Coagulation Factor Abnormalities in Patients with Congenital Disorders of Glycosylation

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Introduction

Congenital disorders of glycosylation (CDG) are a family of rare inherited genetic diseases that cause a variety of debilitating symptoms and often result in death in infancy or childhood[4].

- Glycosylation is a vital process in most cells of the human body, by which glycans are affixed onto proteins and lipids[2].
- There are two main types of glycosylation observed, N-glycosylation and O-glycosylation, each producing their own unique detrimental effects[2].
- Symptoms of CDG include physical and mental developmental impairments, muscular dysfunction, nutritional malabsorption, coagulation abnormalities and multisystem organ failure[1,5].
- Patients with PMM2-CDG are at higher risk for thrombosis and often exhibit coagulation problems[3]. It is especially important to consider coagulation difficulties when discussing surgery to reduce the risk of unexpected complications due to blood loss[6]. By determining which coagulation factors are most relevant to blood clotting, PMM2-CDG patients can be advised prior to having any surgical procedures.

Background

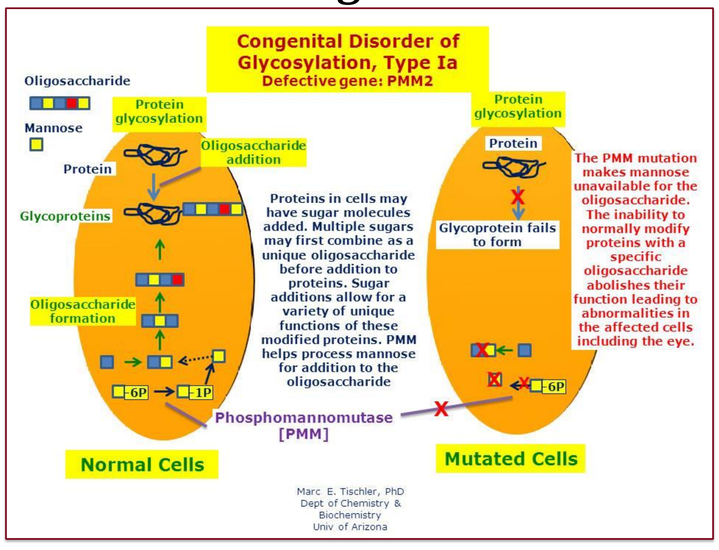

Figure 1. Diagram showing the pathophysiology of PMM2-CDG. In PMM2-CDG patients, a mutation in the phosphomannomutase enzyme prevents normal glycosylation for various proteins in the body, causing a wide range of ailments in several bodily systems[4].

Analysis

- **Methods**
  - Data on coagulation factors from a sample of n=50 patients at the Mayo Clinic with confirmed PMM2-CDG was collected and analyzed. Coagulation factors of interest were antithrombin III, prothrombin time, INR, Factor IX, Facter XI, and protein C. Following collection, patient data was de-identified and compiled in Microsoft Excel.
  - Patients' medical records will be further analyzed for known thrombotic events or other health conditions related to coagulation in an attempt to establish correlation between abnormal test results and past health history.

- **Results**
  - The most frequent coagulation protein abnormal results shown were antithrombin III, PT, INR, Factor IX, Factor XI, and protein C. The readings of INR and PT were usually elevated but all the rest of the coagulation factors were lower than normal. Notable results were visualized as scatterplots made using Microsoft Excel, shown below. The normal range is highlighted in green.

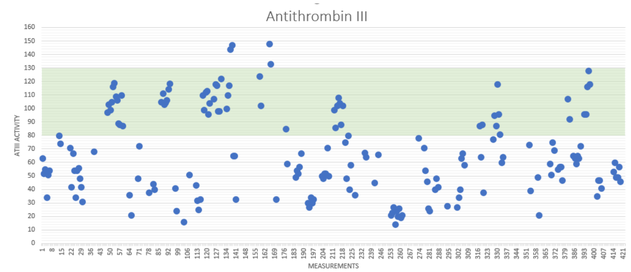

Figure 2: Scatterplot showing the distribution of antithrombin III results.

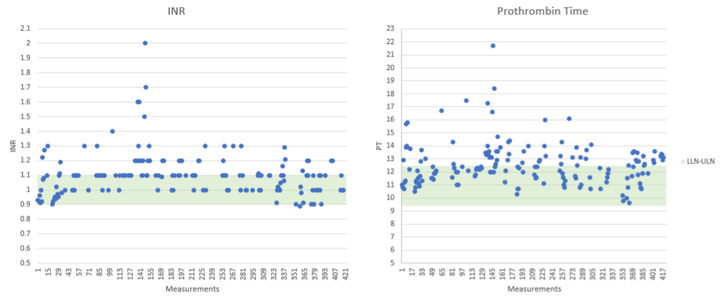

Figure 3: Scatterplot showing the distribution of INR (left) and PT (right) results.

Conclusions and Future Research

Based on the results observed in this study, we conclude that antithrombin III, prothrombin time and INR are affected by mutations in the PMM2 gene. Abnormal readings of these coagulation factors were seen in most of the patients.

Further testing of coagulation factors in existing patients and new patients is advised to confirm or refute the conclusions in this project. Past medical history along with current health issues should be evaluated, as well as any coagulation abnormalities in family members.

Other factors of interest:

- Whether or not the coagulation factor readings change with the patient's age
- If there are any results that fluctuate between normal and abnormal over the course of the patient's life
- If there is any correlation between the patient's gender and the readings collected

Additionally, it would be noteworthy to determine if the quantity of proteins produced is normal but the glycosylation is hindered, therefore reducing the quantity of glycoproteins formed. We currently have glycoproteomics data on file for less than 20% of patients in the sample but can obtain data on the rest of the patients as well. This knowledge could help develop treatment therapies that can target the specific pathway that is affected.

It is of great importance to better understand the genotypes and phenotypes of this family of diseases, as well as develop more effective ways of improving the quality of life of those affected by them.

References

[1]Chang, I. J., He, M., & Lam, C. T. (2018). Congenital disorders of glycosylation. *Annals of Translational Medicine, (6)*24, 1-13. http://dx.doi.org/10.21037/atm.2018.10.45

[2]Jaeken, J. (2010). Congenital disorders of glycosylation. *Annals of the New York Academy of Sciences, (1214)*2010, 190-198. https://doi-org.ezp1.lib.umn.edu/10.1111/j.1749-6632. 2010.05840.x

[3]Linssen, M., et al (2013). Thrombotic complications in patients with PMM2-CDG. *Molecular Genetics and Metabolism, (109)*1, 107-111. https://doi-org.mclibrary.idm.oclc.org/10.1016/j.ymgme.2013.02.006

[4]Ng, B. J. & Freeze, H. H. (2018). Perspectives on glycosylation and its congenital disorders. *Trends in Genetics, (34)*6, 466-476. https://doi.org/10.1016/j.tig.2018.03.002

[5]Tischler, M. E. (n.d.) *Congenital disorder of glycosylation, type Ia* [Poster presentation]. University of Arizona. https://disorders.eyes.arizona.edu/disorders/congenital-disorder- glycosylation-type-ia

[6]Yuste-Checa, P., et al (2015). The effects of PMM2-CDG on the folding, activity, and stability of the PMM2 protein. *Human Mutation, (36)*9, 851-860. https://doi-org.ezp2.lib.umn.edu/10.1002/humu.22817