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

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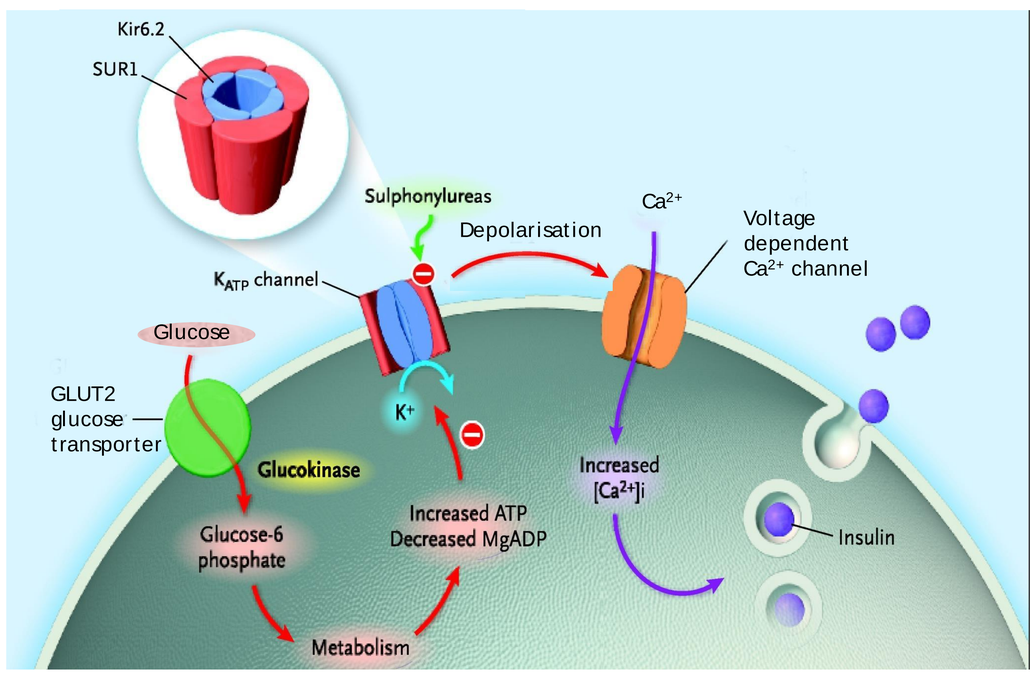
Background

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

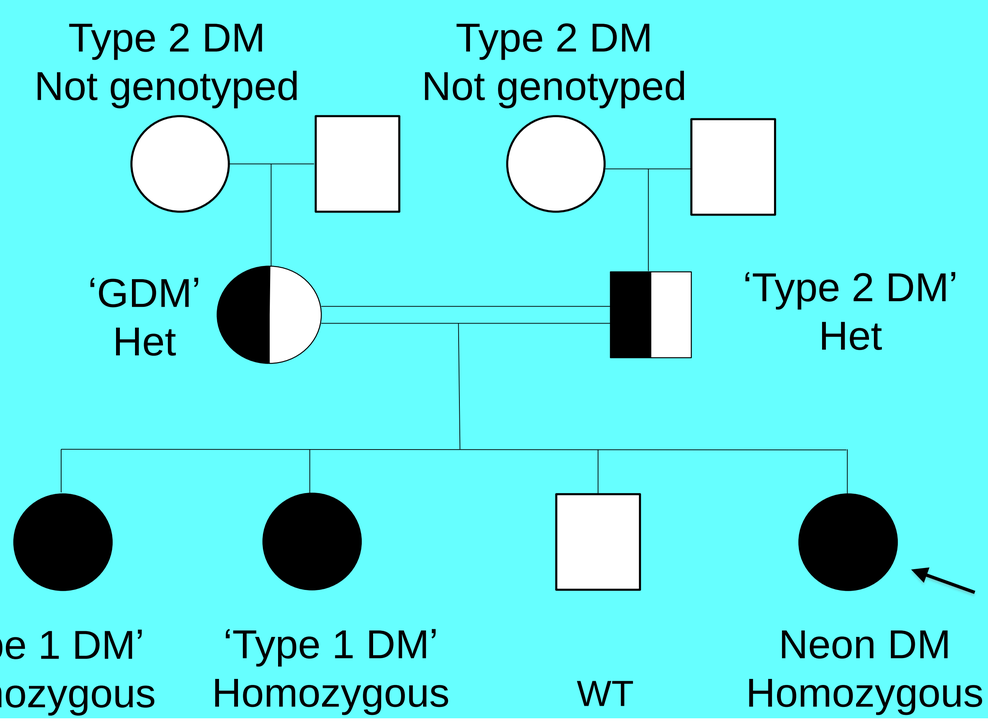
Family history

- 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.
- Targeted next-generation sequencing: homozygous missense mutation (c.661G>A, p.Gly221Lys) in a highly conserved region of *GCK*, coding for the hexokinase domain.

Genetic analysis for *GCK* c.661G>A

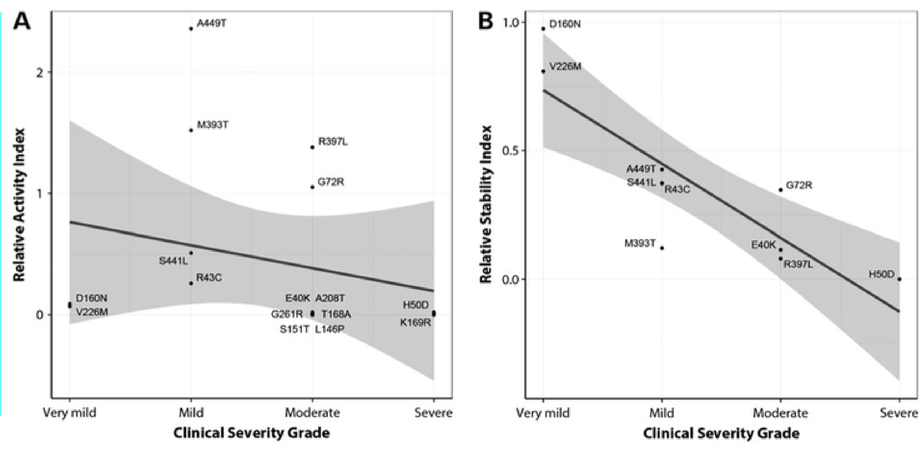


Functional Aspects of the c.661G>A *GCK* mutation

- In the heterozygous state, p.Gly221Lys causes GCK 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.

Functional activity of known missense mutations in GCK in NDM.

The only other GCK mutation described in DM developing at later age, is p.V224M (siblings at 9 and 15 yrs of age) which shows loss of function but good protein stability.[4]



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. Guazizini B, Human Mutation 1997, Mutation in brief #162 (on line)
4. Raimondo A, Hum Mol Genet 2014; 23: 6432–6440

Summary

- **First description of homozygous *GCK* p.Gly221Lys mutation in permanent neonatal diabetes.**
- **Second homozygous *GCK* mutation in patients presenting with insulin dependent diabetes later in childhood.**
- **Specialist CSII therapy with neonatal adaptations allows for for good control of neonatal diabetes.**

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