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LETTER TO THE EDITOR

Carbohydrate-deficient glycoprotein syndromes become congenital disorders of glycosylation: An updated nomenclature for CDG

Authors: Participants, ''First International Workshop on CDGS'', Leuven, Belgium, November 12–13, 1999 (see attached list of Participants)

During the last few years, progress in identifying the molecular defects of the carbohydrate-deficient glycoprotein syndromes has been very rapid. Up to this date, six different gene defects have been elucidated. The plethora of defects that will eventually be identified makes it indispensable to use a simple and straightforward nomenclature for this group of diseases.

A group of specialists in this field met for a round-table discussion at the ''First International Workshop on CDGS'' in Leuven, Belgium, November 12–13, 1999, and came up with the following recommendations.

1. **CDG stands for ''Congenital Disorders of Glycosylation''.**
2. **The disorders are divided into *groups*, based on the biochemical pathway affected: group I refers to defects in the initial steps of N-linked protein glycosylation. These deficiencies affect the assembly of dolichylpyrophosphate linked oligosaccharide and/or its transfer to asparagine residues on the nascent polypeptides; group II refers to defects in the processing of protein-bound glycans or the addition or other glycans to the protein. This grouping no longer refers directly to the isoelectric focusing pattern of serum transferrins or other serum glycoproteins.**
3. **CDG *types* are assigned to one of the groups and will be numbered consecutively as they are identified: Ia, Ib, . . . , IIa, IIb, . . . , etc. The currently distinguished types are: CDG-Ia (*PMM2*), CDG-Ib (*MPI*), CDG-Ic (*ALG6*), CDG-Id (*ALG3*), CDG-Ie (*DPM1*), CDG-IIa (*MGAT2*).**
4. **No new designations will be made unless the genetic defect is established. Untyped cases are considered ''x'' cases (CDG-x) until the genetic defect is known.**

Keywords: **metabolic disorder, ALG3, ALG6, DPM1, MPI, MGAT2, PMM2**

Introduction

At the "First International Workshop on CDGS" in Leuven, Belgium, November 12–13, 1999, a round-table was organized to discuss the nomenclature of the novel and rapidly expanding group of metabolic disorders caused by defects in protein glycosylation.

Several questions were raised. (i) The definition of the term CDG was discussed and a new definition was suggested. (ii) The need for a novel classification was debated and a new basis for the division of CDG into groups was proposed. (iii) New names and acronyms for the CDG types were discussed and a new nomenclature was suggested.

We briefly present the different views and arguments that were raised and considered at the discussions and we summarize the conclusions.

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(i) A new name for this family of disorders

The "Carbohydrate-Deficient Glycoprotein Syndromes" is a correct but difficult name for this expanding group of diseases. However, the acronym CDG (or CDGS) is already in common use. Therefore it was recommended that the acronym CDG be retained but be re-defined as "Congenital Disorders of Glycosylation".

Attention is drawn to the fact that these are inborn disorders and we therefore suggest the term "congenital". The term "glycoprotein" in the original definition restricts the definition and hence preference is given to the term "glycosylation". "Glycosylation" rather than "N-glycosylation" is suggested because it is anticipated that, in addition to defects in the synthesis or processing of N-glycans, defects are likely to be discovered in the future which affect O- or C-glycosylation. In this way, defects in pathways involved in all forms of glycosylation can eventually be included into this family of disorders.

It is suggested that the only accepted acronym will be "CDG". The S in the acronym CDGS is no longer required since D now represents "disorders". There was a concern among some of the participants that the use of CDG instead of CDGS will lead to problems in retrieving older literature. However, this was considered a minor problem and the uniform use of CDG is strongly recommended in all future publications.

(ii) A new classification for the CDG groups

Almost all participants at the meeting agreed that the nomenclature needs a revision, because it is becoming complex and confusing. Various choices can be made in the classification and nomenclature of the members in this family of diseases. Group classification can be based on cell biological criteria, e.g. a distinction can be made between defects that are situated in the Golgi and pre-Golgi compartments. Groups can also be named on the basis of an established biochemical and/or genetic defect and numbered consecutively as they are discovered; the name of the disease would include a reference to the specific biochemical or genetic defect. Also, the nomenclature could combine several systems of classification.

The meeting participants agreed that a nomenclature that includes the name of a specific enzyme or gene would be preferable to basic scientists but would be difficult in clinical practice and teaching. Therefore, preference has been given to a division of the known types of CDG into two groups based on the location in the biochemical pathway in which the defect occurs. It is proposed that the first group includes all defects in N-glycosylation that affect the assembly of the dolichylpyrophosphate oligosaccharide precursor of N-glycans and/or the transfer of oligosaccharide from dolichylpyrophosphate to an asparagine residue on the nascent proteins. The second group includes all defects that are localized to steps in the processing of N-glycans or the addition of other glycans to the proteins. This suggestion would allow inclusion in the second group not only of defects in N-glycosylation but also in O- or C-glycosylation, although an alternative could be to add additional groups if and when such defects are discovered. It is stressed that this division is not linked to the cellular compartments in which these processes take place or to the isoelectric focusing patterns of serum transferrins or other serum glycoproteins.

This division leaves room for the generation of novel groups and types, if required. Other options, like naming the disease after the discoverer(s) or propagating the use of trivial names, have been discarded.

The acronym CDG also permits easy distinction from the acquired disorders of glycosylation (which could be designated ADG).

(iii) A new nomenclature for CDG

No new types should be created unless the genetic defect is known.

A large majority of the participants opted to be conservative when naming the two new CDG groups, and has agreed that Roman numbers will refer to the two groups (groups I and II). In the acronym, the group and type will be separated from CDG by a hyphen (e.g. CDG-Ia). For the time being, the use of the Roman numerals III, IV, ... is to be avoided.

The names of the most common types of CDG will therefore not change. Every separate CDG disease should be referred to as a "type" of CDG, as used in the previous sentence. However, it is suggested that the word "type" should be omitted from the actual name of the disease, e.g., the most frequent type, the deficiency of phosphomannomutase caused by mutations in *PMM2*, will now be called CDG-Ia. Similarly, the deficiency of phosphomannose isomerase, caused by

Table 1. Congenital Disorders of Glycosylation or CDG (as of 15/11/1999)

Group/type	*Defect and defective gene*		*Acronym*
Group I	Defects in N-linked protein glycosylation due to deficiencies in the assembly of the dolichylpyrophosphate linked oligosaccharides and/or its transfer to asparagine residues on the nascent polypeptides.		**CDG-I**
Type Ia	Phosphomannomutase	*PMM2*	CDG-Ia
Type Ib	Phosphomannose isomerase	*MPI*	CDG-Ib
Type Ic	Dolichyl-PP-Glc:Man9GlcNAc2-PP-dolichyl alpha 1,3-glucosyl-transferase	*ALG6*	CDG-Ic
Type Id	Dolichyl-PP-Man:Man5GlcNAc2-PP-dolichyl alpha1,3-mannosyl-transferase	*ALG3*	CDG-Id
Type Ie	Dolichol-P-Man synthase 1	*DPM1*	CDG-Ie
Group II	Defects in the processing of N-glycans or addition of other glycans to proteins		**CDG-II**
Type IIa	UDP-GlcNAc:alpha-6-D-mannoside beta-1,2-N-acetylglucosaminyl-transferase II (GnT II)	*MGAT2*	CDG-IIa
Type x	Genetic basis unknown		**CDG-x**

mutations in *MPI*, will remain CDG-Ib. The deficiency of the DolPP-Man9GlcNAc2 dependent glucosyltransferase, caused by mutations in the human ortholog of yeast *ALG6*, will become CDG-Ic, and thus the former CDG type V will no longer be used. The deficiency of the DolPP-Man5GlcNAc2 dependent mannosyltransferase, caused by mutations in the gene *ALG3*, the human ortholog of yeast *ALG3*, will be called CDG-Id, rather than CDG type IV as previously suggested. The deficiency of dolichylmannose synthase-1 (*DPM1*) will be called CDG-Ie. The deficiency in N-acetylglucosaminyltransferase II, encoded by *MGAT2*, will be called CDG-IIa. Novel defects related to the processing of protein-bound N-glycans, and possibly the addition of O- and C-glycans, will become further types of CDG-II. The names CDG type III, CDG type IV and CDG type V will no longer be used. Cases identified in the literature as CDG types I, III, IV or V, in which the genetic defect remains to be elucidated, will be re-classified as CDG-x. Those published cases for which a genetic defect has been established should be integrated into the above classification.

It is important to mention that the analysis of serum transferrin by isoelectric focusing is still an important diagnostic tool, because it allows a preliminary assignment of cases to either CDG group I or CDG group II. However, a definitive diagnosis requires additional biochemical and genetic analysis. It has also to be stressed that a normal transferrin pattern in isoelectric focusing does not exclude CDG.

The currently known CDG types, the corresponding deficiencies and their genes are listed in Table 1.

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