What’s in a name?
A CDG by any other name would smell as sweet

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July 25, 2019
CDGs originally described in 1980 in twin sisters...

...who were subsequently found to have hyposialylation of serum and CSF transferrin.

Subsequent history

• 2 additional patients in 1987

• 7 more in Sweden in 1989

• 26 patients presented by Drs. Jaeken and Stibler at 5th ICIEM (Asilomar, June 1-5, 1990)
  – renamed carbohydrate-deficient glycoprotein syndrome (CDGS)
New subtypes

• New variant described in 1991
  – type II

• Further subtypes identified
  – type III
  – type IV
Enzymatic and molecular identification

• Enzyme deficiency for CDGS type II identified in 1994
  - gene in 1996

• Type I enzyme identified in 1995
  - gene in 1997

• Enzyme and gene deficiencies responsible for type IV described in 1999
  Körner C et al. EMBO J. 1999 Dec 1;18(23):6816–22
New classification proposed

• First International Workshop on Carbohydrate-Deficient Glycoprotein Syndromes
  – Leuven, Belgium, November 12-13, 1999

• Named according to type of TIEF abnormality followed by letter in the order in which they were described
  – CDGS type I → CDG-Ia
  – CDGS type II → CDG-IIa
LETTER TO THE EDITOR

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

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

<table>
<thead>
<tr>
<th>Group/type</th>
<th>Defect and defective gene</th>
<th>Acronym</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type Ia</td>
<td>Phosphomannomutase</td>
<td>PMM2</td>
</tr>
<tr>
<td>Type Ib</td>
<td>Phosphomannose isomerase</td>
<td>MPI</td>
</tr>
<tr>
<td>Type Ic</td>
<td>Dolichyl-PP-Glc:Man9GlcNAc2-PP-dolichyl alpha 1,3-glucosyltransferase</td>
<td>ALG6</td>
</tr>
<tr>
<td>Type Id</td>
<td>Dolichyl-PP-Man:Man5GlcNAc2-PP-dolichyl alpha 1,3-mannosyltransferase</td>
<td>ALG3</td>
</tr>
<tr>
<td>Type Ie</td>
<td>Dolichol-P-Man synthase 1</td>
<td>DPM1</td>
</tr>
<tr>
<td><strong>Group II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IIa</td>
<td>UDP-GlcNAc:alpha-6-D-mannoside beta-1,2-N-acetylglicosaminyltransferase II (GnT II)</td>
<td>MGAT2</td>
</tr>
<tr>
<td><strong>Type x</strong></td>
<td>Genetic basis unknown</td>
<td></td>
</tr>
</tbody>
</table>
Issues with classification

- Some disorders of N-glycosylation not associated with TIEF abnormalities
  - CDG-IIb

- TIEF only assesses N-glycosylation
  - disregards defects in O-glycosylation

- Disorders involving lipid glycosylation discovered

- No biological insight about basic protein defect

- Soon would run out letters
  - mutations in NUS1: CDG-laa
New nomenclature

• Include official gene symbol (not in italics) followed by “-CDG”
  – CDG-Ia → PMM2-CDG

• Adopted in 2008
  – issues noted earlier
On the nomenclature of congenital disorders of glycosylation (CDG)

J. Jaeken · T. Hennet · H. H. Freeze · G. Matthijs

Received: 25 June 2008/Submitted in revised form: 12 August 2008/Accepted: 22 August 2008/Published online: 24 October 2008
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CDG nomenclature: Time for a change!

Jaak Jaeken a,*, Thierry Hennet b, Gert Matthijs c, Hudson H. Freeze d

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b Institute of Physiology, University of Zürich, CH-8057 Zürich, Switzerland
c Center for Human Genetics, Katholieke Universiteit Leuven, BE-3000 Leuven, Belgium
d Burnham Institute for Medical Research, La Jolla, CA 92037, USA
Classification – Quo vadis

• 105 CDGs

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.

<table>
<thead>
<tr>
<th>ALG1-CDG *</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>psychomotor disability, microcephaly, refractory epilepsy, hypotonia; cerebral atrophy</td>
</tr>
<tr>
<td>Liver</td>
<td>hepatosplenomegaly</td>
</tr>
<tr>
<td>Dyshormorphic features</td>
<td>large fontanel, hypertelorism, micrognathia</td>
</tr>
<tr>
<td>Other</td>
<td>nonimmune foetal hydrops, hypogonadism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALG2-CDG *</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>psychomotor disability, epilepsy; hypomyelination</td>
</tr>
<tr>
<td>Eyes</td>
<td>bilateral iris coloboma, cataract</td>
</tr>
<tr>
<td>Liver</td>
<td>hepatomegaly</td>
</tr>
</tbody>
</table>

Table 1

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Function</th>
<th>Disorder OMIM</th>
<th>Gene OMIM</th>
<th>Main clinical features</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-linked pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPAGT1–CDG</td>
<td>DPAGT1</td>
<td>GlcNAc-1-P transferase</td>
<td>608093</td>
<td>191350</td>
<td>ID, Hy, Sz, M, infections, early death, CMS</td>
<td>2003</td>
<td>PMID: 12872255</td>
</tr>
<tr>
<td>ALG1–CDG</td>
<td>ALG1</td>
<td>β1-4 mannosyltransferase</td>
<td>608540</td>
<td>605907</td>
<td>ID, Hy, Sz, M, infections, early death</td>
<td>2004</td>
<td>PMID: 14709599</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>PMID: 14973778</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>PMID: 14973782</td>
</tr>
<tr>
<td>ALG2–CDG</td>
<td>ALG2</td>
<td>α1-3 mannosyltransferase</td>
<td>607906</td>
<td>607905</td>
<td>ID, Hy, Sz, infections, hypomyelination, hepatomegaly, early death, CMS</td>
<td>2003</td>
<td>PMID: 12684507</td>
</tr>
<tr>
<td>ALG2–CMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2013</td>
<td>PMID: 23404334</td>
</tr>
</tbody>
</table>

https://www.ncbi.nlm.nih.gov/books/NBK453018/
Nosology of IEMs

• Redefinition of IEMs
  – presence of metabolite identifiable by classical techniques no longer a prerequisite
  – requires only that impairment of biochemical pathway be intrinsic to pathomechanism


Table 1 Criteria used for inclusion of an inborn error of metabolism in the current nosology

- The disruption of a metabolic pathway is considered necessary and sufficient for inclusion
- Regardless of laboratory abnormalities in standard biochemical tests
- Regardless of association with clinical manifestations of disease (unless the defect is universal to all humans)
- Severity alone is not considered sufficient for separation into different entries when a single gene product is involved
- A different pathomechanism is considered necessary for separation into different entries when a single gene product is involved, regardless of the mode of inheritance
- The involvement of different gene products is considered sufficient for separation into different entries, even if the phenotype is similar
- The error must have been reported in more than a single family, and the involvement of the gene product must have been well characterized on an enzymatic or molecular level

## TOTAL NUMBER OF DISORDERS - BY TOP CATEGORY

<table>
<thead>
<tr>
<th>Top Category</th>
<th>Well Characterized</th>
<th>Provisional</th>
<th>Count All</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. DISORDERS OF NITROGEN-CONTAINING COMPOUNDS</td>
<td>199</td>
<td>30</td>
<td>229</td>
</tr>
<tr>
<td>B. DISORDERS OF VITAMINS, COFACTORS AND MINERALS</td>
<td>126</td>
<td>14</td>
<td>140</td>
</tr>
<tr>
<td>C. DISORDERS OF CARBOHYDRATES</td>
<td>77</td>
<td>6</td>
<td>83</td>
</tr>
<tr>
<td>D. MITOCHONDRIAL DISORDERS OF ENERGY METABOLISM</td>
<td>244</td>
<td>42</td>
<td>286</td>
</tr>
<tr>
<td>E. DISORDERS OF LIPIDS</td>
<td>187</td>
<td>33</td>
<td>220</td>
</tr>
<tr>
<td>F. DISORDERS OF TETRAPYRROLES</td>
<td>25</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>G. STORAGE DISORDERS</td>
<td>69</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>H. DISORDERS OF PEROXISOMES AND OXALATE</td>
<td>30</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td><strong>I. CONGENITAL DISORDERS OF GLYCOSYLATION</strong></td>
<td><strong>135</strong></td>
<td><strong>11</strong></td>
<td><strong>146</strong></td>
</tr>
<tr>
<td>J. MISCELLANEOUS DISORDERS</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>FINAL TOTAL</strong></td>
<td><strong>1092</strong></td>
<td><strong>142</strong></td>
<td><strong>1234</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Quo vadis</th>
<th>“Essentials” book</th>
<th>Nosology</th>
</tr>
</thead>
<tbody>
<tr>
<td>G6PC3 deficiency</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>G6PT1 deficiency</td>
<td>-</td>
<td>✔</td>
<td>-</td>
</tr>
<tr>
<td>SLC26A2 deficiency</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>TRIP11 deficiency</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Mucolipidosis</td>
<td>-</td>
<td>✔</td>
<td>-</td>
</tr>
<tr>
<td>NGLY1 deficiency</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
Issues

1. Lack of biochemical marker
   a) tissue-specific biochemical marker
   b) lack of knowledge
   c) no biochemical markers

2. Same gene, different disease?

   1. Glycoprotein degradation

   2. Secondary glycosylation abnormalities
1a) Tissue-specific glycosylation abnormalities

- TRIP11 deficiency
- G6PC3 deficiency
- SEC23B deficiency
TRIP11 deficiency

- Impairment of LAMP1 and LAMP2 glycosylation in fibroblasts
- Altered glycosylation of decorin

G6PC3 deficiency

- Hypoglycosylation of gp91(phox) on electrophoresis

- Incomplete glycosylation in neutrophil $N$- and $O$-glycomes (MS)

SEC23B deficiency

- Component of COPII complex
- Hypoglycosylation of RBC membrane proteins (band 3)

Proposed solution: At least one tissue

Example: **α-dystroglycanopathies**


1b) Lack of biomarker: lack of knowledge?

- MAGT1 deficiency: discovered in 2008, type 1 pattern on serum TIEF noted this year

- ARCN1 deficiency: described in 2016

- COPA (α subunit of COPI vesicles)


1c) No biochemical markers

- Polycystic liver disease
  - ALG8 (1), SEC61B (2), SEC63 (3), GANAB (4) and PRKCSH (5)

- SEC63 deficiency in some classifications, SEC61B deficiency (2 unrelated patients) in none

Proposed solution: pathway approach

Example: sulfate transporter deficiency

2) Same gene, different disease? – *PMM2*

- HI + PKD in 7 children from 11 unrelated families
  - *PMM2* promoter mutation (c.-167G>T) in all

Same gene, different disease? – COG4

COG4-CDG

Control

Saul-Wilson syndrome
Same gene, different disease? – *EXT2*

<table>
<thead>
<tr>
<th></th>
<th>MHE</th>
<th>AREXT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone involvement</td>
<td>Osteochondromas</td>
<td>Osteopenia, scoliosis</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>-</td>
<td>ID, seizures</td>
</tr>
<tr>
<td>Inheritance</td>
<td>AD</td>
<td>AR</td>
</tr>
<tr>
<td>Mutations</td>
<td>Truncating, missense</td>
<td>Missense</td>
</tr>
<tr>
<td></td>
<td>(catalytic)</td>
<td></td>
</tr>
</tbody>
</table>
Same gene, different disease? – *ALG13*

<table>
<thead>
<tr>
<th></th>
<th>XLD</th>
<th>XLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Girls</td>
<td>Boys</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>Severe epilepsy/ID</td>
<td>Seizures</td>
</tr>
<tr>
<td>Multisystemic involvement</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Glycosylation abnormalities</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Mutation</td>
<td>Recurrent c.320A&gt;G p.(Asn107Ser)</td>
<td>Variable*</td>
</tr>
</tbody>
</table>

* One boy with recurrent mutation had milder presentation than girls

Proposed solution: Different mechanism/symptoms = different disease

• Do they represent different disorders?

• If so, what should we call them?
  – EXT2-MHE vs AREXT2
  – COG4-CDG vs COG4-SWS
  – XLD vs XLR ALG13-CDG
3) Degradation disorders

- Mucolipidosis

- NGLY1-CDDG: yes; oligosaccharidoses no?
4) Secondary glycosylation abnormalities - Carbohydrate disorders

• Galactosemia

  “our findings of decreased serum TBG and abnormal sialotransferrin pattern... are a further argument for grouping classic galactosaemia as a CDG syndrome”


• Proposed mechanisms
  – decreased UDP-Gal for galactosylation
  – accumulated Gal-1-P inhibits Golgi galactosyltransferases
Galactosemia

• Four truncated glycans (serum transferrin)
  

• Increased fucosylation and branching (serum transferrin)
  

• Abnormal IgG glycosylation
  – increased core fucosylated neutral glycans
  – decreased core fucosylated bisected glycans
  – decreased non-fucosylated bisected glycans
  – decreased N-linked mannose-5 glycans

Galactosemia

Hereditary fructose intolerance

Secondary glycosylation abnormalities
Non-carbohydrate disorders

## Secondary glycosylation abnormalities

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gene of interest</th>
<th>Main phenotypes</th>
<th>Plasma N-linked</th>
<th>Plasma O-linked</th>
<th>Urine oligosaccharides</th>
<th>Fibroblast N-linked</th>
<th>Fibroblast O-linked</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>OFD1</td>
<td>Molar tooth sign, hypotonia, central apnea, oral motor dysfunction, cleft palate, dysmorphia</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>14</td>
</tr>
<tr>
<td>27</td>
<td>ERCC6</td>
<td>Global developmental delay, scoliosis, hypotonia</td>
<td>Borderline</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Borderline</td>
<td>Normal</td>
<td>38</td>
</tr>
<tr>
<td>28</td>
<td>ERCC6</td>
<td>Global developmental delay, scoliosis, hypotonia</td>
<td>Normal</td>
<td>Not tested</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Normal</td>
<td>38</td>
</tr>
<tr>
<td>29</td>
<td>ERCC6</td>
<td>Global developmental delay, scoliosis, hypotonia</td>
<td>Normal</td>
<td>Not tested</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Normal</td>
<td>38</td>
</tr>
<tr>
<td>30†</td>
<td>Unknown*</td>
<td>FCSMN: impaired tactile sensation, tongue fasciculations, bulbar signs, neck muscle weakness, shoulder girdle muscle atrophy</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Unpublished case</td>
</tr>
<tr>
<td>31†</td>
<td>Unknown*</td>
<td>FCSMN: impaired tactile sensation, tongue fasciculations, bulbar signs, neck muscle weakness</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Unpublished case</td>
</tr>
<tr>
<td>32†</td>
<td>Unknown*</td>
<td>FCSMN: impaired tactile sensation, tongue fasciculations, bulbar signs, neck muscle weakness, chorea</td>
<td>Borderline</td>
<td>Borderline</td>
<td>Not tested</td>
<td>Borderline</td>
<td>Abnormal</td>
<td>Unpublished case</td>
</tr>
<tr>
<td>33†</td>
<td>Unknown*</td>
<td>FCSMN: impaired tactile sensation, tongue fasciculations, bulbar signs, neck muscle weakness, shoulder girdle muscle atrophy, chorea</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Not tested</td>
<td>Borderline</td>
<td>Abnormal</td>
<td>Unpublished case</td>
</tr>
<tr>
<td>34†</td>
<td>Unknown*</td>
<td>FCSMN: Chorea, frontal lobe dementia, scoliosis, involuntary movements</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Not tested</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Unpublished case</td>
</tr>
<tr>
<td>35†</td>
<td>Unknown*</td>
<td>FCSMN: Chorea, muscle fibrillation, impaired tactile sensation</td>
<td>Borderline</td>
<td>Normal</td>
<td>Not tested</td>
<td>Borderline</td>
<td>Normal</td>
<td>Unpublished case</td>
</tr>
<tr>
<td>36†</td>
<td>Unknown*</td>
<td>FCSMN: Tongue fasciculations, skeletal muscle atrophy, sensorimotor neuropathy</td>
<td>Abnormal</td>
<td>Borderline</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Unpublished case</td>
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<tr>
<td>37†</td>
<td>Unknown*</td>
<td>FCSMN: Tongue fasciculations, bulbar signs, neck muscle weakness, shoulder girdle muscle atrophy</td>
<td>Normal</td>
<td>Normal</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Unpublished case</td>
</tr>
</tbody>
</table>

Points for discussion

• Is presence of biochemical abnormalities necessary in at least a few patients?
  – if not, follow a “pathway-approach”?

• Different pathomechanisms, different disease?
  – COG4-CDG vs COG4-SWS
  – XLD vs XLR ALG13-CDG
  – EXT2-MHE vs AREXT2

• Degradation disorders?

• Secondary glycosylation abnormalities?

• Unified ICIMD
Obrigado!