Permanent neonatal diabetes mellitus due to a novel homozygous GCK mutation in a premature baby with IUGR and its management

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**Background**

Non-syndromic neonatal DM is most often due to gene variants in ABCC1, KCNJ11, INS or 6q24. Glucokinase (GCK) acts as the glucose sensor of β-islet cells, regulating insulin secretion in response to changing glucose concentrations. Heterozygous loss-of-function mutations lead to MODY 2, causing mild hyperglycaemia, which does not usually require treatment.1 Homozygous GCK mutations are a very rare cause of ND.2

**Index Case**

- Baby girl, born at 36+2 weeks gestation
- Birth weight 1610 g (0.4th centile)
- Consanguineous parents
- Hyperglycaemia (16-20 mmol/L) developed on day 1
- Insulin <1 mU/L, C-peptide 75 pmol/L
- Normal pancreas seen on USS

**Family history**

- Mother: gestational DM but remained on Metformin.
- Father and both grandmothers: Type 2 DM diagnosed at 40-50 years of age, treated with Metformin
- Two sisters: anti-GAD negative Type 1 DM from 12-13 years, treated with MDI insulin (HbA1c approximately 11%, insulin requirement 1-1.5 U/kg)

**Genetic analysis**

- Sanger sequencing: no mutations in ABCC8, KCNJ11, INS and EIF2AK3.
- Methylation analysis: normal 6q24 methylation.

**Functional Aspects of the c.661G>A GCK mutation**

- In the heterozygous state, p.Gly221Lys causes MODY 3
- Homozygous p.Gly221Lys has not previously been described
- Both sisters are homozygous for this mutation but only presented with diabetes at the age of 12-13 years.

**CSII Treatment**

- IV insulin at a dose of 0.6 – 0.8 U/kg was required
- CSII with Medtronic pump (640G).
- Medtronic Silhouette Teflon Cannulas (13mm), inserted at a shallow angle (5-10°) in the thighs.
- Medtronic pump adjustments: dilution of insulin x 10, low glucose suspend, manual corrections and manual boluses.
- At 6 months: insulin dose 0.5U/kg (35% basal), HbA1c 6.3%.

**References**

1. Steele AM, JAMA 2014; 311(3):279-286
2. De Franco, Lancet 2015; 386:957-63
3. Guazzini B, Human Mutation 1997, Mutation in brief #162 (on line)

**Summary**

- Second homozygous GCK mutation in patients presenting with insulin dependent diabetes later in childhood.
- Specialist CSII therapy with neonatal adaptations allows for good control of neonatal diabetes.

![Image of a diagram](image-url)