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CDG nomenclature: Time for a change!

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Congenital disorders of glycosylation (CDG) are a rapidly growing disease family with about 40 diseases reported since its first clinical description in 1980 [1]. The large majority of these are diseases of protein hypoglycosylation, but in recent years several defects in lipid glycosylation have also been identified [2,3]. Most protein glycosylation disorders are due to defects in the N-glycosylation pathway, the remaining ones affecting the O-glycosylation pathway or combined N-and O-glycosylation pathways. No defects in C-glycosylation have been detected yet. The first described CDG patients were shown to have an abnormal serum transferrin (Tf) isoelectrofocusing (IEF) pattern with increases in the di-and asialotransferrin fractions [4]. They were found to have deficient phosphomannomutase (PMM) activity [5] and mutations in the PMM2 gene [6]. PMM-deficient patients were designated as CDG-Ia. Subsequently, a patient was discovered with a serum Tf IEF pattern characterized by increases not only of the even (2 and 0) but also of the uneven (3 and 1) sialoTf bands [7]. Since these patterns were qualitatively different, we called the latter a type 2 pattern as opposed to the type 1 pattern seen in PMM deficiency. In the patient with the type 2 pattern, a deficiency was demonstrated to be in a Golgi glycosyltransferase, namely N-acetylglucosaminyltransferase II [8]. This disease was labeled CDG-IIa. New patients were classified as CDG-I or CDG-II according to the Tf IEF pattern, and each new defect took the next letter of the alphabet.

We presently count 14 CDG-I diseases (CDG-Ia up to CDG-In), and 8 CDG-II diseases (CDG-IIa up to CDG-IIh). Since this nomenclature is based on the Tf IEF pattern, it relates only to N-glycosylation diseases associated with deficient sialylation. Gradually it became clear that CDG-I defects were limited to defects in pre-ER or ER proteins whereas CDG-II defects were caused by defects in Golgi or Golgi-associated proteins. However, some of these disorders also show abnormal O-glycosylation such as the COG defects (review in [9]) and the V-ATPase defect in cutis laxa type II [10]. Also, it appeared that a patient with an alpha-glucosidase I deficiency in the ER had a normal Tf IEF pattern [11]. Still this patient was labeled as CDG-IIb, which is an inconsistency of this classification. For this reason and for a number of other reasons explained elsewhere [12], we strongly suggest that this nomenclature should be discontinued in favor of a transparent designation of glycosylation disorders and that it be applied to new and established types of CDG. We propose using only the official gene symbol (not in italics) followed by '-CDG' (list of approved gene names at http://www.genenames.org). A classification of the known types of CDG, along with the traditional and new nomenclature, is shown in Table 1 (adapted from [12]).

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Table 1

Proposed nomenclature for CDG (nomenclature to be superseded is included in italics and enclosed in parenthesis).[a]

Disease name	Defective protein	OMIM
A. Defects in protein N-glycosylation		
PMM2-CDG (*CDG-Ia*)	Phosphomannomutase 2	601785
MPI -CDG (*CDG-Ib*)	Phosphomannose isomerase	602579
ALG6-CDG (*CDG-Ic*)	Dol-P-Glc: Man_9-$GlcNAc_2$-P-P-Dol glucosyltransferase (glucosyltransferase 1)	603147
ALG3-CDG (*CDG-Id*)	Dol-P-Man: Man_5-$GlcNAc_2$-P-P-Dol mannosyltransferase (mannosyltransferase 6)	601110
ALG12-CDG (*CDG-Ig*)	Dol-P-Man: Man_7-$GlcNAc_2$-P-P-Dol mannosyltransferase (mannosyltransferase 8)	607143
ALG8-CDG (*CDG-Ih*)	Dol-P-Glc: Glc_1-Man_9-$GlcNAc_2$-P-P-Dol glucosyltransferase (glucosyltransferase 2)	608104
ALG2-CDG (*CDG-Ii*)	GDP-Man: Man_1-$GlcNAc_2$-P-P-Dol mannosyltransferase (mannosyltransferase 2)	607906
DPAGT1-CDG (*CDG Ij*)	UDP-GlcNAc: Dol-P-GlcNAc-P transferase	608093
ALG1-CDG (*CDG-Ik*)	GDP-Man: $GlcNAc_2$-P-P-Dol mannosyltransferase (mannosyltransferase 1)	608540
ALG9-CDG (*CDG-Il*)	Dol-P-Man: Man_6-and Man_8-$GlcNA_2$-P-P-Dol mannosyltransferase (mannosyltransferase 7-9)	608776
RFT1-CDG (*CDG-In*)	Flippase of $Man_5GlcNAc_2$-PP-Dol	611633
MGAT2-CDG (*CDG-IIa*)	*N*-acetylglucosaminyltransferase 2	602616
GCS1-CDG (*CDG-IIb*)	Glucosidase 1	606056
TUSC3-CDG	Oligosaccharyltransferase subunit	601385
MGAT1-CDG	Oligosaccharyltransferase subunit	300716
B. Defects in protein O-glycosylation		
*O-xylosylglycan synthesis		
• EXT1/EXT2-CDG (multiple cartilaginous exostoses)	Glucuronyltransferase/*N*-acetylglucosaminyltransferase	608177/608210
• B4GALT7-CDG	β-1, 4-galactosyltransferase 7	604327
**O-N*-acetylgalactosaminylglycan synthesis		
•GALNT3-CDG (familial tumoral calcinosis)	Polypeptide *N*-acetylgalactosaminyltransferase 3	601756
**O*-xylosyl/N-acetylgalactosaminylglycan synthesis		
•SLC35D1-CDG (Schneckenbecken dysplasia)	Solute carrier family 35 (UDP-glucuronic acid/UDP-*N*-acetylgalactosamine dual transporter), member D1	610804
**O*-mannosylglycan synthesis		
•POMT1/POMT2-CDG (cong. Muscular dystrophy spectrum)	*O*-mannosyltransferase 1	607423
•POMGNT1-CDG (cong. Muscular dystrophy spectrum)	*O*-mannose β-1, 2-*N*-acetylglucosaminyltransferase	606822
•FKTN-CDG (cong. muscular dystrophy spectrum)	Fukutin	607440
•FKRP-CDG (cong. muscular dystrophy spectrum)	Fukutin-related protein	606596
•LARGE-CDG (cong. muscular dystrophy spectrum)	*N*-acetylglucosaminyltransferase-like protein	603590

Disease name	Defective protein	OMIM
*_O_-fucosylglycan synthesis		
•LFNG-CDG (spondylocostal dysostosis type 3)	_O_-fucose-specific β-1, 3-_N_-acetylglucosaminyltransferase	602576
•B3GALTL-CDG (Peters plus syndrome)	_O_-fucose-specific β-1, 3-glucosyltransferase	610308
C. Defects in glycosphingolipid and glycosylphosphatidylinositol anchor glycosylation		
ST3GAL5-CDG (Amish infantile epilepsy)	Lactosylceramide α-2, 3 sialyltransferase (GM3 synthase)	609056
PIGM-CDG (glycosylphosphatidylinositol deficiency)	Phosphatidylinositolglycan, class M	610273
D. Defects in multiple glycosylation and other pathways		
DPM1-CDG (*CDG-Ie*)	GDP-Man: Dol-P-mannosyltransferase (Dol-P-Man synthase 1)	603503
MPDU1-CDG (*CDG-If*)	Lec35 (Man-P-Dol utilization 1)	608799
B4GALT1-CDG (*CDG-IId*)	β-1, 4-galactosyltransferase 1	607091
GNE-CDG (hereditary inclusion body myopathy)	UDP-GlcNAc epimerase/kinase	600737
SLC35A1-CDG (*CDG-IIf*) (CMP-sialic acid transporter deficiency)	CMP-sialic acid transporter	605634
SLC35C1-CDG (*CDG-IIc*) (GDP-fucose transporter deficiency)	GDP-fucose transporter	605881
*Dolichol pathway -DK1-CDG (*CDG-Im*)	Dolichol kinase	610768
*COG[b] complex		
•COG7-CDG (*CDG-IIe*)	Component of conserved oligomeric Golgi complex 7	606978
•COG1-CDG (*CDG-IIg*)	Component of conserved oligomeric Golgi complex 1	606973
•COG8-CDG	Component of conserved oligomeric Golgi complex 8	606979
•COG4-CDG	Component of conserved oligomeric Golgi complex 4	606976
•COG5-CDG	Component of conserved oligomeric Golgi complex 5	606821
*V-ATP$_{ase}$		
•ATP6VOA2-CDG (cutis laxa type II)	V0 subunit A2 of vesicular H(+)-ATPase	611716
•SEC23B-CDG (CDAII)	COPII component SEC23B	610512

[a] Adapted from [12].

[b] Conserved oligomeric Golgi.