by Nijmegen. Importantly, it is worth mentioning that some patients may have been counted twice, as samples traveled extensively especially in the early days of genetic diagnostics.

Finally, the number of reported molecularly unsolved cases was relatively small (less than 100). The total number of diagnosed CDG patients in Europe might reasonably exceed 2500 when adding those from the United Kingdom, Ireland, and the countries of Northern and Southern Europe.
Table 1
Overview of CDG organ involvement and symptoms/signs Items before the semicolon are clinical symptoms and signs, and the items after the semicolon are results of paraclinical investigations.

| ALG1-CDG |  |
|---|---|
| **Brain** | psychomotor disability, microcephaly, refractory epilepsy, hypotonia; cerebral atrophy |
| Liver | hepatosplenomegaly |
| Dysmorphic features | large fontanel, hypertelorism, micrognathia |
| Other | nonimmune foetal hydrops, hypogonadism |

| ALG2-CDG |  |
|---|---|
| **Brain** | psychomotor disability, epilepsy; hypomyelination |
| Eyes | bilateral iris coloboma, cataract |
| Liver | hepatomegaly |

**Myasthenic syndrome, congenital, 14, with tubular aggregates**

| **Muscles** | slowly progressive motor disability, waddling gait, hypotonia, absent reflexes, muscle weakness (proximal more than distal) including mild facial weakness, myasthenia |
| **Skeleton** | lumbar lordosis, scapular winging |

| ALG3-CDG |  |
|---|---|
| **Brain** | developmental disability, microcephaly, epilepsy, axial hypotonia, hyporeflexia; cerebellar and corpus callosum hypoplasia |
| Eyes | strabismus, epicanthus, optic atrophy, iris coloboma, cortical blindness |
| Skeleton | arthrogryposis, clubfoot |
| Dysmorphic features | facial dysmorphism (dysplastic ears, broad flat nasal bridge, abnormalities of the uvula and high-arched palate), pectus excavatum and hypoplastic nipples |
| Other | failure to thrive with vomiting, diarrhoea |

| ALG4-CDG |  |
|---|---|
| **Brain** | psychomotor disability, epilepsy, cortical blindness, dysarthria, wide-based gait, ataxia, intention tremor; agenesis of the corpus callosum |
| Eyes | hyperopia; atrophic retinal pigmentation, reduction of retinal vascularization |
| Skeleton | distal limb defects |
| Other | endocrine (hyperandrogenism, hyperinsulinemic, hypoglycaemia) and gastrointestinal disturbances |

| ALG5-CDG |  |
|---|---|
| **Heart** | ventricular septal defects, patent ductus arteriosus |
| Liver | hepatomegaly, multiple cystic intra- and extrahepatic bile ducts, cholestasis |
| Kidneys | diffuse renal microcysts |
| Skeleton | camptodactyly, clubfoot |
| Dysmorphic features | craniofacial dysmorphism (asymmetric skull, large fontanel, hypertelorism, low-set and abnormally positioned ears, long philtrum), short neck |
| Other | diarrhoea (protein-losing enteropathy), vomiting, massive ascites; hypoalbuminemia |

| ALG6-CDG |  |
|---|---|
| **Brain** | psychomotor disability, microcephaly, epilepsy, hypotonia; diffuse brain atrophy with delayed myelination |
| Heart | pericardial effusion |
| Liver/spleen | hepatosplenomegaly |
| Kidneys | cystic renal disease |
| Other | failure to thrive, esotropia, inverted nipples |

**Gillessen-Kaesbach-Nishimura syndrome**

| **Brain** | microcephaly; ectopic gray matter, focal laminar necrosis and migration abnormalities in the cerebellum |
| **Heart** | ventricular septal defect, double outlet right ventricle with anomalous outflow tract |
| **Liver** | periporal hepatic fibrosis, cystic dilation of the bile ducts, mild ductal dilation of the pancreas |
| Kidneys | polycystic kidneys (Potter type I) |
| Skeleton | brachymelia, lethal mesosomic osteochondrodysplasia, decreased ossification of the frontoparietal bones, thickening of the occipital bones, ‘butterfly’ vertebrae, distinctive shape of the iliac bones, bowed and thickened radii and ulnae, lack or partial ossification of the cervical vertebral bodies, round ilia, delayed ossification of the pubic bones, and thick, round pelvis, and short tubular bones with metaphysal flaring |
| Dysmorphic features | facial dysmorphism (microbrachycephaly, abundant hair, hypertelorism with telecanthus, low-set, posteriorly rotated and fleshy ears, sloping forehead, aniridia, antverted nares, broadened nose, long palpebral fissures, flat philtrum with upturned upper lip, micrognathia, cleft palate), short neck, short extremities with ulnar deviation of the hands and deformed feet |
| Other | diaphragmatic hernia, abnormal lung lobulation |

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| Table 1 (continued) |
|---------------------|
| **ALG11-CDG** *    |
| Brain: developmental disability, epilepsy, hypotonia; abnormal brainstem auditory response consistent with deafness |
| Eyes: strabismus, delayed pupil reaction and fixation, no blink reflex, lack of visual tracking |
| Muscles: opisthotonus |
| Dysmorphic features: craniofacial dysmorphism (small head, high forehead with low hairline, long philtrum, retrognathia), scoliosis, fat pads, inverted nipples |
| Other: poor feeding, recurrent vomiting, instability of body temperature |

| **ALG12-CDG** *    |
| Brain: disabled motor and mental development, microcephaly, hypotonia; widening of the lateral ventricles without hydrocephalus |
| Eyes: blindness |
| Heart: cardiomyopathy and other cardiac abnormalities |
| Skeleton: unique short limb skeletal dysplasia with delayed ossification of cervical vertebrae and signs of generalized epiphyseal dysplasia including lack of ossification of the pubic bones, knee epiphyses, and tall |
| Dysmorphic features: facial dysmorphism, supragluteal fat pads |
| Other: male genital hypoplasia, immunodeficiency, IgG deficiency, recurrent ear, nose, throat, and respiratory infections, failure to thrive, generalized oedema, deafness |

| **ALG13-CDG** *    |
| Epileptic encephalopathy, early infantile, 35 |
| Brain: psychomotor disability, epilepsy; hydrocephalus, myelination deficiency, wide sulci, hypoarrhythmia on EEG |
| Dysmorphic features: facial dysmorphism (coarse face, hypertelorism, low-set ears, mild retromicrognathia), small hands and feet, joint contractures, and scoliosis |
| Other: neonatal feeding problems, self-mutilation, sleep disturbance |

| **ALG14-CDG** *    |
| Myasthenic syndrome, congenital, 15, without tubular aggregates: |
| Muscles: congenital myasthenia, multiple joint contractures in adulthood |

| **ATP6AP1-CDG** ** Immunodeficiency 47** |
| Liver: neonatal jaundice, hepatosplenomegaly; histology: steatosis, fibrosis, micronodular cirrhosis, abnormal mitochondria |
| Other: recurrent bacterial infections associated with hypogammaglobulinemia |

| **ATP6V0A2-CDG** ** Cu/Zn lax, autosomal recessive, type II A** |
| Brain: developmental and mental disability, microcephaly, seizures, hypotonia; bilateral pachygyria, cobblestone-like malformation predominantly in the posterior frontal, parietal, and parietal regions |
| Eyes: high myopia |
| Skeleton: persistent fontanelles, slight oxycephaly, pigeon breast, hip dislocation, static scoliosis, flat feet, joint hyperlaxity |
| Dysmorphic features: bossing of the forehead, reversed V eyebrows, downsloping of palpebral fissures, large anterior fontanel, prominent supraorbital ridges, midface hypoplasia, antverted nares, short nose, small mouth |
| Skin: overfolding and wrinkling of the skin (unaffected face), but no hyperelasticity |

| **Wrinkly skin syndrome** |
| Brain: mental disability, microcephaly, epilepsy |
| Heart: atrial septum aneurysm |
| Skeleton: poorly developed and hypotonic skeletal musculature, with winging of the scapulae |
| Dysmorphic features: craniofacial dysmorphism |
| Skin: wrinkled skin of hands, feet and abdominal wall, decreased elastic recoil of the skin; elastic fibre abnormalities |

| **B3GLANT2-CDG** ** Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 11** |
| Brain: polymicrogyria, hydrocephalus, cerebellar cysts, pontocerebellar hypoplasia, frontotemporal leukoencephalopathy, and cobblestone ossific apices |
| Eyes: myopia, microphthalmia; optic nerve hypoplasia |
| Muscles: dystrophy |

| **B3GLALT6-CDG** ** Ehlers-Danlos syndrome, hypermobile type, 2** |
| Brain: developmental disability |
| Muscles: hypotonia |
| Skeleton: general osteopenia, hypermobile joints |
| Dysmorphic features: aged appearance, short stature, craniofacial disproportion |
| Skin: defective wound healing, loose, elastic skin |

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Table 1 (continued)

| Condition | Clinical Features |
|-----------|-------------------|
| Spondyloepimetaphyseal dysplasia with joint laxity, type 1, with or without fractures | |
| **Muscles** | hypotonia |
| **Heart** | congenital heart disease |
| **Skeleton** | brachydactyly of hands and feet, progressive severe kyphoscoliosis, thoracic asymmetry, elbow deformities with radial head dislocation, dislocated hips, clubfeet, tapered fingers with spina bifida distal phalanges, platypod dysplasia, spondyloepimetaphyseal dysplasia with bone fragility, multiple early-onset fractures, minimal metaphyseal and epiphyseal abnormalities at the knees |
| **Dysmorphic features** | oval face, flat midface, prominent eyes with blue sclerae, long philtrum, palatal abnormalities |
| B3GALT3-CDG | Multiple joint dislocations, short stature, craniofacial dysmorphism, with or without congenital heart defects |
| **Eyes** | wide-set eyes, propotasis, blue sclerae |
| **Heart** | dilated cardiomyopathy |
| **Skeleton** | shortened metacarpals and spotty deformity of the tuft of the thumb (so-called 'delta phalanx'), metacarpal ossification centers leading to supernumerary carpal bones, pseudoclubbing of fingers, deep palmar creases, kyphoscoliosis, severe hyperextensibility of all joints except for the elbows, dislocations of shoulders, elbows, proximal radioulnar joints, mild shortening of the first metacarpal bone, delayed and dissociated bone age, mild dysplasia of the hip joints, and foot deformities; osteopenia. Foot deformity with brachymetatarsia and brachymetapody |
| **Dysmorphic features** | prominent forehead, brachymetapody, thick eyebrows, large eyes with downslanting palpebral fissures, depressed nasal bridge, micrognathia or microretrognathia |
| B4GALNT1-CDG | Spastic paraplegia 26, autosomal recessive |
| **Brain** | intellectual disability; cortical atrophy and white matter hyperintensities |
| **Eyes** | cataract |
| **Muscles** | spastic paraplegia, gait abnormalities due to lower limb spasticity, hyperreflexia, extensor plantar responses, muscle weakness and atrophy; axial sensorimotor neuropathy |
| **Skeleton** | mild upper limb involvement, including decreased vibration sense at the ankles, pseudosublithary dysarthria, pes cavus, scoliosis |
| B4GALT7-CDG | Fhigio-Danie syndrome with short stature and limb anomalies |
| **Brain** | mental disability, mild hypotonia |
| **Skeleton** | short stature, bowing of extremities, multiple dislocations, defective deciduous teeth, mild pectus carinatum, bilateral elbow contractures with decreased supination, hyperextensivity of the shoulders, wrists, fingers, and knees, varus bowing of the larger legs, marked pes planus, and long toes; scoliosis, dysplasia of some bones, early bone attrition with multiple ossification centres, metaphyseal enlargement |
| **Dysmorphic features** | facial dysmorphism (relatively small face with prominent forehead, flattened nasal bridge, large and protuberant eyes, small ears, deep nasolabial folds, small mouth, curvy and fine hair, scanty eyebrows and eyelashes, telecanthus), short neck, pectus excavatum |
| **Other** | joint laxity, skin hyperextensibility, loose, elastic skin, delayed wound healing with thin, atrophic scars, multiple nevi, periodontitis, papyraceous scars, bruising, varicose veins, bilateral cryptorchidism |
| B3GALT1-CDG | Peters-plus syndrome |
| **Brain** | developmental/intellectual disability, macrocephaly, microcephaly; hydrocephaly, cerebral atrophy |
| **Eyes** | Peters’ anomaly (central corneal clouding, thinning of posterior cornea, iridocorneal adhesions), cataracts, congenital glaucoma |
| **Skeleton** | growth deficiency (starts prenatally; growth hormone deficiency in some patients) |
| **Dysmorphic features** | prominent forehead, hypoplastic columna, long philtrum, depressed nasal bridge, antverted nostrils, thin vermilion border of the upper lip, cleft lip/palate, ear abnormalities, broad neck, urogenital malformations |
| CAC-CDG | Epileptic encephalopathy, early infantile, 50 |
| **Brain** | disabled psychomotor development, early-onset epilepsy |
| **Other** | normoxic anaemia characterized by anisopikilocytes, acanthocytes, and schistocytes |
| CCDC15-CDG | **Brain** | psychomotor disability, hypotonia |
| **Liver** | neonatal jaundice, liver failure, hepatosplenomegaly; increased serum transaminases; histology: variable fibrosis, necrosis, cirrhosis |
| **Dysmorphic features** | mild dysomorphic features, such as long face and ptosis |
| CHSY1-CDG | Tentaryn cerebral brachydactyly syndrome |
| **Eyes** | macrophthalmia, blue sclerae, remnants of pupillary membrane; tilted optic discs |
| **Skeleton** | preaxial brachydactyly, phalangeal duplication, symphalangism and hyperphalangism of digits 1-3, ulnar deviation of the fifth finger; accessory ossicles of digits 2-5 |
| **Dysmorphic features** | micrognathia, talon cusp of upper central incisors, cleft palate |
| **Other** | growth deficiency, sensorineural deafness |
| COG1-CDG | **Brain** | psychomotor delay, microcephaly, seizures, mental retardation, hypotonia, hypotonicity |
| **Eyes** | macrosomia, blue sclerae, remnants of pupillary membrane; tilted optic discs |
| **Skeleton** | preaxial brachydactyly, phalangeal duplication, symphalangism and hyperphalangism of digits 1-3, ulnar deviation of the fifth finger; accessory ossicles of digits 2-5 |
| **Dysmorphic features** | micrognathia, talon cusp of upper central incisors, cleft palate |
| **Other** | growth deficiency, sensorineural deafness |

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Table 1 (continued)

| COG2-CDG ** | Brain | developmental disability, acquired microcephaly, spastic quadriplegia; diffuse cerebral atrophy, thin corpus callosum, small pituitary gland |
|-------------|-------|----------------------------------------------------------------------------------------------------------------------------------|
|             | Liver | dysfunction                                                                                                                    |
| COG4-CDG ** | Brain | psychomotor disability, microcephaly, axial hypotonia, mild peripheral hypertonia, ataxia, hyperreflexia; diffuse cerebral atrophy, thinning of corpus callosum |
|             | Eyes  | nystagmus                                                                                                                      |
|             | Liver | hepatomegaly, liver cirrhosis                                                                                                    |
|             | Dysmorphic features | down-sloping frontal area, thick hair                                                                                           |
|             | Other | recurrent respiratory infections, failure to thrive in infancy with recurrent diarrhoea                                           |
| COG5-CDG ** | Brain | moderate mental disability, truncal ataxia, mild hypotonia; pronounced atrophy of the cerebellum and brainstem                   |
| COG6-CDG ** | Brain | developmental disability, microcephaly, epilepsy                                                                             |
|             | Liver | hepatomegaly; increased serum transaminases; histology: macrovesicular steatosis, cirrhosis                                     |
|             | Kidneys | proximal tubulopathy                                                                                                           |
|             | Dysmorphic features | broad palpebral fissures, retrognathia, anal anteversion                                                                     |
|             | Other | vomiting, diarrhea, failure to thrive, inflammatory bowel disease, recurrent infections; primary combined immunodeficiency with hypogammaglobulinemia and defective cellular immunity without lymphopenia |
| COG7-CDG ** | Brain | developmental disability, microcephaly, epilepsy, hypotonia; cerebral atrophy                                                |
|             | Eyes  | poor ocular fixation                                                                                                            |
|             | Heart | cardiac insufficiency                                                                                                           |
|             | Liver | hepatomegaly, jaundice; cholestasis                                                                                                |
| Skeleton    | dysmorphic features | craniofacial dysmorphism (low-set dysplastic ears, micrognathia, flat face, full lips, protruding tongue), short neck, wrinkled skin, inverted nipples |
|             | Other | failure to thrive, diarrhoea; anaemia, thrombocytopenia, proteinuria                                                          |
| COG8-CDG ** | Brain | psychomotor disability, epilepsy, ataxia, hypotonia; cerebellar atrophy, slight brainstem atrophy, axonal neuropathy          |
|             | Eyes  | alternating esotropia, pseudoptosis                                                                                              |
|             | Other | spontaneous hematomas                                                                                                           |
| DDOST-CDG * | Brain | developmental disability, hypotonia; disordered myelination                                                                    |
|             | Eyes  | external strabismus                                                                                                              |
|             | Liver | dysfunction                                                                                                                     |
| Skeleton    | Other | advanced bone age, osteopenia                                                                                                    |
|             | Other | failure to thrive, gastroesophageal reflux, constipation, ear infections, and oromotor dysfunction                             |
| DHDDS-CDG * | Retinitis pigmentosa 59 | decreased visual acuity, impaired night vision; diffuse pigmented retinal degeneration with vascular attenuation, cone-rod dysfunction, bone spicule-like pigmentation, absent electroretinographic response |
|             | Multisystem disease | epilepsy, fundus oculi: pale papilla; electroretinogram: no response to any type of stimulation, enlarged liver; mild dilatation of the biliary duct; transient increase of serum transaminases, renal failure |
|             | (continued on next page)                                                                                                                                                      |
Table 1 (continued)

| Disorder                  | Clinical Features                                                                 |
|---------------------------|-----------------------------------------------------------------------------------|
| **Muscles**               | axial hypotonia, peripheral hypertonia                                           |
| **Heart**                 | severe brachycardia                                                               |
| **Dysmorphic features**   | microcephaly, cryptorchidism                                                      |
| **Other**                 | intra-uterine growth retardation and decreased fetal movements during pregnancy, poor sucking with frequent regurgitations, failure to thrive, sensorineural deafness |
| **DOLK-CDG**              | discontinued psychomotor development with lack of speech, epilepsy, hirsutism (EEG) |
| **Brain**                 | progressive bilateral nystagmus                                                   |
| **Eyes**                  | progressive bilateral nystagmus                                                   |
| **Muscles**               | hypotonia, tetraplegia                                                           |
| **Heart**                 | dilated cardiomyopathy (sometimes isolated)                                      |
| **Other**                 | ichthyosis, sparse eyebrows and eyelashes, minimal hair growth                  |
| **DPAGT1-CDG**            | discontinued psychomotor development with lack of speech, epilepsy, hirsutism (EEG) |
| **Brain**                 | progressive microcephaly, intractable epilepsy, hypotonia, cerebral atrophy       |
| **Eyes**                  | strabismus, nystagmus, bilateral cataracts                                       |
| **Liver**                 | jaundice                                                                         |
| **Dysmorphic features**   | micrognathia, arched palate, fifth finger clinodactyly, single flexion creases of the hands, skin dimples on the upper thighs |
| **Other**                 | frequent apnoeas, respiratory insufficiency, joint contractures, tremor, feeding difficulties, cryptorchidism |
| **Myasthenic syndrome, congenital, 13, with tubular aggregates**      | limbgirdle congenital myasthenic syndrome; structural and functional abnormalities of the neuromuscular junction, tubular aggregates on muscle biopsy, predominantly in proximal limb muscles |
| **Muscles**               | limb-girdle congenital myasthenic syndrome; structural and functional abnormalities of the neuromuscular junction, tubular aggregates on muscle biopsy, predominantly in proximal limb muscles |
| **Skeleton**              | scoliosis                                                                        |
| **DPM1-CDG**              | developmental disability, microcephaly, epilepsy, hypotonia, cerebellar ataxia with dysmetria, tremor, ataxic gait; cerebral atrophy, T2-weighted hyperintensities of the dentate nucleus |
| **Brain**                 | strabismus, nystagmus, cortical blindness; optic nerve atrophy, macular retinopathy |
| **Eyes**                  | strabismus, nystagmus, cortical blindness; optic nerve atrophy, macular retinopathy |
| **Muscles**               | dystrophy, with increased variation in fibre size, areas of necrosis, hypoglycosylation of alpha-dystroglycan |
| **Dysmorphic features**   | craniofacial dysmorphism (trigonocephaly, prominent forehead, thick metopic suture, hypertelorism, high nasal bridge, smooth philtrum, micrognathia, gothic palate, teeth malocclusion), hemangiomas, camptodactyly, small hands with dysplastic nails |
| **Other**                 | hydroptysis, respiratory distress, apnoeas, patent ductus arteriosus              |
| **DPM2-CDG**              | developmental disability, microcephaly, epilepsy, hypotonia, cerebellar ataxia with dysmetria, tremor, ataxic gait; cerebral atrophy, T2-weighted hyperintensities of the dentate nucleus |
| **Brain**                 | strabismus, nystagmus, cortical blindness; optic nerve atrophy, macular retinopathy |
| **Eyes**                  | strabismus, nystagmus, cortical blindness; optic nerve atrophy, macular retinopathy |
| **Muscles**               | dystrophy on muscle biopsy                                                       |
| **Skeleton**              | severe congenital contractures of the joints, scoliosis                          |
| **Dysmorphic features**   | myopathic facies, micrognathia, teeth malocclusion                                |
| **Other**                 | respiratory infections                                                            |
| **DPM3-CDG**              | waddling gate; moderate muscular dystrophy with variation in fibre size, multiple internal nuclei, necrotic fibres, rimmed vacuoles, fibre splitting, interstitial fibrosis |
| **Muscles**               | waddling gate; moderate muscular dystrophy with variation in fibre size, multiple internal nuclei, necrotic fibres, rimmed vacuoles, fibre splitting, interstitial fibrosis |
| **Heart**                 | dilated cardiomyopathy                                                            |
| **EOCT-CDG**              | Adams-Oliver syndrome 4                                                           |
| **Eyes**                  | microphthalmia                                                                   |
| **Heart**                 | atrial and ventricular septal defects, patent ductus arteriosus                   |
| **Other**                 | aplasia cutis congenita (scalp) and terminal transverse limb defects with hypoplastic or absent nails and variably absent distal phalanges |
| **EXT1-CDG**              | exostoses, multiple, type 1                                                       |
| **Skeleton**              | multiple exostoses (projections of bone capped by cartilage), most numerous in the metaphyses of long bones, but also occurring on the diaphyses of long bones, deformity of forearms (resembling Madelung deformity), hands, legs, flat bones, vertebrae, and ribs but the skull is usually not involved |
| **Chondrosarcoma**        | chondrosarcoma of the pelvic bone, fibulae, and femora                           |
| **EXT2-CDG**              | exostoses, multiple, type 2                                                       |
| **Skeleton**              | multiple exostoses (projections of bone capped by cartilage), most numerous in the metaphyses of long bones, but also occurring on the diaphyses of long bones, deformity of forearms (resembling Madelung deformity), hands, legs, flat bones, vertebrae, and ribs but the skull is usually not involved |

(continued on next page)
| Table 1 (continued) |  |
|---------------------|---|
| **Seizures, scoliosis, and macrocephaly syndrome** |  |
| **Brain** | psychomotor disability, macrocephaly, epilepsy, hypotonia, brain haemorrhage |
| **Muscles** | wide-based gait, tremor |
| **Heart** | ventricular septal defect, hypertension |
| **Liver** | dysfunction |
| **Kidneys** | haematuria with proteinuria, sometimes associated with haemolytic-uremic syndrome |
| **Skeleton** | scoliosis, overlapping toes; low bone density |
| **Dysmorphic features** | coarse facies with hypertelorism |
| **Other** | skin sensitivity, gastrointestinal problems (gastroesophageal reflux, bowel malrotation, diarrhoea/constipation); cryptorchidism in males |

**FKRP-CDG**

**Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 5**

| **Brain** | psychomotor disability, hypotonia; agyria, absence of corpus callosum and cerebellar vermis, congenital hydrocephalus associated with a Dandy-Walker-like malformation, ventricular dilatation, aqueductal stenosis, dysplastic and small cerebellum and pons, cobblestone lissencephaly, pachygyria, hypoplastic brainstem, cerebellar cysts, white matter abnormalities |
| **Eyes** | myopia, anterior chamber abnormalities, microphthalmia, corneal clouding, coloboma, retinal pigmentary changes, asymmetric pupils, absent pupillary light reflexes, cataracts, rarefaction of pigment epithelium, no demarcation of the macula, bilateral retinal detachment |
| **Muscles** | dystrophy |
| **Heart** | left ventricular hypertrophy |
| **Other** | elevated serum creatine kinase |

**Muscular dystrophy-dystroglycanopathy (congenital with or without mental retardation), type B, 5**

| **Brain** | mental disability, hypotonia; cerebellar cysts |
| **Muscles** | wasting and weakness of shoulder girdle muscles and upper limbs, facial weakness, pronation of the forearm, Achilles tendon contractures, leg hypertrophy |
| **Other** | elevated serum creatine kinase |

**Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 5**

| **Muscles** | developmental disability, waddling gait, muscle cramps, frequent falls, hypotonia, proximal muscle weakness, shoulder girdle and hip girdle weakness, hypertrophy of tongue, calf muscles and thigh, absence of scapular winging, Achilles tendon contractures, restrictive respiratory insufficiency; histology: dystrophic changes |
| **Heart** | dilated cardiomyopathy, left ventricular wall motion abnormalities |
| **Skeleton** | hyperlordosis, kyphoscoliosis, spinal fusion |
| **Other** | elevated serum creatine kinase |

**FKTN-CDG**

**Cardiomyopathy, dilated, 1X**

| **Muscles** | mild or no limb-girdle muscle involvement; minimal dystrophic features but hypoglycosylation of alpha-dystroglycan |
| **Heart** | dilated cardiomyopathy |

**Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 4**

| **Brain** | intellectual disability, epilepsy; cerebellar microgyria, fibroglial proliferation of the leptomeninges, hydrocephalus, focal interhemispheric fusion, hypoplasia of the corticospinal tracts, presence of cerebellar cysts, frontoparietal pachygyria, cephalocele, flattening of thepons and brainstem, marked cerebellar vermis hypoplasia, cortical brain atrophy, absent corpus callosum, lissencephaly, ventricular dilatation; subcortical white matter abnormalities, patchy periventricular hypointensities, white matter hyperintensities |
| **Eyes** | strabismus, myopia, hyperopia, microphthalmia, congenital cataracts, buphthalmos, optical atrophy, retinal dysplasia and detachment |
| **Muscles** | diffuse and progressive muscle weakness and atrophy with axial and proximal limb predominance, moderate facial involvement, severe and progressive restrictive respiratory insufficiency, diffuse amyotrophy, progressive knee and ankle contractures, calf muscles hypertrophy; histology: muscle dystrophy with dystroglycanopathy |
| **Heart** | dilated cardiomyopathy (from 2nd decade), structural defects |
| **Skeleton** | congenital arthrogryposis multiplex, spinal rigidity, scoliosis, congenital hip dislocation |
| **Other** | elevated serum creatine kinase |

**Muscular dystrophy-dystroglycanopathy (congenital with or without mental retardation), type B, 4**

| **Brain** | white matter changes |
| **Muscles** | generalized weakness; dystrophy and evidence of dystroglycanopathy |
| **Other** | increased serum creatine kinase |

**Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 4**

| **Muscles** | disabled motor disability, waddling gait, limb-girdle muscular dystrophy, proximal muscle weakness, frequent falls, hypertrophy of lower limb muscles, decreased deep tendon reflexes, mild hypotonia, decreased muscle strength, calf hypertrophy; histology: dystrophic features with dystroglycanopathy |
| **Skeleton** | lumbar lordosis, pectus excavatum, club feet |
| **Other** | increased serum creatine kinase |

(continued on next page)
Table 1 (continued)

| Condition                                      | GALT3-CDG                                                                 | GANAB-CDG                                                                 | GFPT1-CDG                                                                 | GMPPA-CDG                                                                 | GMPPA-Congenital, type A, 14 | GMPPA-Congenital, type B, 14 | GMPPA-Congenital, type C, 14 | GNE-CDG                                                                 | ISPD-CDG                                                                 |
|------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------|-------------------------------|-------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Soft tissues around major joints               | ectopic calcifications (shoulders, elbows, knees ...), intolerable pain, skin ulcerations, secondary skin and bone infections; hyperphosphatemia | *vascular calcifications, angiod streaks of the retina, dental abnormalities, testicular microthiasis*<br>*hyperostosis-hyperphosphatemia syndrome (recurrent long bone lesions)* | *peripheral nerve involvement, muscle weakness due to defect at neuromuscular junction, waddling gate, muscle cramps, easy fatigability* | Other | increased serum creatine kinase | Increased serum creatine kinase | Other | intellectual disability, microcephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Other | developmental disability, macrocephaly, epilepsy | Other | intellectual disability, macrocephaly, epilepsy, hypotonia | Other | intellectual disability, macrocephaly, epilepsy | Other | microphthalmia, cataracts, Peters anomaly, optic nerve hypoplasia, retinal dysplasia, retinal detachment |
| Liver                                          | occasional presence of liver cysts, sometimes liver dysfunction           |                                                                         |                                                                          | Other | psychomotor disability | Other | Other | intellectual disability, microcephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Other | developmental disability, macrocephaly, epilepsy | Other | intellectual disability, macrocephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Other | intellectual disability, macrocephaly, epilepsy | Other | microphthalmia, cataracts, Peters anomaly, optic nerve hypoplasia, retinal dysplasia, retinal detachment |
| Kidneys                                         | polycystic kidney disease, usually mild with onset in mid- to late-adulthood |                                                                         |                                                                          | Eyes | strabismus, cataracts, ptosis | Eyes | Eyes | intellectual disability, microcephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Eyes | hepatosplenomegaly | Eyes | intellectual disability, macrocephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Eyes | intellectual disability, macrocephaly, epilepsy | Eyes | microphthalmia, cataracts, Peters anomaly, optic nerve hypoplasia, retinal dysplasia, retinal detachment |
| Muscles                                         | histology: small type I fibres and tubular aggregates in both fiber types |                                                                         |                                                                          | Muscle | amblyopia | Muscle | Muscle | intellectual disability, macrocephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Muscle | dysmorphic features | Muscle | intellectual disability, macrocephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Muscle | intellectual disability, macrocephaly, epilepsy | Muscle | microphthalmia, cataracts, Peters anomaly, optic nerve hypoplasia, retinal dysplasia, retinal detachment |
| Other                                           |                                                                          |                                                                          |                                                                          | Other | progressions | Other | Other | intellectual disability, macrocephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Other | increased serum creatine kinase | Other | intellectual disability, macrocephaly, drug-resistant epilepsy, hypotonia; cerebellar hypoplasia | Other | intellectual disability, macrocephaly, epilepsy | Other | microphthalmia, cataracts, Peters anomaly, optic nerve hypoplasia, retinal dysplasia, retinal detachment |

(continued on next page)
Table 1 (continued)

| Condition                                      | Muscles                                                                 | Dysmorphic features                             | Other                                                                 |
|------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------|
| R. Péanne et al. European Journal of Medical Genetics 61 (2018) 643–663 | severe muscular dystrophy, weakness in the upper and lower limb girdles, tongue and calf hypertrophy, reduced forced respiratory vital capacity; muscle biopsies: dystrophic changes with hypoglycosylated alpha-dystroglycan | facial dysmorphism (large fontanel, frontal bossing, deep-set eyes, retrognathia, small, simple, low-set ears) | neural tube defects, limb deformations; visceral malformations, brain vascular anomalies |
| Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 7 | proximal upper and lower limbs affected, calf hypertrophy, scapula winging, reduced forced respiratory vital capacity; Histology: dystrophic changes with hypoglycosylated alpha-dystroglycan | increased serum creatine kinase, myoglobinuria after exercise |                                                                      |
| LARGE-CDG                                        |                                                                       |                                                 |                                                                      |
| Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 6 |                                                                       |                                                 |                                                                      |
| Brain                                            | intellectual disability; periventricular and temporal white matter changes, posterior concavity of the brainstem, hypoplastic pons, frontoparietal pachygyria | muscle hypertrophy of the tongue, calves, thighs, and shoulder girdle, and predominantly lower limb weakness with positive Gowers sign and waddling gait |                                                                      |
| Eyes                                             | nystagmus; abnormal electroneurogram                                   |                                                 |                                                                      |
| Muscles                                          | muscle hypertrophy of the tongue, calves, thighs, and shoulder girdle, and predominantly lower limb weakness with positive Gowers sign and waddling gait | muscle hypertrophy of the tongue, calves, thighs, and shoulder girdle, and predominantly lower limb weakness with positive Gowers sign and waddling gait |                                                                      |
| Spondylometastomal dysostosis 3, autosomal recessive | long, slender fingers, camptodactyly of the left index finger, extensive congenital vertebral anomalies with severe shortening of the spine; vertebral ossification centres in the thoracic spine with fitted angular shape |                                                                      |                                                                      |
| MAN1B1-CDG **                                    |                                                                       |                                                 |                                                                      |
| Brain                                            | intellectual disability                                               |                                                 |                                                                      |
| Dysmorphic features                              | craniofacial dysmorphism (dolichocephaly, downsizing palpebral fissures, hypertelorism, broad and long eyebrows, flat philtrum, thin upper lip, triangular and pointed chin, prominent nose) |                                                                      |                                                                      |
| Other                                            | truncal obesity                                                       |                                                 |                                                                      |
| MGA72-CDG **                                     |                                                                       |                                                 |                                                                      |
| Brain                                            | psychomotor disability, microcephaly, epilepsy, stereotypic movements | muscle atrophy                                   |                                                                      |
| Dysmorphic features                              | craniofacial dysmorphism (retrognathia, large and posteriorly rotated ears, beaked nose, long philtrum, thin vermilion border of the upper lip, large mouth, diastema, gum hypertrophy, long eyelashes, thick eyebrows), short neck, thoracic deformity, distal limb anomalies; radioulnar synostosis |                                                                      |                                                                      |
| Other                                            | chronic feeding problems with severe diarrhoea, gastroesophageal reflux and volvulus, recurrent respiratory infections, lack of pubertal development, sensorineural hearing loss |                                                                      |                                                                      |
| MGDS-CDG                                         |                                                                       |                                                 |                                                                      |
| Brain                                            | developmental disability, epilepsy, hypotonia; cerebral atrophy, small corpus callosum | optic nerve atrophy                              |                                                                      |
| Eyes                                             |                                                                        | hepatomegaly                                    |                                                                      |
| Skeleton                                         | recurrent bone fractures, thoracic scoliosis                         |                                               |                                                                      |
| Dysmorphic features                              | prominent occip, retrognathia, short palpebral fissures, broad nose, high-arched palate, long eyelashes, generalized oedema |                                                                      |                                                                      |
| Other                                            | sensorineural hearing loss, hypoplastic genitalia, chronic constipation, hypoventilation, feeding problems; hypogammaglobulinemia |                                                                      |                                                                      |
| MPOU1-CDG *                                      |                                                                       |                                                 |                                                                      |
| Brain                                            | intellectual disability, epilepsy, ataxia                             |                                                 |                                                                      |
| Eyes                                             | strabismus, nystagmus, amaurosis, optic atrophy                       |                                                 |                                                                      |
| Skeleton                                         | dwarfism                                                              |                                                 |                                                                      |
| Other                                            | feeding difficulties, hyperkeratosis, erythroderma; transient growth hormone deficiency |                                                                      |                                                                      |
| MPI-CDBG *                                       |                                                                       |                                                 |                                                                      |
| Liver                                            | congenital hepatic fibrosis, microvascular steatosis, cirrhosis       |                                                 |                                                                      |
| Other                                            | secretory diarrhoea with protein-losing enteropathy, intestinal lymphangiectasia, recurrent thrombotic events, life-threatening gastrointestinal bleeding, frequent bacterial/viral gastroenteritis, hyperinsulinemic hypoglycaemia |                                                                      |                                                                      |
| NANS-CDG Spondyloepimetaphyseal dysplasia, Camera-Genevieve type |                                                                       |                                                 |                                                                      |
| Brain                                            | developmental disability, microcephaly, epilepsy, ataxia; hydrocephalus, cerebral atrophy with nonspecific white matter changes, hypoplastic corpus callosum | facial dysmorphism (prominent forehead, synophrys, sunken nasal bridge, prominent bulbous nasal tip, full lips a.o.) |                                                                      |
| Skeleton                                         | spondyloepimetaphyseal dysplasia (shortening of trunk and limbs, premature carpal ossification, platyspondyl, longitudinal metaphyseal striations and small epiphyses) |                                                                      |                                                                      |
| Dysmorphic features                              | facial dysmorphism (prominent forehead, synophrys, sunken nasal bridge, prominent bulbous nasal tip, full lips a.o.) |                                                                      |                                                                      |

(continued on next page)
Table 1 (continued)

| Syndrome | Brain | Other |
|----------|-------|-------|
| NUS1-CDG * | developmental disability, microcephaly, epilepsy, hypotonia; cortical atrophy | | |
| | visual impairment; mottling of the retinal pigment epithelium, macular lesions | | |
| | scoliosis | | |
| | failure to thrive, hearing impairment, hypertrichosis | | |
| PGAP1-CDG | developmental disability, microcephaly, hypotonia, stereotypic movements, dyskinetic movements; thinning of the corpus callosum, delayed myelination, absence of corpus callosum, cerebellar vermiform hypoplasia; signal abnormalities in the central tegmental tracts of the pons | | |
| | strabismus, nystagmus, visual impairment; retinal dystrophy | | |
| | facial dysmorphism (prominent forehead, high-arched eyebrows, deep-set eyes, large abnormal earlobes, upplanting palpebral fissures, large mouth with abnormal teeth), short neck, abnormal hand morphology | | |
| PGAP2-CDG Hyperphosphatasia with mental retardation syndrome 3 | developmental disability, microcephaly, epilepsy, hypotonia; brain atrophy | | |
| | atrial septal defect | | |
| | broad nasal bridge, cleft palate | | |
| | sensorineural hearing loss, Hirschsprung disease; increased serum alkaline phosphatase | | |
| PGAP3-CDG | developmental disability, microcephaly, epilepsy, hypotonia | | |
| | facial dysmorphism (hypertelorism, upplanting palpebral fissures, broad nasal bridge, short nose, long philtrum, tented upper lip, full cheeks, and large fleshly earlobes) | | |
| | increased serum alkaline phosphatase | | |
| PGM1-CDG ** | cerebral thrombosis | | |
| | weakness of the pelvic-girdle muscles; histology: abnormal subsarcolemmal and sarcoplasmic accumulations of normally structured, free glycogen | | |
| | dilated cardiomyopathy | | |
| | chronic hepatitis, steatosis, fibrosis | | |
| | Pierre-Robin sequence, cleft palate, bifid uvula | | |
| | growth deficiency; hypogonadotropic hypogonadism | | |
| PGM3-CDG Immunodeficiency 23 | developmental disability, myoclonus, ataxia, dysarthria; myelination defect | | |
| | high-arched palate, narrow palpebral fissures | | |
| | recurrent infections, atopic diatheses, including asthma and allergies, autoimmune and immune-mediated disease (cutaneous leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, and autoimmune hemolytic anemia); lymphopenia, neutropenia, increased serum IgA, IgG, IgD, cytokine abnormalities | | |
| | hearing loss, cutaneous vasculitis | | |
| PIGA-CDG Multiple congenital anomalies-hypotonia-seizures syndrome 2 | developmental disability, epilepsy, hypotonia; thin corpus callosum, white matter immaturity, delayed myelination, absence of septum pellucidum, lack of olfactory bulb and tracts, cerebellar hypoplasia, dysplastic pons, abnormal cortical lamination | | |
| | hyperreflexia, contractures | | |
| | facial dysmorphism (Pierre-Robin sequence, prominent occiput, enlarged fontanel, high anterior hairline, depressed nasal bridge, short and anteverted nose, malar flattening, upslanting palpebral fissures, overfolded helix, small mouth with downturned corners, absence of teeth), short neck | | |
| | hypoplastic nails; increased serum alkaline phosphatase in some patients | | |
| PIGC-CDG | developmental disability, epilepsy | | |
| PIGG | developmental and intellectual disability, epilepsy, hypotonia; thin corpus callosum, asymmetry of the lateral ventricles, cerebellar hypoplasia, cerebral atrophy | | |
| | hyporeflexia | | |
| PIGL-CDG CHIME syndrome | | | (continued on next page)
Table 1 (continued)

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | intellectual disability, epilepsy                                             |
| Eyes              | retinal coloboma                                                             |
| Heart             | transposition of the great vessels, ventricular septal defect, tetralogy of Fallot |
| Skeleton          | short stature                                                                |
| Skin              | ectrodactyly, high arched palate, narrow palate                              |
| Dysmorphic features | craniofacial dysmorphism (brachycephaly, micrognathia, flat face, depressed nasal bridge, small nose and mouth, small and abnormally shaped ears, upslanting palpebral fissures, epicanthal folds, synophrys, bitemporal narrowing, high arched palate, short neck, hypoplasia distal phalanges, anal stenosis, imperforate anus, diaphragmatic hernia) |
| Other             | hearing loss                                                                  |

**PIGM-CDG**

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | epilepsy                                                                     |
| Liver             | portal vein thrombosis                                                       |

**PIGN-CDG**

Multiple congenital anomalies-hypotonia-seizures syndrome 1.

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | developmental/intellectual disability, epilepsy, hypo-/hypertonia, spasticity; cerebellar atrophy, progressive white matter disease |
| Eyes              | nystagmus, roving eye movements                                               |
| Liver             | splenomegaly                                                                 |
| Kidneys           | hydronephrosis                                                               |
| Dysmorphic features | craniofacial dysmorphism (brachycephaly, micrognathia, flat face, depressed nasal bridge, small nose and mouth, small and abnormally shaped ears, upslanting palpebral fissures, epicanthal folds, synophrys, bitemporal narrowing, high arched palate, short neck, hypoplasia distal phalanges, anal stenosis, imperforate anus, diaphragmatic hernia) |
| Other             | gastroesophageal reflux                                                      |

**PIGO-CDG**

Hyperphosphatasia with mental retardation syndrome 2

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | developmental/intellectual disability, microcephaly, epilepsy, hypotonia, left coronal synostosis; enlarged ventricles |
| Heart             | atrial septal defect, peripheral pulmonary stenosis                          |
| Dysmorphic features | facial dysmorphism (wide-set eyes with long palpebral fissures, short nose with broad nasal bridge and tip, torted mouth); anal stenosis, anal atresia (with perineal fistula), brachytelephalangy, nail hypoplasia |

**PIGP-CDG**

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | intellectual disability, epilepsy, hypotonia, peripheral hypertonia; thin corpus callosum |
| Eyes              | cortical visual impairment, episodes of sustained eye deviation             |

**PIGQ-CDG**

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | developmental disability, epilepsy                                           |

**PIGT-CDG**

Peroxyemal nocturnal hemoglobinuria 2 (a germline mutation associated with a somatic mutation)

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Other             | hemolytic anemia; frequent hemolytic crises; abdominal pain; diarrhea, headache, arthralgia, dyspnea, fatigue, cold-induced urticaria |

**Multiple congenital anomalies-hypotonia-seizures syndrome 3**

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | psychomotor disability, epilepsy, hypotonia; frontotemporal atrophy, cerebellar hypoplasia |
| Eyes              | strabismus, nystagmus, visual impairment                                      |
| Heart             | restrictive cardiomyopathy, patent ductus arteriosus                         |
| Liver             | nephrocalcinosis, uterine stenosis/dilation                                  |
| Skeleton          | scoliosis, pectus excavatum, short upper extremities, slender long bones, arthrogryposis; wide and long femoral necks, delayed bone age, osteoporosis, osteopenia, large secondary ossification centers |
| Dysmorphic features | craniofacial dysmorphism (macrocephaly, brachycephaly, high forehead with bitemporal narrowing, long philtrum with a deep groove, open mouth, micrognathia, malar flattening, upslanting palpebral fissures, depressed nasal bridge with anteverted nares, downturned corners of the mouth, tented lip, high arched palate, tooth abnormalities) |
| Other             | macrosomia; tooth abnormalities; decreased serum alkaline phosphatase; increased serum calcium |

**PIGV-CDG**

Hyperphosphatasia with mental retardation syndrome 1

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | developmental/intellectual disability, epilepsy                             |
| Muscles           | hypotonia                                                                    |
| Heart             | ventricular septal defect                                                    |
| Kidneys           | hydronephrosis                                                               |
| Dysmorphic features | craniofacial dysmorphism (macrocephaly, cleft lip/palate, hypertelorism, broad nasal bridge, tented mouth, simple cupped ears with thickened helices), brachytelephalangy |
| Other             | displaced anus, Hirschsprung disease, hypoplastic terminal phalanges, hypoplastic nails, hearing impairment; elevated serum alkaline phosphatase |

**PIGW-CDG**

Hyperphosphatasia with mental retardation syndrome 5

| Phenotypic Domain | Key Features                                                                 |
|-------------------|------------------------------------------------------------------------------|
| Brain             | intellectual disability, epilepsy, hypotonia                                 |
| Dysmorphic features | broad nasal bridge, tented upper lip                                         |
| Other             | hyperphosphatasia                                                           |

(continued on next page)
| Table 1 (continued) |
|----------------------|
| **PIG-Y-CDG** Hyperphosphatasia with mental retardation syndrome 6 |
| **Brain** | developmental disability, microcephaly, epilepsy, behavioural disturbances |
| **Eyes** | congenital cataracts |
| **Muscles** | variation in muscle fiber size with small rounded atrophic fibers and increased fibrosis |
| **Kidneys** | dilatation of the renal collecting systems, increased echogenicity of renal parenchyma |
| **Skeleton** | osteopenia |
| **Dysmorphic features** | faciocranial dysmorphism (bitemporal narrowing, long palpebral fissures, depressed nasal bridge with upturned nares, deep-set eyes, fleshy earlobes), short neck, brachytelephalangy, proximal limb shortening; hip dysplasia |
| **Other** | necrotizing enterocolitis, chronic lung disease; increased serum alkaline phosphatase and creatine kinase |

| **PMM2-CDG** |
|----------------------|
| **Brain** | psychomotor disability, hypotonia, ataxia, stroke-like episodes, peripheral polyneuropathy; cerebellar hypoplasia |
| **Eyes** | internal strabismus, retinitis pigmentosa |
| **Muscles** | hyporeflexia |
| **Liver** | mild hepatopathy |
| **Dysmorphic features** | fusiform phalanges of the fingers, prominent labia majora, inverted nipples, symmetric fat accumulations, lipodystrophy of the buttocks |
| **Other** | thrombotic tendency, pericarditis, increased serum insulin and growth hormone |

| **POMT1-CDG** Dyschondrosteoarthritis 2 |
|----------------------|
| **Skin** | hypo-hyperpigmentation in reticular pattern on flexural skin, hyperkeratotic papules on neck, chest and back; electron microscopy: melanocytes lack melanosomes |

| **POGLUT1-CDG** Dyschondrosteoarthritis 4 |
|----------------------|
| **Skin** | brownish macular and lentiginous lesions on extremities, trunk and neck; histology: digitiform acanthosis, focal hypergranulosis |

| Limb-girdle muscular dystrophy type 2Z |
|----------------------|
| **Muscles** | proximal muscle weakness affecting first lower limbs, and later upper limbs; histology: dystrophy, dystroglycanopathy |
| **Other** | impaired respiratory function; increased serum creatine kinase |

| **POMGNT1-CDG** Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 3 |
|----------------------|
| **Brain** | psychomotor disability, microcephaly, epilepsy, hypotonia; hydrocephalus, cerebellar hypoplasia/dysplasia, cerebellar cysts, cortical dysplasia, brainstem abnormalities, pontine hypoplasia, ventricular dilatation, polymicrogyria, pachygyria, agyria, cobblestone cortex, white matter abnormalities, lissencephaly, complete or partial absence of corpus callosum |
| **Eyes** | cataracts, glaucoma, high myopia, microphthalmia, buphthalmos; retinal dysplasia, optic nerve hypoplasia |
| **Muscles** | dystrophy, dystroglycanopathy |
| **Dysmorphic features** | faciocranial dysmorphism (everted lower lip, short nasal bridge, mild micrognathia, midface hypoplasia) |

| Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 3: |
|----------------------|
| **Brain** | intellectual disability; ventricular dilatation, diffuse white matter changes, cerebellar cysts, pontine hypoplasia |
| **Eyes** | strabismus, myopia; optic atrophy |
| **Muscles** | dystrophy; dystroglycanopathy |

| Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 3: |
|----------------------|
| **Muscles** | proximal muscle weakness and wasting, hypertrophy of the calves and quadriceps; histology: dystrophic changes, dystroglycanopathy |
| **Other** | increased serum creatine kinase |

| Retinitis pigmentosa 76 |
|----------------------|
| **Eyes** | nystagmus, reduced visual acuity, constricted visual fields; peripapillary atrophy, bone spicule pigmentation, narrow retinal vessels, peripapillary atrophy, tigroid appearance of the fundus, retinal thinning with absent inner/outer segment junctions, chorioretinal atrophy, flat fovea, optic disc pallor, cystoid macular edema |

| **POMT1-CDG** Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 1 |
|----------------------|
| **Brain** | development/intellectual disability, epilepsy, hypotonia; hydrocephaly, ventricular dilatation, frontal bossing, ventriculomegaly, minimal cortical development, no visible gyri, vermis and cerebellar hypoplasia, cerebellar cysts, cobblestone lissencephaly with agyria and agenes of the corpus callosum, encophalocoele, pachygyria/agyria, Dandy-Walker-like malformation, frequent flattening of the pons and brainstem, polymicrogyria, white matter abnormalities |
| **Eyes** | microphthalmia, exophthalmia, buphthalmos, megalocornea, glaucoma, cataract, coneval clouding, progressive myopia; retinal atrophy, retinal detachment |
| **Muscles** | dystrophy, dystroglycanopathy |
| **Other** | increased serum creatine kinase |

(continued on next page)
Table 1 (continued)

| Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 1 |  |
|---|---|
| Brain | Psychomotor disability, hypotonia; enlarged osseous magna, cerebellar hypoplasia |
| Muscles | Dystrophy, muscle wasting, pseudohypertrophy of calf and quadriceps muscles |
| Skeleton | Joint contractures, scoliosis |
| Dysmorphic features | Macroglossia |
| Other | Increased serum creatine kinase |

| Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 1 |  |
|---|---|
| Brain | Intellectual disability, microcephaly |
| Muscles | Limb-girdle muscular dystrophy, muscle pseudohypertrophy; dystroglycanopathy |
| Heart | Cardiomyopathy |
| Skeleton | Scoliosis |
| Other | Increased serum creatine kinase |

**POMT2-CDG**

| Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 2 |  |
|---|---|
| Brain | Developmental/intellectual disability, microcephaly, epilepsy, hypotonia; hydrocephalus, cobblestone lissencephaly, pachygyria with preferential frontoparietal involvement, polymicrogyria, cerebellar hypoplasia/dysplasia, aplasia of the corpus callosum, smooth cortical mantle, brainstem hypoplasia, pontine hypoplasia, ventricular dilatation, pachygyria, polymicrogyria, heterotopia, cerebellar cysts, periventricular white matter abnormalities |
| Eyes | Peters anomaly, cataracts, microphthalmia, buphthalmos, persistent pupillary membrane, hypermetropia, congenital glaucoma, progressive myopia, retinal atrophy |
| Muscles | Muscle weakness, contractures, muscle hypertrophy of the lower limbs; histology: muscular dystrophy, dystroglycanopathy |
| Dysmorphic features | Cleft lip and palate, macroglossia |
| Other | Increased serum creatine kinase |

| Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 2 |  |
|---|---|
| Brain | Developmental/intellectual disability, microcephaly, hypotonia; cortical atrophy, cerebellar vermis hypoplasia without brainstem involvement, flat pons, ventriculomegaly, hypoplasia of the corpus callosum; periventricular white matter abnormalities |
| Eyes | Myopia, strabismus; pigmentary retinopathy |
| Muscles | Muscle weakness in face, trunk, girdle muscles, tongue, calf muscle hypertrophy, diffuse joint contractures, decreased or absent deep tendon reflexes; histology: dystrophy, dystroglycanopathy |
| Heart | Left ventricular hypertrophy, aortic root dilatation |
| Skeleton | Scoliosis, hip dislocation |
| Other | Micropenis, cryptorchidism; increased serum creatine kinase |

| Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 3 |  |
|---|---|
| Muscles | Limb-girdle muscular dystrophy, calf hypertrophy; histology: dystrophic and inflammatory changes, dystroglycanopathy |

**PRKCSH-CDG**

Polysplenic liver disease 1

| Liver | Multiple liver cysts |

**RFT1-CDG** *

| Brain | Developmental/intellectual disability, microcephaly, early-onset epilepsy, hypotonia, hypertonia, hyporeflexia |
| Eyes | Decreased visual acuity |
| Dysmorphic features | Micrognathia, short neck, adducted thumbs, valgus foot deformities, inverted nipples |
| Other | Feeding difficulties, failure to thrive, sensorineural deafness, short stature |

**SEC23B-CDG**

Dysarthropathic anemia, congenital, type II

| Liver | Splenomegaly, cholecystis |
| Blood | Dysarthropathic anemia: increased reticulocytes, multinucleated erythroblasts, increased erythrocyte osmotic fragility and hypoglycosylation of red blood cell membranes |

**SLC35A1-CDG** **

| Brain | Developmental disability, microcephaly, epilepsy, ataxia, hyporeflexia |
| Kidneys | Proteinuria |
| Dysmorphic features | Facial dysmorphism, webbed neck |
| Other | Bleeding diathesis, macrothrombocytopenia |

**SLC35A2-CDG** **

| Brain | Intellectual/developmental disability, microcephaly, epilepsy, hypotonia; small cerebellum, thinning of the corpus callosum, delayed myelination, cerebellar and cerebral atrophy |
| Kidneys | Acute nephrotic syndrome |
| Dysmorphic features | Facial dysmorphism (coarse faces, thick eyebrows, broad nasal bridge, thick lips, semi-open mouth, maxillary prognathism) |
| Other | Poor feeding, recurrent infections, shortened limbs |

(continued on next page)
Table 1 (continued)

| SLC35A3-CDG | Arthrogryposis, mental retardation, and seizures |
|-------------|-----------------------------------------------|
| Brain       | intellectual disability, microcephaly, autism spectrum disorder, epilepsy |
| Muscles     | hypotonia                                      |
| Skeleton    | arthrogryposis, deviation of the distal phalanges, swan-neck deformity, knee and hip dislocation |
| Dysmorphic features | retromicrognathia                           |

| SLC35C1-CDG |  |
|-------------|-----------------------------------------------|
| Brain       | intellectual disability, microcephaly, epilepsy, hypotonia; cortical atrophy |
| Skeleton    | dwarfism                                       |
| Dysmorphic features | facial dysmorphism                        |
| Other       | recurrent infections with neutrophilia (pneumonia, periodontitis, otitis media, and cellulitis without pus formation), Bombay blood group |

| SLC35D1-CDG Schneckerbecker dysplasia |  |
|--------------------------------------|-----------------------------------------------|
| Skeleton    | dwarfism, large head, flat midface, cleft palate, narrow chest, short spayed ribs, round vertebral bodies, snail-shaped ilia, dumbbell-shaped short long bones, brachydactyly, precociously ossified carpal and tarsal bones |
| Other       | stillborn or lethal in newborn period |

| SLC9A8-CDG ** |  |
|--------------|-----------------------------------------------|
| Brain        | psychomotor disability, epilepsy, hypotonia; cerebellar atrophy |
| Eyes         | strabismus, nystagmus, hyperopia, astigmatism |
| Skeleton     | short stature, short limbs, craniosynostosis, osteopenia |
| Other        | recurrent infections, hearing impairment |

| SRR5A3-CDG * |  |
|--------------|-----------------------------------------------|
| Brain        | developmental/intellectual disability, hypotonia; cerebellar atrophy, vermis malformations, hypoplasia of the pituitary gland |
| Eyes         | visual loss, nystagmus, congenital malformations (coloboma, hypoplasia of the optic disc, ...) |
| Heart        | dilated cardiomyopathy |
| Skin         | palmoplantar keratoderma, ichthyosiform dermatitis, hypertrichosis, dark skin of the dorsum of hands and feet |
| Other        | increased serum transaminases, decreased antithrombin III |

| Kahri syndrome |  |
|----------------|-----------------------------------------------|
| Brain          | severe intellectual disability, psychomotor disability |
| Eyes           | cataracts with onset in late adolescence, iris coloboma |
| Skeleton       | kyphosis, contractures of large joints |
| Dysmorphic features | bulbous nose with broad nasal bridge, thick lips |

| SSR4-CDG * |  |
|------------|-----------------------------------------------|
| Brain      | developmental/intellectual disability, epilepsy, hypotonia; thin corpus callosum, decreased periventricular white matter, absence of septum pellucidum |
| Eyes       | strabismus, deep-set eyes |
| Skeleton   | scoliosis |
| Dysmorphic features | facial dysmorphism (micrognathia, large mouth with widely spaced teeth, large ears, hypoplastic vermilion of the upper lip), excess skin around the neck, fat pads, hypoplastic apiiform papillae, clinodactyly of fourth and fifth toes |
| Other      | failure to thrive, gastrointestinal reflux |

| ST3GAL3-CDG Epileptic encephalopathy, early infantile, 15. Mental retardation |  |
|-----------------|-----------------------------------------------|
| Brain           | developmental/intellectual disability, epilepsy, hypotonia, irritability |

| ST3GAL5-CDG Salt and pepper developmental regression syndrome |  |
|-----------------------------|-----------------------------------------------|
| Brain                       | psychomotor disability, microcephaly, epilepsy, hypotonia, hyporeflexia of upper limbs, hyperreflexia of lower limbs, irritability, choreoathetotic movements; white matter lesions, cortical atrophy |
| Eyes                        | nystagmus, optic atrophy |
| Skin                        | dyspigmentation, hyperpigmented macules mainly on extremities, hypopigmented macules (less common) |
| Other                       | poor feeding, vomiting, failure to thrive |

| STT3A-CDG * |  |
|-------------|-----------------------------------------------|
| Brain       | psychomotor disability, microcephaly, epilepsy, hypotonia; cerebellar atrophy |
| Eyes        | poor visual tracking |
| Other       | failure to thrive |

| STT3B-CDG * |  |
|-------------|-----------------------------------------------|
| Brain       | psychomotor disability, microcephaly, epilepsy, hypotonia; cerebellar atrophy |
| Eyes        | optic nerve hypoplasia |
| Liver       | liver involvement |
| Other       | failure to thrive, microopen, hypoplastic scrotum; thrombocytopenia |

(continued on next page)
Table 1 (continued)

| **TMEM165-CDG**<sup>**</sup> |  |
|-----------------------------|--|
| Brain | psychomotor disability, epilepsy, white matter abnormalities, hypoplasia of the pituitary gland |
| Eyes | strabismus, ptosis |
| Muscles | muscle weakness |
| Liver | hepatosplenomegaly |
| Skeleton | growth deficiency, kyphoscoliosis; osteoporosis, anterior beaking of vertebrae, dysplastic vertebrae, ribs, fourth metacarpals and metatarsals, hypoplasia of femoral heads and epiphysis, metaphysis, and diaphysis dysplasia |
| Dysmorphic features | facial dysmorphism (macrocephaly, midface hypoplasia, tongue protrusion, downslanting palpebral fissures, flat nose, and low-set posteriorly rotated ears, long philtrum, high-arched palate), short and broad neck, broad thorax, sacral dimple, absent second toenails |
| Other | wrinkled skin, dense hair, long and dense eyelashes, abnormal fat distribution, joint laxity, fever episodes, amenorrhea imperfecta, delayed dentition, hoarse voice |

| **TMEM199-CDG**<sup>**</sup> |  |
|-----------------------------|--|
| Brain | psychomotor disability, hypotonia |
| Liver | steatosis, fibrosis, vacuolization of hepatocytes, decreased serum ceruloplasmin, hypercholesterolemia, increased serum alkaline phosphatase |

| **TMEM5-CDG**<sup>**</sup> | Muscular dystrophy-dystrophicanopha (congenital with brain and eye anomalies), type A, 10 |
|-----------------------------|--|
| Brain | developmental disability, microcephaly; severe cobblestone lissencephaly, occipital neural tube defects, occipital encephalocele, hydrocephaly, brainstem atrophy, dilated ventricles, widespread pachygyria |
| Eyes | microphthalmia, cataract, opaque cornea; retinal dysplasia |
| Muscles | hypotonia |
| Dysmorphic features | facial clefts |
| Other | gonadal dysgenesis; increased serum creatine kinase |

| **TRAPPC11-CDG**<sup>†</sup> | Muscular dystrophy, limb-girdle, type 2S |
|-----------------------------|--|
| Brain | developmental/intellectual disability, epilepsy, choreiform movements, dystonia, ataxia; tremor; cerebral/cerebellar atrophy, reduced white matter volume |
| Eyes | strabismus, myopia, cataracts, alacrima |
| Muscles | proximal muscle weakness with shoulder girdle muscles less severely affected than hip girdle muscles, cramps; histology: dystrophic changes with necrotic and regenerating fibers, endomyal fibrrosis, increased lipid droplets |
| Liver | hepatomegaly; increased serum transaminases, steatosis |
| Skeleton | scoliosis, lordosis, hip dysplasia |
| Other | restrictive pulmonary function, achalasia; increased serum creatine kinase |

| **TUSC3-CDG**<sup>*</sup> |  |
|-----------------------------|--|
| Brain | mental disability |

| **VPS13B-CDG**<sup>‡</sup> | Cohen syndrome |
|-----------------------------|--|
| Brain | psychomotor disability, microcephaly, epilepsy, hypotonia; cerebellar hypoplasia, large corpus callosum |
| Eyes | myopia, decreased visual activity; chorioretinal dystrophy, optic atrophy |
| Heart | mitral valve prolaps |
| Skeleton | lordosis, genua valga, narrow hands, mild shortening of metacarpals |
| Dysmorphic features | facial dysmorphism (maxillary hypoplasia, prominent central incisors, micrognathia, short philtrum), thick hair, low hairline |
| Other | truncal obesity with slender extremities, short stature, delayed puberty; growth hormone deficiency, leukopenia, neutropenia |

| **XYLT1-CDG**<sup>§</sup> | Desbuquois dysplasia 2 |
|-----------------------------|--|
| Brain | intellectual disability, hypotonia |
| Skeleton | short stature, short extremities, multiple dislocations of large joints, plump and stocky long bones with metaphyseal widening, short femoral necks, broad ribs, shortened clavicles, epiphyseal dysplasia, advanced carpal and tarsal ossification |
| Dysmorphic features | macrocephaly, facial dysmorphism (flat face with prominent eyes, synophrys, deep nasal ridges, full lips, long philtrum), broad thumbs, clinodactyly, coxa valga |
| Other | truncal obesity |

| **XYLT2-CDG**<sup>|</sup> | Spondylo-ocular syndrome |
|-----------------------------|--|
| Brain | learning difficulties |
| Eyes | nystagmus, cataract (juvenile); retinal detachment |
| Heart | atrial septal defect, mitral valve prolapse, dysplastic aortic valve |
| Skeleton | normal height with short trunk, immobile spine with thoracic kyphosis, lumbar lordosis, osteoporosis, marked platyspondyly, advanced bone age, bone fragility, multiple vertebral compression fractures with generalized vertebral flattening |
| Dysmorphic features | low posterior hairline, facial dysmorphism, short webbed neck, shield chest, long fingers and toes, overriding second and third toes |
| Other | hearing impairment, undescended testes |

* refers to a type 1 serum transferrin pattern, while ** refers to a type 2. † indicates that the glycosylation of serum transferrin has not been investigated.
Eastern Europe. The prevalence of CDG in Europe could then approach 0.1–0.5/100,000, which is far from the one of only PMM2-CDG calculated on the basis of carrier frequencies (1/20 000; Schollen et al., 2000, 1/77 000; Vals et al., 2017). Thus, CDG is still largely under-diagnosed, even in Europe, the most active region with regard to CDG screening worldwide. This under-diagnosis leads to under-treatment since some CDG are treatable, in particular MPI-CDG (mannose; de Lonlay et al., 2001), and PGM1-CDG and SLC35A2-CDG (galactose; Morava, 2014; Dörre et al., 2015).

The number of molecularly unsolved CDG patients (after exclusion of galactosemia and fructosemia, see section 2.3 for more details) decreases thanks to targeted and whole exome sequencing. As expected, CDG-I appeared to be much more frequent than CDG-II. This is logical since 30 of the known 105 CDG show a Tf IEF type 1 pattern, while only 18 CDG show a type 2 pattern (48 in total; review in Jaeken and Péanne, 2017). Thus only about half of the known CDG are picked up by this test. Among these 48 CDG, eleven did not show up in this survey performed by our network.

In conclusion, these preparatory results on CDG frequency will be a helpful tool in accompanying the development of new therapeutics for CDG patients and should be followed by setting up a patient register containing full clinical and biological data.

### 2.3. Treatment

#### 2.3.1. Therapeutic trials in cells

An important pitfall in the field of many inherited metabolic disorders is the lack of good cellular models for testing therapeutic drugs. The cells most commonly used are patient-derived fibroblasts. However in diseases such as CDG these cells are not representative for the cells that are involved in CDG pathophysiology. Furthermore, for testing mutation-specific therapies cellular models are needed with specific mutations. Recently, the generation of induced pluripotent stem cells (iPSCs) and the number of reports on its applications have rapidly increased because these cells provide a unique platform to carry out in vitro drug screening tests (Thiessler et al., 2016). Nevertheless, the generation of a battery of iPSCs bearing different mutations for successful therapeutic evaluation is a complex task. This prompted B. Pérez and coworkers to develop other cellular models. They have generated a biobank of patient-derived fibroblasts overexpressing hypomorphic mutant alleles. This cellular model allows a rapid screening of potential drugs to be selected for further evaluation in neurons or hepatocytes derived from iPSCs and, in the last step, for evaluation in animal models (unpublished results). In addition, methodologies to generate knock-out cell lines for specific gene defects have been established within the EURO-CDG network, including Hap1, HEK293 and C2C12 cells.
2.3.2. Treatment strategies in patients

MPI-CDG was the first CDG with a fairly effective treatment. Initial studies showed significant clinical improvement on dietary intervention with oral mannose (1 g/kg per day divided in 3–4 doses), improving the serum transferrin isof orm pattern, coagulation anomalies, hypoglycemia and rhabdomyolysis. Mannose therapy acts by its transformation into mannose-6-phosphate, thus restoring the defective pathway. Some patients require higher doses and a few patients do not tolerate mannose due to recurrent hemolysis. Although mannose reduces serum transaminase levels, it does not cure the liver disease in MPI-CDG. Several MPI-CDG patients are known with progressive liver cirrhosis and liver failure on mannose therapy. Liver transplantation has been shown to be beneficial in a few patients with full clinical recovery (Janssen et al., 2014).

PGM1-CDG involves several metabolic pathways, including glycolgenolysis, glycolysis and glycosylation. Galactose therapy has been introduced based on the hypogalactosylation pattern of protein glycans in this disorder. It improves the mixed type of N-glycosylation defect. While the Tf IEF type 2 pattern normalizes quickly, a full restoration is rarely observed. Depending on the patient, dietary galactose in a dose of 0.5–1.5 g/kg per day decreased serum transaminase levels and increased coagulation factors, especially antithrombin. Some patients showed better endocrine control, and a decrease in the frequency of hypoglycemia and rhabdomyolysis. Muscle weakness and cardiomyopathy seem to be unaffected by the galactose intervention in PGM1 deficiency. In a few patients uridine was added, but the effect hereof is not clear yet (Tegtmeier et al., 2014; Morava, 2014; Wong et al., 2017).

CAD-CDG is a disorder in the pyrimidine biosynthesis, important for glycosylation through its role in nucleotide biosynthesis. Both the severe seizures and the microcytic anemia are treatable by oral uridine supplements (Koch et al., 2017). Uridine is an efficient treatment because it is a product of the defective pathway. Monosaccharide supplementation is a partial treatment for individual patients in several other N-glycosylation disorders. Oral galactose supplementation improved seizures and a few blood parameters including Tf IEF in a subset of SLC35A2-CDG patients (Dörre et al., 2015), and the bleeding diathesis, endocrine function and Tf IEF in TMEM165-CDG (Morelle et al., 2017). Both galactose and manganese improved the transferrin isof orm and the seizure disorder in SLC9A8-CDG (Park et al., 2015). The treatment with mannose, galactose, manganese, and a possible treatment with chaperones for PMM2-CDG is illustrated in Fig. 3. Oral fucose treatment improved the immune disorder and decreased infection frequency in a few patients with SLC35C1-CDG (Wild et al., 2002).

Besides in MPI-CDG, liver transplantation has also been performed with partial success in CCDC115-CDG (Janssen et al., 2016a, 2016b). Heart transplantation was successful in 2 children with mild DOLK-CDG (Kapusta et al., 2013), and bone marrow transplantation led to improvement of the immune disease in PGM3-CDG (Stray-Pedersen et al., 2014). Other potential therapeutic approaches aim at specific symptoms like hypoglycemia, hypothyroidism, pericarditis. Congenital myasthenia such as in DPAGT1-CDG can be treated with cholinesterase inhibitors (Finlayson et al., 2013).

2.4. Pathophysiology

A disordered glycosylation machinery does not only influence the glycoprotein and glycolipid homeostasis, but can also have a significant secondary impact on other cellular pathways. The other way around, some metabolic diseases such as galactosemia and fructose intolerance, cause a secondary glycosylation disorder. They show a type 1 pattern. Equally, alcoholism show a type 1 pattern while infections with neuraminidase-producing bacteria cause a type 2 pattern.

Although these hypoglycosylation devious side effects were expected, they were somewhat out of the scope and began to gain center stage just recently. First of course is the polyisoprenoid (or mevalonate) pathway which is necessary for the synthesis of cholesterol and the oligosaccharide lipid-carrier dolichol. Both are directly associated with and influenced by the glycosylation process. A group of CDG, most prominently exemplified by the COG-related CDG, is secondary to perturbation of the in- and outward vesicular trafficking at the Golgi apparatus (Reyners et al., 2011). Since these transport processes play central roles independent of protein glycosylation, the related disorders are probably caused by a combination of protein hypoglycosylation and defects in exo- and endocytosis, lysosomal function, and/or autophagy. There is also a rising interest in pathways leading to the generation of other metabolites such as aminoacids, acylcarnitines and lipids. In a patient with ATP6AP1-CDG, dysregulated levels of several amino acids (e.g. arginine) and strong up-regulated levels of acylcarnitines of the long and very long species were found. Besides, within the main and minor lipid classes reduced amounts of e.g. phosphatidylcholine in combination with abnormalities of the plasmalogens were detected (C. Thiel and co-workers, unpublished results).

It is worth mentioning that, as in CDG, defects in the metabolism of amino acids and in the biosynthesis and remodelling of phospholipids, sphingolipids and complex fatty acids can lead to pathology of the nervous system and many other organs (de Koning, 2013; Lamari et al.,

![Fig. 3. Schematic representation of some promising CDG treatments. Even if more treatments are being investigated (for instance for SLC35A2-CDG, CAD-CDG, SLC39A8-CDG or SLC35A1-CDG), only the therapeutic approaches developed within the European EURO-CDG network are illustrated.](image)
2015). More metabolomic analyses of patient material as well as of CDG animal models will help to further elucidate the role of glycosylation in other pathways. This will be of major help in understanding the complex pathophysiology underlying a glycosylation deficiency and in establishing new therapeutic approaches.

2.5. Patients and parents involvement

The parents have been very active in raising awareness for CDG and in helping families. They have also contributed to the commitment of the basic and clinical research community for CDG. At the risk of not being comprehensive and forgetting to honour several organisations that have been active in CDG – and the people that are the drivers behind these associations - we want to name a few that have contributed significantly. First, there have been parents associations in Denmark (Den Danske CDG Forening), in Germany (Glycokids), in Sweden (Svenska CDG-Föreningen) and later associations were founded in Canada (Foundation Glycosylation (the FoG)), France (Les P’tits CDG), the Netherlands (CDG Netherlands), Portugal (Associação Portuguesa CDG, APCDG), Spain (AES CDG), and the UK (CDG UK), who have been very active at the national level. Prior to these, the American CDG Family Network Inc. has organized meetings in association with the EUROGLYCAN, EUROGLYCANET and EURO-CDG networks, a.o. in Leuven (1999) and in Worms (2008).

In 2013, the Portuguese CDG Association has organised in Barcelona the first World Conference on CDG, a gather of patients, parents, policy makers, representatives from industry and scientists. The second and third World Conference took place in Lyon in 2015 and in Leuven in 2017, the latter again in conjunction with EURO-CDG. Reports and videos of these gatherings are available (http://www.apcdg.com/). Thanks to joint programs for patients, clinicians and basic scientists, a strong impetus is given to research in the field of CDG. A very interesting leaflet providing general information on CDG to parents has been developed by clinicians, scientists from the Barcelona Hospital Sant Juan de Déu, together with the parents (see http://www.euroglycanet.org/az/digitalAssets/1006_P05-Barcelona-Triptico_CDG.pdf). Other information is available at the patients’ and parents’ association websites.

For information on ‘inclusive education’ see https://www.includ-ed.eu/, http://aaate.net/ and https://www.european-agency.org/.

3. The future of CDG

3.1. Developments in the diagnostics of CDG: protein-specific glycoprofiling and metabolic labelling as functional diagnostic tools

About 50 genetic glycosylation defects are known that can be screened for by TF IEF (Jaeken and Péanne, 2017). The identification of novel types of CDG-I, with a defect in the cytosol or endoplasmic reticulum (ER), has been very successful thanks to direct metabolic labelling of cultured CDG patients’ cells with radioactive [2-3H] mannose (Péanne et al., 2013). Following lipid-linked oligosaccharide (LLO) analysis, the culprit gene could relatively easily be identified thanks to the high level of conservation of the N-glycosylation pathway in the ER between humans and yeast. Next-generation sequencing, via whole-exome sequencing or targeted gene panels, has replaced LLO analysis, the culprit gene could relatively easily be identified. For identification of CDG-II defects, glycan structural analysis by glycomics has been instructive to define genetic defects, such as MGAT2-, SLC35C1-, SLC35A1-, B4GALT1-and MAN1B1-CDG, that are directly associated with enzymes and transporters involved in the Golgi processing of glycans (Jaeken and Péanne, 2017). However, the newer forms of CDG-II with defects in vesicular trafficking and ion homeostasis are clearly more difficult to elucidate. The discovery of a CDG-II patient with COG7–deficiency increased the awareness of the impact of abnormal trafficking on glycosylation in humans (Reyners et al., 2011; Wu et al., 2004). Similarly, the identification of mutations in the V-ATPase complex (ATP6V0A2, ATP6V1E1, and ATP6V1A) and in V-ATPase assembly factors (ATP6AP1, CDDC115 and TMEM199) extended the causes of CDG to intracellular compartmental pH defects (Jansen et al., 2016a, 2016b; Kornak et al., 2008; Van Damme et al., 2017). This is also true for defects in TMEM165 and SLC39A8, two genes that link CDG to deficiency of the trace element manganese (Park et al., 2015; Potelle et al., 2017). These observations suggest that any defect that disturbs the function and organization of the Golgi complex may lead to abnormal glycosylation and thus to CDG. As a result, the number of candidate genes becomes very large. In the majority of cases, glycomics profiling of total serum N-linked glycoproteins does not result in sufficiently specific signatures to directly diagnose the respective CDG-II defects. Since plasma biomarkers are highly relevant and easily accessible for CDG diagnostics and subtyping, future efforts will aim at the development of proteome-wide analysis of glycopeptides to identify protein-specific CDG biomarkers. For example, immunoglobulin glycosylation was shown to be affected in MOGS-CDG, while transferrin remained unaffected (Sadat et al., 2014).

Exome sequencing has greatly facilitated the search for novel genes and is now commonly used in CDG-II diagnostics. On the other hand, disorders like EXT1-and EXT2-CDG, which are not captured by testing for abnormal serum protein glycosylation, indicate that there may be many more monogenic disorders with relevant tissue-specific glycosylation deficiencies. The confirmation of this kind of effect of genetic variants is highly challenging, due to the limited availability of easy read-out systems for visualization and analysis of glycosylation deficiencies in patient material. The advent of bioorthogonal click chemistry with the emergence of metabolic oligosaccharide engineering (MOE) has opened a completely new field of investigation (Ovryn et al., 2017). This extremely powerful strategy allows via a chemical reaction to decipher in living cells a specific metabolic pathway without interfering with it. The available chemical toolbox and the strategies to study glycosylation in normal and pathophysiological conditions are constantly growing. In the field of CDG, the use of two unprotected monosaccharide reporters, namely N-4-pentynoylneuraminic acid (SiaNAI) and N-(4-pentynoyl) mannosamine (ManNAI) has proved to be an effective method to track glycoconjugate sialylation defects (Vanbelseleaere et al., 2013; Gilorini et al., 2016). Such labeling strategies, coupled to the use of different azido functionalized fluorescent probes allowed to quantitatively measure the Golgi glycosylation efficiency in CDG patient cells. This assay was successfully applied in COG-, TMEM165-, CDDC115- and TMEM199-CDG patient fibroblasts (Vanbelseleaere et al., 2013; Jansen et al., 2016a, 2016b), showing a drastically reduced incorporation of monosaccharide reporters, which was restored upon complementation with wild-type gene. This novel approach will also facilitate the confirmation of novel CDG-II defects in Golgi homeostasis, as still many Golgi defects are expected to be discovered.

3.2. Beyond genetics: epigenetic studies

Epigenomics or alterations to chromatin (modifications of DNA and histones) can be divided in chromatin marks (individual chemical modifications) and features (multiple linked modifications and more complex elements). Examples of the first are DNA methylations and histone acetylations, and of the latter chromatin interactions, RNA modifications and non-coding RNAs (reviewed in Stricker et al., 2017). A large body of literature documents epigenetic regulation of glycosylation, mostly by showing aberrant glycosylation in cancer. A change in cytosine methylation within the promoter of certain glyco-genes is responsible for the expression of cancer-associated carbohydrate antigens, in gastrointestinal, pancreatic and breast cancer. Other examples of epigenetic regulation of glyco-genes include FUT7 in leukocytes and the transcription factor HNF1A, a master regulator of plasma protein fucosylation (Zoldos et al., 2013; Lauc et al., 2014). Treatments of
cultured cells with epigenetic inhibitors reveal that N-glycome profiles drastically change, which indicates that many glycosylation-related genes are regulated by DNA and histone modifications (Saldova et al., 2011). To the best of our knowledge, there are no clear examples of CDG caused by epigenetic changes, probably because we are not looking for such defects. However, we are quite convinced that epigenetic disorders will become an important CDG chapter.

3.3. In search for novel treatments

The functional characterization of phosphomanomutase 2 (PMM2) disease-causing mutations has suggested that PMM2-CDG could be a conformational disease and that therapies addressed to improve the protein folding would be able to ameliorate the clinical symptoms (Yuste-Checa et al., 2015). From a 10,000 compound library screening, 8 possible pharmacological chaperone (PCs) were selected. The compound 1-(3-chlorophenyl)-3,3-bis(pyridine-2-yl)urea stood out, based on its pharmacochemical properties, the absence of inhibitory effect on PMM enzymatic activity and the improved stability of a number of destabilizing mutant proteins. PMM activity assays were performed with soluble cell extracts from healthy and patient-derived fibroblasts overexpressing wild type PMM2 or PMM2 with the mutations p.Asp65Tyr, p.Pro113Leu, p.Arg162Trp and p.Thr237Met. These results have provided the first proof-of-concept of a possible treatment for PMM2-CDG and identified a promising chemical structure as a starting lead for the development of therapeutic agents against this severe orphan disease (Yuste-Checa et al., 2017). Future clinical trials aim at D-galactose use in different CDG, liposomal mannose-1-phosphate and chaperone therapy in PMM2-CDG (Fig. 2), and possibly PMM enzyme replacement therapy. However, there are major hurdles for enzyme replacement, because it is difficult to target deficiencies in the cytosol, the endoplasmic reticulum or the Golgi compartment. The finding that GDP-mannose levels are tightly controlled by a feedback loop involving GMPPA (Koehler et al., 2013) opens the possibility that PMM2 defects could be treated by pharmacological intervention aimed at suppressing the inhibition exerted by GMPPA on GMPBP, the catalytic subunit of GDP-mannose pyrophosphorylase.

3.4. CDG reference network

MetabERN is an European non-profit network established by the EU to facilitate access to the best available care and to address the needs of all European patients affected by any rare inherited metabolic disease (IMD) and their families. MetabERN already involves 69 specialized metabolic centers from 19 countries and is continuously growing. It aims to promote prevention, accelerate diagnosis and improve standards of care across Europe for patients with an IMD. It is entirely patient- and expert-led. The 7 subnetworks focus on disorder groups, one of which is disorders of glycosylation and intracellular trafficking. This subnetwork aims at initiating natural history studies and therapeutic trials in different CDG.

3.5. eHealth at the service of the patient

Nanotechnology is invading daily life and this should profit the patients. The CDG patient community as well as the researchers involved in CDG would benefit from the development and use of specific apps for the follow-up of patients. Indeed, CDG is characterized by frequent and often severe clinical events throughout the life of the patients. Examples are seizures, bleeding, infections, but also events like hospitalisation, change of drug treatment, frequency of physical therapy sessions, etc. A detailed, online registration would allow the collection of data necessary for the natural history of the different types of CDG. A mobile tool would be especially welcome, given the extreme genetic heterogeneity of CDG, the broad clinical spectrum and variable symptoms, the rarity of most of the types of the disease and the large geographical distribution of the patients. The different compounds of the app should be developed in collaboration with clinicians and patients’ representatives, and the data collected in accordance with national and international laws on medical records and privacy. The app should be useful to inform caretakers of critical events, and allow rapid clinical action if needed (alert function).

4. Conclusion

CDG are a family of, largely not yet treatable, genetic diseases. Like for all patients, it is of utmost importance to provide the best possible care and support to these patients and their families. These include a well-organized, multidisciplinary medical approach and follow-up, optimal paramedical services (physiotherapy, speech therapy, social service a.o.), regularly updated information (via meetings, letters, social media), and practical help e.g. by specific apps. The patients/families, caregivers, and researchers should form a strong community at the service of the patients. The EURO-CDG initiatives are prominent examples of such collaboration and take the lead in this undertaking. We hope that this survey may contribute to this goal.

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