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Fetal growth restriction due to maternal congenital hyperinsulinism associated with a novel variant in *GLUD1* and intrauterine diazoxide exposure

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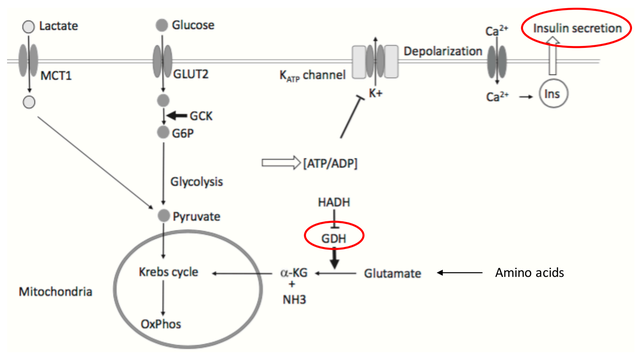
Introduction

Congenital hyperinsulinism (CHI) is a rare disease due to an inappropriate secretion of insulin by pancreatic β-cells. Most forms are due to loss-of-function mutations of *ABCC8* or *KCNJ11* genes, encoding the subunits of the K+ATP channel SUR1 and Kir6.2 (1-2). The second leading cause of CHI are gain-of-function mutations in the glutamate dehydrogenase (GDH) encoded by the *GLUD1* gene associated with an impaired ammonia processing (Hyperinsulinism-hyperammonemia syndrome) (3). Hypoglycemia will typically occur after fasting or after ingestion of a protein meal. GDH mediates conversion of glutamate to alpha-ketoglutarate and ammonia **(Figure 1**) (4). These mutations are dominantly inherited or the novo. In contrast to most K+ATP channel mutations, patient with *GLUD1* CHI respond to diazoxide treatment, a K^+ATP channel activator, but little is known about the potential teratogenic effects of this treatment during pregnancy.

Figure 1: Pancreatic β-cell
Oxidation of essential fuels like glucose and amino acids drives insulin secretion via increase of the ATP/ADP ratio. Adapted from Yorifuji, T. et *al* (4)



GLUT2: glucose transporter 2
GCK: glucokinase
G6P: glucose-6-phosphate
MCT1: monocarboxylate transporter 1
GDH: glutamate deshydrogenase
HADH1: L-3-hydroxyacyl-coenzyme A deshydrogenase
α-KG: α- ketoglutarate
Ins: Insulin

Table 1: Eleven genes of monogenic CHI

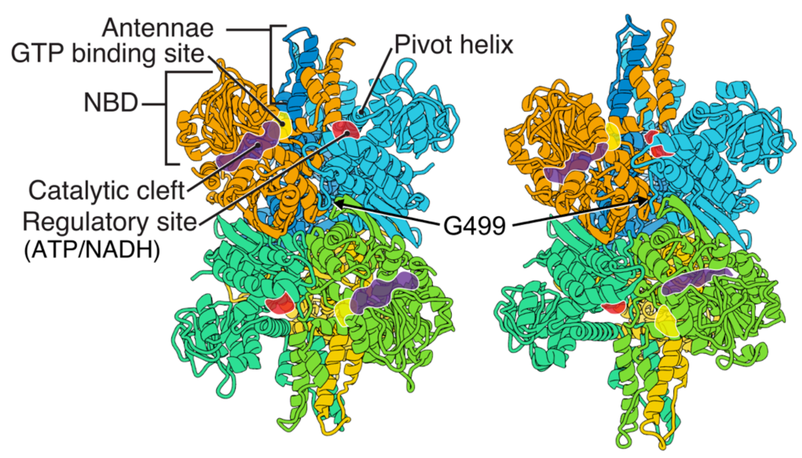
Monogenic CHI	Gene	Locus
SUR1	*ABCC8*	11p15.1
Kir6.2	*KCNJ11*	11p15.1
GHD	*GLUD1*	10q23.3
GCK	*GCK*	7p13
SCHAD	*HADH1*	4q25
UCP2	*UCP2*	11q13.4
HNF4A	*HNF4A*	20q13.12
HNF1A	*HNF1A*	12q24.31
MCT1	*SLC16A1*	1p13.2
HK1	*HK1*	10q22.1
PGM1	*PGM1*	1p31.3

Objective and Method

We report the neonatal outcome after fetal diazoxide exposure (50 mg t.i.d, 3 mg/kg/d) in the case of a maternal CHI.
Whole exome sequencing with bioinformatical targeted analysis of nine of the eleven genes known to cause monogenic CHI **(Table 1)** and one of the gene attributed to Beckwith-Wiedemann Syndrome (*CDKN1C*) was performed in the mother. Direct DNA sequencing of *GLUD1* was done in the newborn.

Results

Whole exome sequencing of the ten selected genes known to cause CHI revealed a maternal novel heterozygous missense *GLUD1* variant c.1496G>T; p.(Gly499Val), predicted to be pathogenic **(Figure 2)**. The mother was treated through the whole pregnancy with diazoxide 50 mg t.i.d and she presented one severe hypoglycemic episode at eleven weeks of gestation due to treatment omission. The newborn was born by cesarean section at 40 weeks of gestation with intrauterine growth restriction (IUGR), birth weight 2300g (<-2SD), length 46 cm (<-2SD), Head circumference 32.5 cm (<-2SD) and no visible malformations. Early feeding was started to prevent potential hypoglycemia. The genetic analysis showed that the newborn was not carrying the maternal *GLUD 1* variant. No structural anomalies were identified on the brain MRI done on day of life 10.



Adapted from Borgnia, M. J. *et al* (5). Using Cryo-electron microscopy to Map Small Ligands on Dynamic Metabolic Enzymes: Studies with Glutamate Dehydrogenase.
NBD, nucleotide binding domain.

Figure 2: **Gly499** locates to the central interface between the subunits of the GDH hexamer. This interface goes through significant structural changes when GDH transitions between open and closed state. GTP has an inhibitory control on GDH while ADP is a positive effector of the enzyme activity. The rate of transition between open and closed state and therefore substrate turnover might depend on the flexibility provided by a glycine at position 499 in the C-terminus.

Discussion and Conclusion

This is the case of a newborn at risk of inherited CHI who was exposed in utero to diazoxide and to maternal hypoglycemic episodes. This newborn had a 50% risk of inheriting CHI and fortunately he was unaffected. Reports of fetal exposure to diazoxide are limited, but in the past intravenous diazoxide has been used in pregnant women for its hypotensive action with risks of placental hypoperfusion, fetal death and transient neonatal hyperglycemia (6), with concentrations in the placenta and fetus supposed to be the same as in the mother. We did not identify postnatal glycemic deregulations in the newborn. However the newborn presented with IUGR, which could be due to limited metabolic fuel in the context of maternal and fetal hypoglycemia, an uteroplacental insufficiency or to a direct deleterious effect of diazoxide on the fetal growth. IUGR per se is a risk factor for hypoglycemia, for structural brain changes and for impaired cognition.
In conclusion, no structural brain anomalies attributable neither to teratogenicity of diazoxide, hypoglycemia nor to IUGR were observed on the brain MRI, however this child is at risk of neurodevelopmental/cognitive impairment and will have to be followed long-term. Functional MRI, investigations of learning and memory skills will have to be repeated.

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