An infant with a novel Kir6.2 mutation causing neonatal diabetes and unexplained lack of response to sulphonylurea

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The authors have no disclosures

BACKGROUND

- Neonatal diabetes (NDM) is defined as diabetes developing before 6 months of age. Incidence 1 in 100,000 live births.
- Permanent NDM (PNDM) is diagnosed in the first six months of life with no remission.
- The majority have a mutation in the ATP-sensitive potassium (KATP) channel (KCNJ11 in 31%, ABCC8 in 13%).
- Autosomal dominant and recessive forms are described.
- The majority of patients with NDM caused by KATP mutations respond to sulphonylureas.

OBJECTIVES

- To describe response to sulphonylurea in an infant with NDM heterozygous for a novel KCNJ11 missense de novo mutation (W68G) and use of in vitro studies of sulphonylurea response to guide treatment.

CASE HISTORY

- A girl born at 37 weeks gestation. Severe intrauterine growth retardation.
- Maternal gestational diabetes in third trimester. Lean phenotype. Diet control.
- Mother Irish, father Sikh Indian
- Birth weight 1.95kg (<0.4th centile)
- Hyperglycaemia noted on day one of life
- Initially treated with subcutaneous insulin which was difficult due to size of infant and erratic glycaemic control.
- Novel KCNJ11 missense de novo mutation (W68G) diagnosed within 2 weeks.
- Glibenclamide commenced on day 20 of life. Dose slowly increased but failed to respond to dose 1mg/kg/day. Meanwhile, insulin pump commenced 2 months of life.

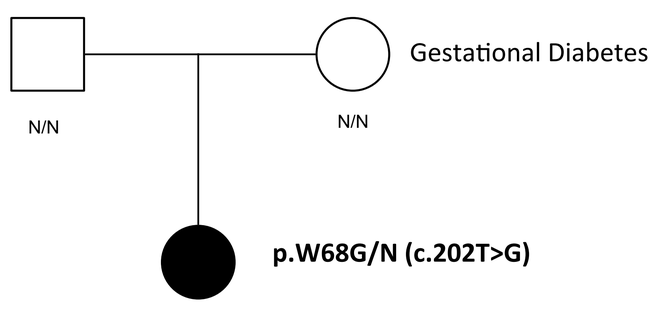

Figure 1: Family Pedigree. De novo mutation in patient.

RESULTS

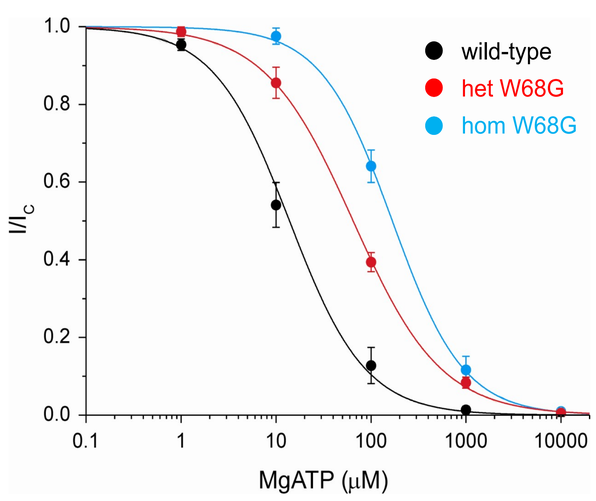

Figure 2: Concentration-inhibition relationship for ATP block of KATP currents in excised patches measured at -60mV in the presence of Mg. The IC50 for ATP block was 14 micromol/l (wild-type; n=6), 65 micromol/l (heterozygous; n=6) and 168 micromol/l (homomeric mutant; n=5). Physiological range of ATP concentrations inside pancreatic beta cells (1-5 mM) is indicated by the bar.

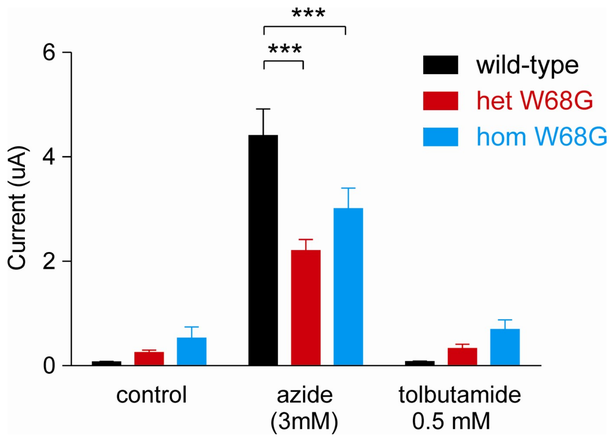

Figure 3: Steady-state whole-cell KATP currents evoked by a voltage step from –10 to –30 mV before (Control) and after application of 3 mmol/l Na-azide, and after application of 0.5mmol/l tolbutamide for oocytes injected with Kir6.2 (black; n=9), a 1:1 mixture of Kir6.2 and Kir6.2-W68G (red; n=10) or Kir6.2-W68G (blue; n=10) mRNA, plus SUR1 mRNA. (Two-way ANOVA followed by Bonferroni multiple comparison post-test; *** p<0.001).

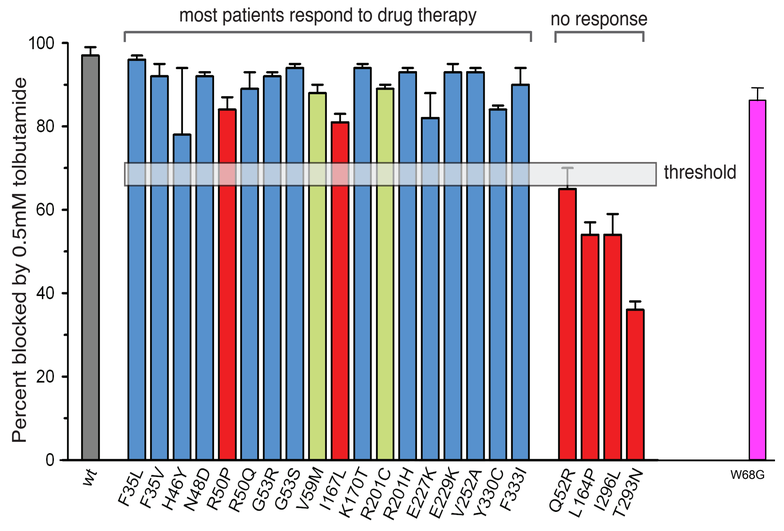

Figure 4: Showing the extent of block produced by the sulphonylurea tolbutamide for wild-type channels (>90%m, far left) and many different mutant channels. The gray bar indicates a crucial threshold. Almost all people who have the mutation that lies above the threshold can transfer to sulphonylurea therapy. None of those with mutations that lie below the line can transfer. Our patient with W68G mutation (in pink) clearly lies above the line indicating the patient should respond.

CLINICAL PROGRESS

- The patient failed to respond to oral glibenclamide up to a total daily dose (TDD) of 1mg/kg/day and was maintained on insulin pump therapy.
- Pancreatic autoantibody tests negative.
- In vitro studies showed the mutation reduced channel inhibition by ATP (Fig. 2,3) accounting for the diabetes. The mutant channel was sufficiently sensitive to sulphonylurea block (Fig 3) that the child would be expected to respond to glibenclamide.
- Glibenclamide was recommenced and slowly increased to a TDD of 2mg/kg/day. A clinical response was noted and expected therapeutic plasma levels were demonstrated.
- The patient has now successfully transferred off insulin and C-peptide response was also demonstrated.
- Improved HbA1c (51mmol/mol; normal range 20-42) along with better weight gain within six weeks.
- Excellent neurodevelopmental progress at one year of age.
- Three times daily dosing required to avoid frequent hypoglycaemia
- Polymorphisms in cyp 2c9 will be analysed.

SUMMARY/CONCLUSIONS

- This patient with a novel de novo Kir6.2 mutation failed to respond to standard doses of 1mg/kg/day of glibenclamide but has successfully responded to 2m/kg/day.
- In vitro studies of patients with novel mutations can help determine expected response to treatment.
- Comparing in vitro sulphonylurea response to that of other known mutations can guide management.

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