# Phosphoglucomutase-1 deficiency presented as adrenal insufficiency

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## Background

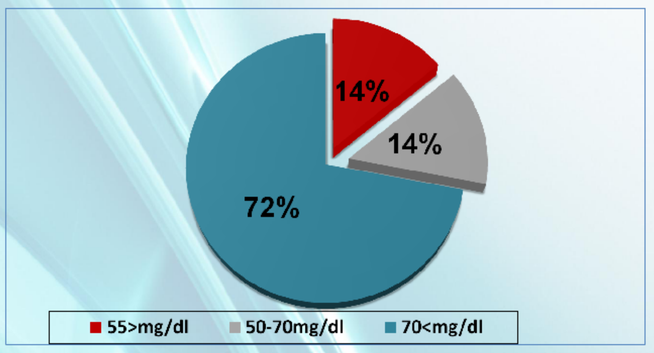
- Protein N-glycosylation is a common process in all organ systems
- During N-glycosylation, glycan precursors are assembled from monosaccharide units to generates mature glycoprotein
- The congenital disorders of glycosylation (CDG) are a group of genetic diseases due to defects in the biosynthesis of glycoprotein's and other glycoconjugates
- Phosphoglucomutase type 1(PGM1) deficiency has been recently classified among the congenital disorders of glycosylation (PGM1-CDG)

**Common clinical presentation:**

- Hepatopathy
- Bifid uvula
- Malignant hyperthermia
- Hypogonadotropic hypogonadism
- Growth retardation
- Hypoglycemia
- Myopathy
- Dilated cardiomyopathy, and cardiac arrest
- **ACTH deficiency has been rarely reported**

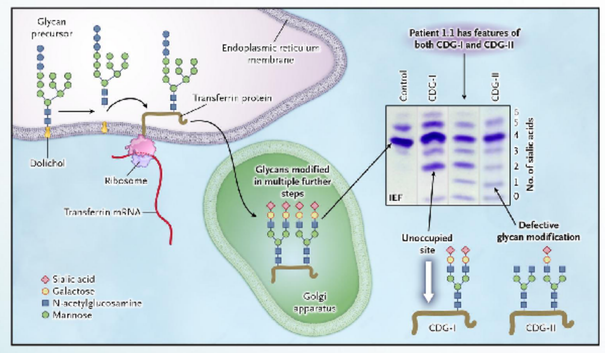
*L.C. Tegtmeyer Etal N Engl J Med 2014;370:533-42.*

**Fig 1. One week glucose distribution of pats. 1**



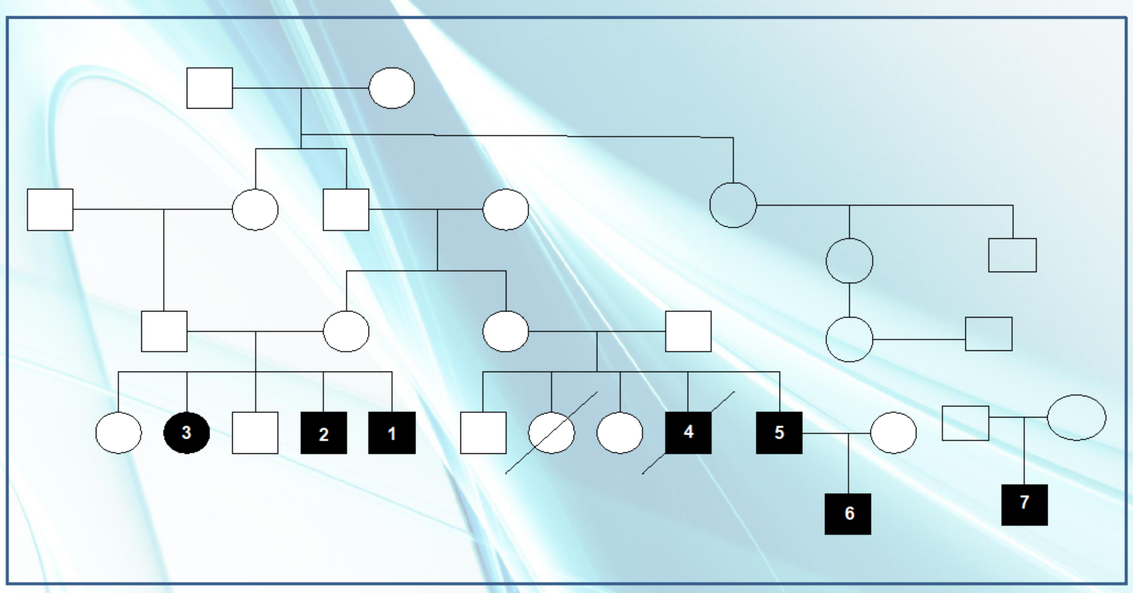

(continuous glucose monitoring data)

**Fig 2. Transferrin Isoelectric focusing**




Tegtmeyer LC et al. N Engl J Med 2014;370:533-542.

**FIG 3:Family Pedigree**




## Table 1. Patients' details

| patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Current age | 14 | 6 | 17 | Died 13.5 | 29 | 2 | 5 |
| Palate | Piere Rubin | Cleft palate | Cleft palate | Bifid uvula | Cleft palate | Bifid uvula | Bifid uvula |
| Abnormal liver function | yes | yes | yes | yes | yes | yes | yes |
| Hypoglycemic events | Severe recurrent | Severe recurrent | resolved | Severe recurrent | resolved | no | yes |
| Cortisol deficiency | yes | yes | mild | yes | | no | no |
| Current height SD | -3.2 | -1.2 | -2.7 | -2 | -3 | -1.9 | -3 |
| LH/ FSH | normal | | normal | | Fathered a child | | |
| Heart | normal | Normal | normal | Cardiac arrest | normal | normal | normal |
| Muscle CPK | normal | normal | normal | normal | normal | normal | |
| Pseudocholinesterase | low | Low | low | | low | | |
| Rhabdomyolysis | no | no | no | no | no | no | no |
| Learning disability | yes | | yes | | | | |

## Table 2. Progressive deteriorating Adrenal function in the patient

| patient | Age | Post hypoglycemia Acth level (3-10) Pmol/l | Post Low dose ACTH test. Cortisol level >20 ng,dl | Post Hypoglycemia Cortisol level >20 ng,dl | Post glucagon stimulstion Cortisol >20 ng,dl |
|---|---|---|---|---|---|
| 1 | 1 year | | 23 | 15 | |
| 1 | 4 years | <1 | 13 | 7 | |
| 1 | 6 years | 3 | 13 | 12.8 | 10 |
| 1 | 7 years | 1.6 | 13 | | |
| 1 | 11 years | | | | 0.5 |
| 2 | 5 days | | | | |
| 2 | 6 month | 5.4 | | 15.9 | |
| 2 | 3 years | | 4 | | |
| 2 | 4 years | 0.9 | | | |
| 3 | 4 years | | 19 | | |
| 3 | 8 years | | 18 | | |
| 4 | 1.5 years | | | 21 | |
| 4 | 4 years | | 13 | 5.9 | |
| 4 | 8 years | 2.8 | 13.8 | | |

## Genetic evaluation

- We performed a whole exome sequencing analysis (Otogenetics) and identified 11 homozygous
- The change: chr1 64059271 c.112A>T, p.Asn38Tyr in phosphoglucomutase 1 (PGM1) was predicted as damaging by Mutation-Taster, Polyphen and PhyloP (Fig 4)
- This variation was reported to be the causative mutation in In a 9-year-old girl with CDG1T (614921) and cleft palate, Pierre-Robin sequence, bifid uvula, increased serum creatine kinase, and abnormal liver enzymes by Tegtmeyer et al. (2014)
- Thus we verified its segregation in the family by PCR amplification In agreement with the suggestion that this is the causative mutation also in our patients we found it segregated as expected in the family
- Transferrin Isoelectric focusing revealed features of both CDG-I and CDG-II ( Fig 2)

**Fig 4. Details on PGM1 Structure and Mutation**

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## Conclusions

- **PGM1 deficiency should be suspected In cases with abnormal palate, disturbed liver function, recurrent hypoglycemia and short stature.**
- **Abnormal Transferrin Isoelectric focusing pattern can support the diagnosis of PGM1 deficiency**
- **ACTH deficiency should be considered in any PGM1 deficient patient with hypoglycemia**

I have nothing to disclose



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