Congenital Disorders of Glycosylation (CDG)

Administration Office
c/o EMQN CIC, Unit 4, Enterprise House
Manchester Science Park Pencroft Way,
Manchester, M15 6SE, United Kingdom.
Tel: +44 161 757 4952
Fax: +44 161 850 1145
Email: admin@erndim.org

Scientific Advisor
Dr Dulce Quelhas
Unidade Bioquimica Genetica
Centro de Genetica Medica Jacinto de Magalhaes, Centro Hospitalar do Porto, EPE, Pr Pedro Nunes 88
Porto, 4099-028, Portugal
Email: dulce.quelhas@chporto.min-saude.pt

Scheme Organisers

1. Sample dispatch

Dr Eline van der Hagen
Streekziekenhuis Koningin Beatrix
MCA Laboratory
Beatrixpark 1
7101 BN Winterswijk
The Netherlands
Email: mca.office@skbwinterswijk.nl

2. Results Website

1) Alessandro Salemma; **2)** Nicola Braik
CSCQ, Swiss Center for Quality Control
2 chemin du Petit-Bel-Air
CH-1225 Chêne-Bourg
Switzerland
Email: 1) Alessandro.Salemma@hcuge.ch;
2) Nicola.Braik@hcuge.ch

Annual Report 2022

Version Number[1]: 01
Date of issue: 11 July 2023

Note: This annual report is intended for participants of the ERNDIM CDG EQA scheme. The contents should not be used for any publication without permission of the Scientific Advisor.

The fact that your laboratory participates in ERNDIM schemes is not confidential, however, the raw data and performance scores are confidential and will only be shared within ERNDIM for the purpose of evaluating your laboratories performance, unless ERNDIM is required to disclose performance data by a relevant government agency. For details, please see the ERNDIM Privacy Policy on www.erndim.org.

1. Scheme Design

The scheme has been designed and planned by the Scientific Advisor (SA) and Scheme Organisers (SO, listed at the top of this page), both appointed by and according to procedures laid down by the ERNDIM Board.

a. Sub-contracted activities:

The samples were aliquoted and dispatched by MCA Laboratory, Netherlands, while the results website (https://cscq.hcuge.ch/cscq/ERNDIM/Initial/Initial.php) is hosted and maintained by CSCQ (Swiss Centre for Quality Control), both on behalf of ERNDIM.

2. Samples

Samples were selected by the Scientific Advisor and tested for suitability in the Scientific Advisor's laboratory (Unidade Bioquimica Genetica, Centro de Genética Médica Jacinto de Magalhães, Centro Hospitalar Universitário do Porto, Portugal). Preparation and dispatch of the EQA samples was done by the relevant Scheme organiser (MCA Laboratory, Winterswijk, Netherlands). All EQA materials are lyophilised plasma or serum samples (25 µl). Laboratories that need a larger sample volume due to their analysis method (e.g., HPLC) were sent extra sample sets for a reduced scheme price.

For the 2022 scheme, 2 samples were provided by the Scientific Advisor, 2 by Dr. Rafael Artuch, from Laboratorio de Bioquímica, Hospital San Joan de Déu, Barcelona, Spain, and 2 by the MCA Laboratory. All samples were obtained following local ethical and consent guidelines.

To be able to continue this scheme we need a steady supply of new patient samples. If you have one or more samples available and are willing to donate these to the scheme, please contact us at admin@erndim.org. Laboratories which donate samples that are used in the scheme are eligible for a 20% discount on the CDG scheme fee in the following year.

[1] **If this Annual Report is not Version 1 for this scheme year, go to APPENDIX 2 (page 7) for details of the changes made since the last version of this document.**

3. **Shipment**
The six samples were sent to the 62 registered laboratories in one parcel on 8th February 2022. Twenty-two laboratories requested a total of 32 extra sample sets and were sent the larger sample volume.

4. **Receipt of results**
Results were submitted to an online results website (cscq.hcuge.ch/cscq/ERNDIM/) which is hosted and maintained by CSCQ. The submission deadlines for the first round (samples CDG-PP-2022-A, -B and -C) and second round (samples CDG-PP-2022-D, -E and -F) were 16th May 2022 and 19 September 2022 respectively. Overall, 59/62 (95%) registered participants submitted results for the 2022 scheme: 54 (87%) laboratories submitted results on time for both submission rounds, with a further 4 laboratories (6.5%) submitting results after the deadlines (2 for each submission deadline). One lab (1.6%) only submitted results for the second round. While a separate three laboratories (4,8%) failed to make a return on either submission round; of these one withdrew from the scheme.

5. **Scoring scheme**
In agreement with ERNDIM rules, we applied a scoring system of 2+2:

Technical aspects: 1 point for identification of an abnormal profile and 1 point for correct identification of the profile as type I or II.

Diagnostic suggestions: This section should be filled for scoring. Just referring to a specialised lab is insufficient. If required, advice can be obtained from a reference laboratory or in collaboration with a clinical colleague. For normal profiles 2 points are scored. For abnormal profiles, comments should be made on the possibility of the presence of a secondary cause in light of the clinical indication. In addition, the correct suggestions should be made for the next step in the diagnostic process that eventually will lead to identification of the genetic defect. Scoring for this part is not so straightforward, but we tried to keep it as consistent as possible. The maximum score achievable with full submission for all samples is 24, while a maximum of 12 points are available for labs that only submitted results for the first or second round. The level for satisfactory performance is 17 points.

For the 2022 scheme onwards, labs that only submit results for 3 or fewer samples in a scheme year will be classed as partial submitters and their performance will not be evaluated. This information is included in the CDG scheme instructions for 2022 onwards. Partial submitters receive a formal Non-submitter letter notifying them of this status and their certificate of participation shows them as not submitting results for the relevant scheme. As the number of participants in the CDG scheme are limited due to the nature of the EQA samples, ERNDIM reserves the right to exclude participants that are classed as partial/non-submitters for 2 out of 3 registered years (i.e., persistent partial and non-submitters) from the scheme.

For the 2014 scheme onwards, another criterion for satisfactory performance is the absence of any “critical error”, which is defined as an error resulting from seriously misleading analytical findings and/or interpretations with serious clinical consequences for the patient. For the 2022 CDG scheme, 2 critical errors were identified. These were agreed at the meeting of the Scientific Advisory Board on 24th and 25th November 2022.

a. **Appeals**
If your laboratory has been assigned poor performance in the 2022 scheme and you wish to appeal against this classification, please use the link given in the Performance Support letter you received to submit your appeal request. The online form should be completed with full details of the reason for your appeal and submitted within one month of receiving your Performance Support Letter. Please note that only appeals submitted using the online response form will be considered.

6. **Results of samples and evaluation of reporting**
The shipped samples were from (CDG) patients and from controls and from a confirmed individual with alcohol abuse. The final results of the six samples with respect to CDG are summarized in Table 1 below.

Table 1: Samples in the 2022 scheme

Sample	Clinical information (age, sex, phenotype)	Diagnosis
CDG-PP-2022-A	F, 10 years, Epileptic encephalopathy, facial dysmorphic features	Normal
CDG-PP-2022-B	M, 1-year, Bilateral congenital hip dislocation, facial dysmorphic features, microcephaly	ATP6V0A2-CDG
CDG-PP-2022-C	M, 3 years, Autistic spectrum behaviour, seizures, deafness	Transferrin polymorphic variant
CDG-PP-2022-D	F, 19 years, Liver fibrosis, increased transaminases	Normal
CDG-PP-2022-E	M, 4 months, Hypoglycaemia, hepatomegaly, proximal tubulopathy	Hereditary fructose intolerance (HFI)
CDG-PP-2022-F	M, 16 years, Intellectual disability, ataxia, low factor XI	PMM2-CDG

All submitted results are treated as confidential information and are only shared with ERNDIM approved persons for the purposes of evaluation and reporting.

For the laboratories that reported their method (59/59, Isofocusing was the method employed most often (19/59), followed by CE (15/59), HPLC (13/59), Mass Spectrometry (7/59) and Other (5/59).

Table 2: Scoring of samples in the 2022 scheme

Sample	No of returns	Technical Aspects (%)	Diagnostic Suggestions (%)	Total (%)
CDG-PP-2022-A	58	96.6%	97.4%	97.0%
CDG-PP-2022-B	56	75.0%	97.3%	86.2%
CDG-PP-2022-C	58	100%	98.3%	99.2%
CDG-PP-2022-D	58	100%	100%	100%
CDG-PP-2022-E	58	95.7%	99.1%	97.4%
CDG-PP-2022-F	55	92.7%	96.4%	94.5%

Table 3: Distribution of scores (for labs that submitted sufficient results for performance to be assessed)

Total Score	No of labs
<60%	0
60 – 69.9%	2
70 – 79.9%	1
80 – 89.9%	7
90 – 99.9%	18
100%	30
Total	**58**

The full anonymised results for all labs that submitted results are given in APPENDIX 1 on page 6 of this report.

CDG-PP-2022-A: Normal

Almost all laboratories reported this sample as normal resulting in a proficiency score of 97.0%.

An abnormal profile interpretation of this sample, without additional Diagnostic Suggestions, was considered a critical error by the Scientific Advisory Board (SAB).

CDG-PP-2022-B: ATP6V0A2-CDG

A type 2 profile was identified by nearly all laboratories and interpreted as abnormal by nearly all as well, resulting in a total proficiency score of 86.2%. The pattern was a classical type 2 pattern and no major differences were noticed when comparing the performance of different methods.

The clinical symptoms are, however, very suggestive of ATP6V0A2-CDG. Therefore, in case of interpretation of a profile as CDG-II, a neuraminidase treatment should be performed to exclude transferrin polymorphism. Identifying the profile as abnormal and indicating ATP6V0A2-CDG -CDG/CDG II as a possible diagnosis and/or suggestion for NGS/WES should be included for total scoring.

A normal profile interpretation of this sample, without additional Diagnostic Suggestions, was considered a critical error by the SAB.

CDG-PP-2022-C: Transferrin polymorphic variant

Most labs using IEF or CE reported an abnormal profile of transferrin, either directly suggesting a protein polymorphism or an abnormal type II profile, resulting in a total proficiency score of 99.2%. It is important to note that the polymorphism was only visible by IEF or CE and not by HPLC, WB, and mass spectrometry. The presence of a polymorphism is clinically without any complication, but this could complicate the interpretation of the profile type. Some labs performed neuraminidase incubation and confirmed the presence of a transferrin polymorphism. For IEF, this additional band migrates precisely at the position of trisialotransferrin, while for CE, the polymorphism is found at the position of pentasialotransferrin or disialotransferrin.

For IEF, the presence of an additional band at trisialotransferrin could also be indicative for MAN1B1-CDG, and care should be taken to really exclude or confirm this polymorphism, in order not to miss a diagnosis of a MAN1B1-CDG. Below, in Figure 1, is shown a transferrin IEF of a MAN1B1-CDG and transferrin polymorphism sample, showing the high level of similarity. Only a single lab suggested the possibility of a MAN1B1-CDG.

MAN1B1-CDG Tf variant Normal ct

Figure 1 – Tf IEF profiles of MAN1B1-CDG, Tf variant and normal control samples. MAN1B1-CDG can resembles a Tf variant Tf IEF pattern

A normal profile interpretation of this sample was not considered a critical error by the SAB, as the presence of a polymorphism is clinically without any complication.

CDG-PP-2022-D: Control

All laboratories reported this sample as normal, resulting in a proficiency score of 100%.

An abnormal profile interpretation of this sample, without additional Diagnostic Suggestions, was considered a critical error by the Scientific Advisory Board (SAB).

CDG-PP-2022-E: Non CDG – untreated Hereditary Fructose intolerance - Secondary cause

A type 1 profile was identified by most laboratories and interpreted as abnormal by nearly all participants, resulting in a proficiency score of 97.4%. Before proceeding with further diagnostics, it is important to rule out secondary causes of abnormal transferrin profiles, such as fructosemia, galactosemia, alcohol abuse and bacterial sialidase.

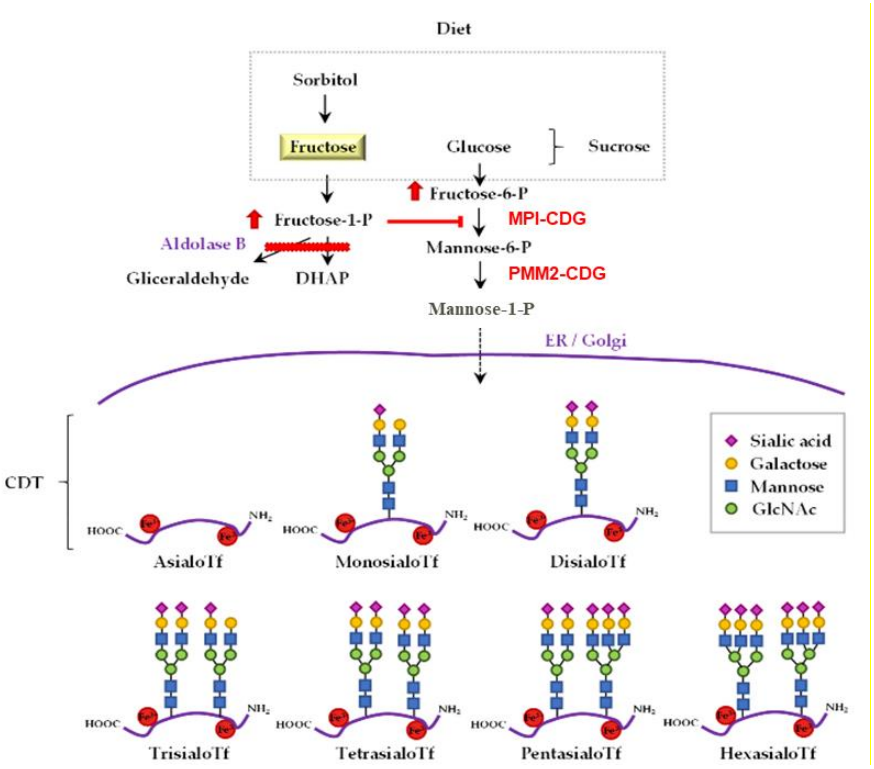

Figure 2 – The connection between fructose metabolism and the profile of sialotransferrins in hereditary fructose intolerance. HFI patients accumulate fructose-1-P (F1P) in the liver due to aldolase B deficiency. Consequently, these patients exhibit abnormal transferrin (Tf) glycosylation patterns because of F1P-mediated competitive inhibition of mannose-6-phosphate isomerase (MPI). In: Transferrin Isoforms, Old but New Biomarkers in Hereditary Fructose Intolerance. Cano, A. et al. J. Clin. Med. 2021, 10, 2932. https://doi.org/10.3390/jcm10132932

A normal profile interpretation of this sample, without additional Diagnostic Suggestions, was not considered a critical error by the SAB, as this is a secondary cause of abnormal pattern.

CDG-PP-2022-F: PMM2-CDG

A type 1 profile was identified and interpreted as abnormal by most laboratories, resulting in a proficiency score of 94.5%. The pattern was a classical type 1 pattern, and no significant differences were noticed when comparing the performance of different methods. The clinical symptoms are, however, somewhat suggestive of PMM2-CDG. Therefore, in case of interpretation of a profile as type 1, a diagnosis of PMM2-CDG should be advised in this situation.

Identification of the profile as abnormal and indicating PMM2-CDG as a possible diagnosis should be included for total scoring. A normal profile interpretation of this sample, without additional Diagnostic Suggestions, was considered a critical error by the SAB.

7. **Preview of the 2023 scheme**
   No changes are planned for the 2023 scheme.

8. **Questions, Comments and Suggestions**
   If you have any questions, comments or suggestions in addition to specific user comments please contact the ERNDIM Administration Office (admin@erndim.org).

9. **Confidentiality Statement**
   This annual report is intended for participants of the ERNDIM Congenital Disorders of Glycosylation scheme. The contents of this report or data derived from the use or analysis of ERNDIM EQA materials must not be used in written publications or oral presentations unless the explicit prior consent of ERNDIM has been granted.

Dr Dulce Quelhas
Scientific Advisor

APPENDIX 1. Detailed scores for submitting laboratories

* CE = Critical Error

2022	Technical, item C							Advice, item D								
Sample ID	A	B	C	D	E	F		A	B	C	D	E	F			
Average score / Lab ID	1.93	1.50	2.00	2.00	1.91	1.85	Total	1.95	1.95	1.97	2.00	1.98	1.93	Total	Total score (max 24)	CE*
1	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
2	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
3	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
4	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
5	2		2	2	2		8	2		2	2	2		8	16	
6	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
7	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
8	2	0	2	2	2	2	10	2	2	2	2	2	2	12	22	
9	2	0	2	2	2	2	10	2	2	2	2	2	2	12	22	CE*
10	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
11	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
12	2		2	2	2	2	10	2		2	2	2	2	10	20	
13	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
14	2	0	2	2	2	2	10	2	2	2	2	2	2	12	22	
15	2	2	2	2	2	0	10	2	0	2	2	2	0	8	18	CE*
16	2	0	2	2	2	2	10	2	2	2	2	2	2	12	22	
17	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
18	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
19	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
20	2	0	2	2	2	0	8	2	2	2	2	2	2	12	20	
21	2	2	2	2	2	0	10	2	2	2	2	2	0	10	20	
22	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
23	2	1	2	2	1	2	10	2	2	2	2	2	2	12	22	
24	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
25	2	1	2	2	2	2	11	2	1	2	2	2	2	11	22	
26	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
27	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
28	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
29	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
30	2	2	2	2	0	2	10	2	2	2	2	2	2	12	22	
31	2	1	2	2	0	2	9	2	2	2	2	1	2	11	20	
32	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
33	2	0	2	2	2	0	8	2	2	2	2	2	2	12	20	
34	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
35	0	2	2	2	2	2	10	0	2	2	2	2	2	10	20	
36	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
37	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
38	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
39	2	0	2	2	2	2	10	2	2	2	2	2	2	12	22	

2022	Technical, item C							Advice, item D							Total score (max 24)	CE*
Sample ID	A	B	C	D	E	F		A	B	C	D	E	F			
Average score / Lab ID	1.93	1.50	2.00	2.00	1.91	1.85	Total	1.95	1.95	1.97	2.00	1.98	1.93	Total		
40	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
41	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
42	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
43	0	2	2	2	2		8	1	2	0	2	2		7	15	
44	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
45	2	0	2	2	2	2	10	2	2	2	2	2	2	12	22	
46	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
47	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
48	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
49	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
50	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
51	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
52	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23	
53	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
54	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
55	2	2	2	2	2		10	2	2	2	2	2		10	20	
56	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
57	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	
58	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24	

APPENDIX 2. Change log (changes since the last version)

Version Number	Published	Amendments
1	11 July 2023	• 2022 annual report published

END OF REPORT