**Mayo Clinic Institutional Review Board**
**IRB Research Protocol**

**Study Title:** Dietary monosaccharide supplementation in patients with congenital disorders of glycosylation

## 1. Study Aim, Background, and Design

Congenital disorders of glycosylation (CDG) are a group of recently discovered metabolic disorders that disrupts the pathways by which sugars are broken down and built in a person's body[1]. Congenital disorders of glycosylation (CDG) cause severe metabolic abnormalities in patients, including hypoglycemia (low blood sugar levels), abnormal liver function, abnormal hormone levels, recurrent infections, muscle symptoms, and developmental problems[2–4]. The symptoms occur due to changes in the normal structure and attachment of the sugar chains on the surface of body proteins[5–7]. The development of effective interventions for congenital disorders of glycosylation is limited because of our poor understanding of the disease. Simple sugars (monosaccharides) such as mannose, galactose, and fucose have been applied as dietary supplements[8–15]. Increased intake of simple sugars has previously shown beneficial effects on the sugar chain structure on body proteins (this is called glycosylation) initially in 9 patients with PGM1 deficiency[16]. The positive effects of monosaccharide supplementation have been demonstrated in cell culture studies of patients as well[16]. Since then, patients with other types of CDGs have been trialed on simple sugar supplements with success[17–19.]

The goal of this study is to collect data from patients diagnosed with congenital disorders of glycosylation and taking a simple sugar supplement. Literature supports that adding these simple sugars to the diet of patients with congenital disorders of glycosylation will improve or normalize specific physiological biomarkers of protein glycosylation. We want to expand the evidence on the beneficial effects of this treatment in clinical practice. The knowledge gained from the investigation of this aim will help us better understand the disrupted metabolic mechanisms underlying these diseases and lead to the identification of new disease biomarkers that can be used to evaluate clinical efficacy in future therapeutic trials[20,21].

Over a two-year period, we will enroll patients diagnosed with congenital disorders of glycosylation and started on oral simple sugar supplements as part of their routine clinical care. To assess the effects of oral monosaccharide supplementation for each participant, changes in participant growth parameters, as well as blood sugar levels, coagulation parameters, liver function, and other measures of organ system function (as appropriate for the specific type of CDG) will be correlated with biomarkers derived from participant blood and urine samples obtained at key time points and then compared to standard normative ranges of data for each measure.

## 2. Subject Population

Over a two-year period, we plan to enroll 15 subjects diagnosed with congenital disorders of glycosylation confirmed by enzyme deficiency in fibroblasts and the presence of two

pathogenic mutations. It is expected that most of these participants will be younger than 21 years old.

The major inclusion criteria for this study are as follows:

Patient has a biochemically and genetically proven congenital disorder of glycosylation

Patient is receiving (or planning to receive) oral simple sugar supplementation

The major exclusion criteria for this study are as follows:

Patient has any of the following conditions:

- Aldolase B deficiency
- Galactosemia
- Hemolytic uremic syndrome
- Severe anemia
- Galactose intolerance

Patient experiences any of the following severe side effects from oral monosaccharides:

- Diarrhea
- Vomiting
- Constipation
- Galactosuria (galactose in the urine)
- Increased liver glycogen storage
- Fatty liver disease

Recruitment will occur in person through the medical genetics clinic under the direction of the principal investigator. The appropriate approved consent and assent documents will be discussed and then be used to enroll each willing participant.

To ensure an adequate number of participants in this study, recruitment will be ongoing. If participants drop out of the study, we will invite other congenital disorders of glycosylation patients from the medical genetics clinic to participate.

## 3. Procedure

1. The participant will remain on his/her regular diet and will be asked to continue their oral monosaccharide supplement as directed by their biochemical geneticist.

2. We collect clinical data from the participant's chart during the period of simple sugar supplementation directed by their biochemical geneticist. This typically includes history (including dietary history) and physical examination every 6 weeks to 6 months (appropriate for the type of CDG) after starting supplementation, blood and urine studies, and imaging and other studies (e.g., ECG, echocardiogram, EEG, and liver ultrasound) as appropriate.

3. No additional laboratory or imaging studies will need to be repeated as this is only a data collection study.

## 4. What is the timeline of the study?

The study investigations will abstract data collected from regular clinical outpatient appointments where each participant is seen throughout a minimum of 1-year of follow-up after starting simple sugar supplementation.

## 5. Risks

As with any study, there is a risk that confidentiality will be compromised. The following safety measures will be used to protect the confidentiality of each participant and his or her data:

1. The researchers will keep all study records (including any codes to data) locked in a secure location and all research records will be labeled with a unique code.
2. A master key that links names and codes will be maintained in a separate and secure location.
3. All electronic files (e.g., database, spreadsheet, etc.) containing identifiable information will be password protected.
4. Any computer hosting such files will also have password protection to prevent access by unauthorized users.
5. Only the members of the research staff will have access to the passwords.
6. Data that will be shared with others will be coded as described above to help disguise and protect patient identity.
7. At the conclusion of this study, the researchers hope to publish their findings. The information will be presented in summary format and no participant will be identified in any publications or presentations.
8. The data will be retained by the researcher without identifiers for possible use in a future project, which will be consistent with the original research purpose.
9. Any master key, audio recording, and any other data will be maintained in accordance with the listed security provisions until destroyed by the researchers.

## 6. Benefits

There are no direct benefits to participants that may be reasonably expected as a result of this research.

## 7. Remuneration

There will be no payment for participation in this research study.

## 8. Costs

This study will collect data as part of regularly scheduled visits to the clinic that are part of the standard treatment for patients affected by CDGs. As such, patients and their insurance will be responsible for paying for tests and procedures, including:

1. Costs of the simple sugar supplement;
2. Any additional laboratory or imaging done as part of routine clinical care
3. Clinical time spent by the principal investigator counseling and working with participants.

## 9. Alternatives

The alternative to participating in this project is to not participate.

## 10. Consent process and documentation

The principal investigator, site-specific co-investigators, or research assistants will review the study and all corresponding documents with any interested potential participants.

No research activity will be conducted until interested potential participants and their families or guardians review the study consent and assent forms, ask any questions, and sign the appropriate documents if interested in participating.

The consent form will give each participant and his or her family or guardians information about why this study is being done and why he or she is being invited to participate. It will also describe what the patient will need to do to participate and any known risks, inconveniences or discomforts that he or she may experience while participating.

Each participant and his or her family or guardians will be encouraged to take some time to think about participating and to discuss it with their family and doctor. The research staff will reinforce that the participant has the right to ask questions at any time. If a participant's parent or guardian signs the consent form and the participant signs the assent form, these forms will be documentation of the participant's agreement to participate. Each participant and his or her family or guardians will be given a copy of all signed forms for their records.

## 11. Qualifications of the Investigators

### Eva Morava, M.D., PhD. – Principal Investigator

Dr. Eva Morava completed her medical studies at the University of Pecs, Hungary, where she specialized in pediatrics and then worked as a staff member in first the Department of Pediatrics and then at the Department of Human Genetics. Dr. Morava furthered her training by completing the neonatology and biochemical genetics fellowship at Tulane University Medical Center.

Following this fellowship, Dr. Morava pursued more training in metabolic pediatrics, working from December 2002 at the Radboud University Nijmegen Medical Center (RUNMC) and then joining the staff as a metabolic pediatrician at the RUNMC beginning in 2004. In 2010, Dr. Morava joined the faculty of the Tulane University Medical Center Hayward Genetics Center as a board-certified biochemical geneticist. In 2018, Dr. Morava joined the clinical genomics faculty of Mayo Clinic.

Dr. Morava is a member of national and international committees and scientific advice groups on biochemical genetics. Her list of publications includes more then 150 peer-reviewed scientific papers. Dr. Morava's research group focuses on syndromic forms of inborn errors of metabolism. Her special interest lies in research of mitochondrial disorders and congenital disorders of glycosylation.

Dr. Morava maintains a strong collaboration with the Institute of Genetic and Metabolic Disease at the Radboud University Medical School and where she established the Nijmegen Center for CDG (www.nijmegencdg.nl). Dr. Morava is currently a full-time professor of pediatrics at Mayo Clinic in Rochester, MN.

**Shawn Tahata, M.D. – Co-Investigator**

Shawn Tahata graduated as a Regents Scholar from the University of Hawaii, Manoa in 2014 with a BS in Biochemistry and a BA in Anthropology. He subsequently completed his medical school training at the University of Pittsburgh School of Medicine. In medical school, Dr. Tahata conducted research on the use of sulforaphane as melanoma prevention in patients with multiple atypical nevi, and on the clinical outcomes of elderly patients with acute myeloid leukemia with induction chemotherapy and high-dose cytarabine consolidation therapy. Dr. Tahata is currently a first-year resident in internal medicine at Mayo Clinic in Rochester, MN.

## 12. References

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