P3-92

Case of family neonatal diabetes with *KCNJ11* gene mutation : dynamics monitoring

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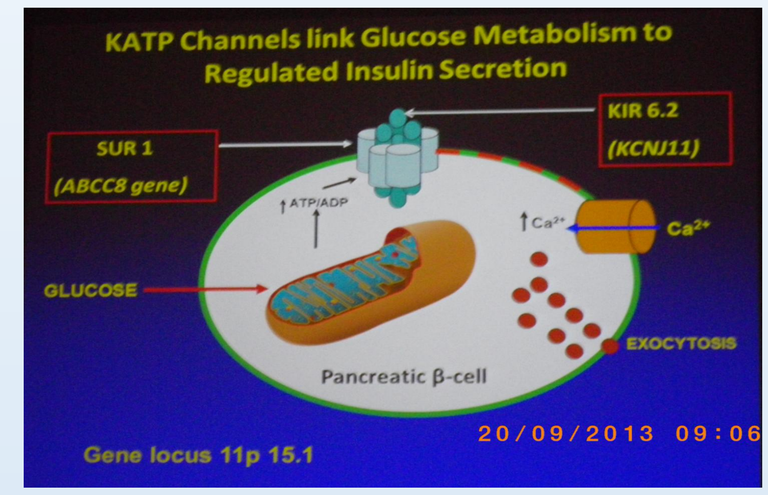
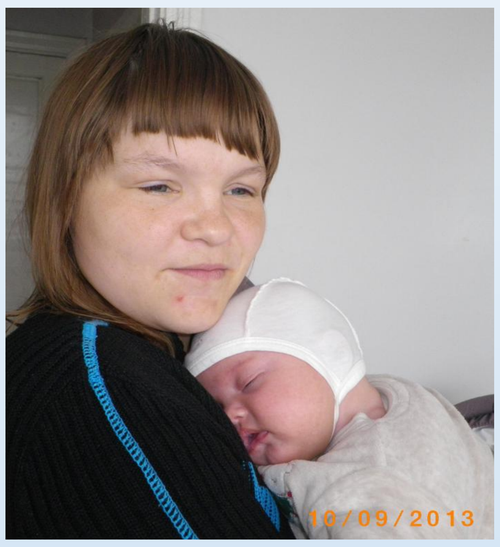
Background: Neonatal diabetes is a rare pathology occurring in around 1 in every 200,000- 400,000 live births. The most common cause of permanent neonatal diabetes (PNDM) is heterozygous activating mutations in the *KCNJ11* gene encoding the pore-forming Kir6.2 subunit of the pancreatic beta cell KATP channel.





CLINICAL CASE

Method: We studied a family (mother and child) with PNDM diagnosed within the first 6 months of life. Carbohydrate metabolism was studied by iPro- 2 monitoring, HbA1c, C-peptide and insulin levels during 8 months of SU therapy. The *KCNJ11* gene was sequenced by Sanger.

Objective and hypotheses: To determine the dynamic of carbohydrate metabolism in family transferred from insulin to sulphonylureas (SU).

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MOLECULAR GENETICS LABORATORY REPORT

Royal Devon & Exeter NHS Foundation Trust, Barrack Road, Exeter, EX2 5AD
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Patient Name: Alisa KEPOVA
Date of Birth: 17/06/2013
Gender: Female
Lab. No.: EX1309086
Sample Received: 07/08/2013
Sample Type: Whole Blood
Our Ref. No.: MY0924K
Referred by: Dr N Shulga, c/o Dr E Globa, Ukrainian Scientific Center of Endocrine Surgery, Kiev, Ukraine
Date of Report: 15/08/2013

GENETIC TESTING FOR NEONATAL DIABETES

Reason for Request
Alisa was diagnosed with diabetes at birth. There is a family history of diabetes affecting her mother who was diagnosed with diabetes at the age of 3 months. Mutation analysis of the *KCNJ11*, *ABCC8* and *INS* genes has been undertaken.

Test methodology
1. Analysis of coding and flanking intronic regions of the *KCNJ11* gene (NM_000525.3) by Sanger sequencing.
2. Analysis of all coding regions and exon/intron boundaries of the *INS* gene (NM_000207.2) by Sanger sequencing.
3. Analysis of all coding regions and exon/intron boundaries of the *ABCC8* gene (U63421 and L78208) by Sanger sequencing.

Result:	Heterozygous mutation identified
Mutation details:	Gene : *KCNJ11* Location : Exon 1 DNA Description : c.602G>A Protein Description : p.Arg201His (p.R201H) Consequence : Missense

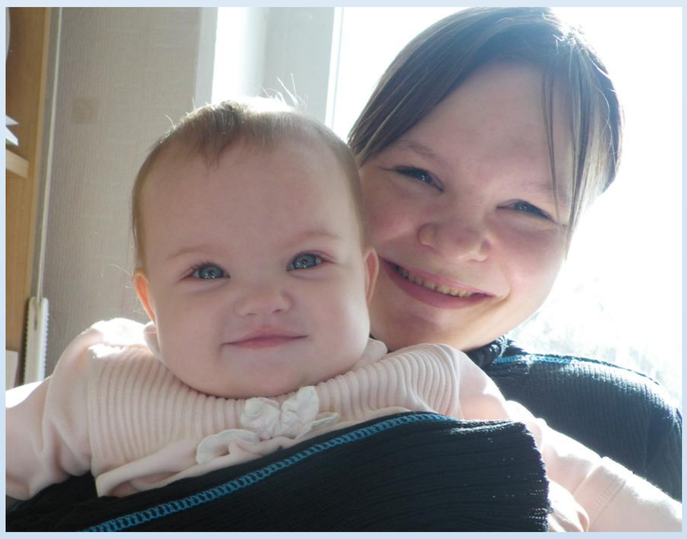
Interpretation
Alisa is heterozygous for a *KCNJ11* missense mutation, p.R201H. This mutation is predicted to be pathogenic and the result confirms a diagnosis of neonatal diabetes due to a mutation in the Kir6.2 subunit of the K-ATP channel (Gloyn *et al* 2004 N Engl J Med 350, 1838-1849). Transfer to sulphonylurea therapy has been successful for all patients with this mutation and results in improved glycaemic control (Pearson *et al* 2006 N Engl J Med 355, 467-477). Each of this patient's offspring will be at 50% risk of inheriting this mutation and developing neonatal diabetes.

This report depends upon, (I) - correct identification of all the samples, (II) - all biological relationships being correctly presented, (III) - accurate diagnosis of the affected individual(s). **Please note that this testing was undertaken as part of a research study.**

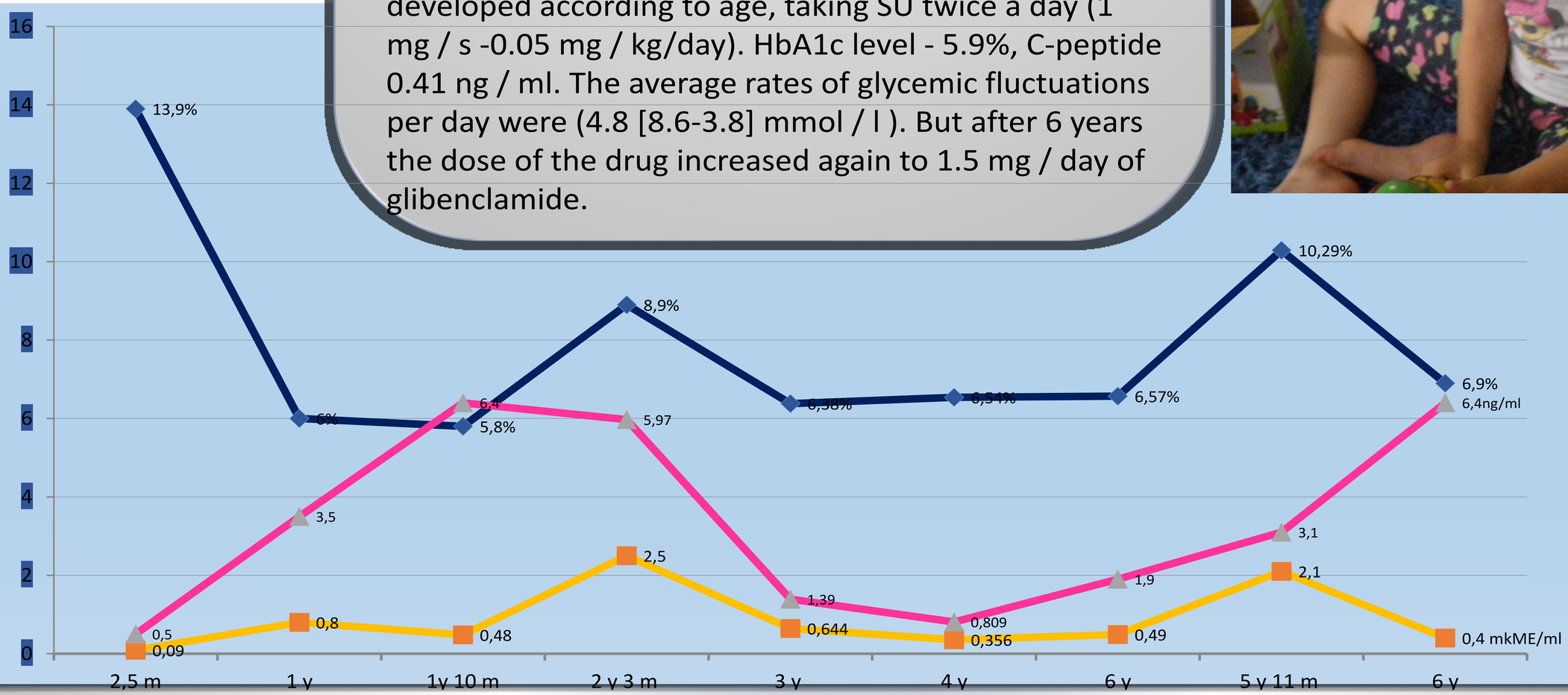
Andrew Parrish
Genetic Technologist

Jayne Houghton PhD
Clinical Scientist

Results:). the mutation in KCNJ11, R201H was identified in the child and the mother at the age of 2 months and 28 years. Insulin has been canceled. At the beginning of treatment, the child's daily dose of SU was divided into 6 doses (0.27 mg / kg / day) with each feeding, but at the age of 10 months, the frequency of taking the drug was 4 doses / day (0.17 mg / kg / day) . After 8 months of SU treatment, an improvement in glycemic control was observed (HbA1c level decreased 5.15% versus 13.9%). The level of C-peptide increased from 0.09 ng/ml to 0.5 ng/ml after 8 months of treatment of SU. Daily monitoring of glycemia showed a noticeable decrease in fluctuations in glycemia and improved glycemic control (from 13.8 [2.6-26.6] mmol / l before treatment with SU to 6.0 [3.3-10.2] mmol / l - after). After 5 years of monitoring, the child grew and developed according to age, taking SU twice a day (1 mg / s -0.05 mg / kg/day). HbA1c level - 5.9%, C-peptide 0.41 ng / ml. The average rates of glycemic fluctuations per day were (4.8 [8.6-3.8] mmol / l). But after 6 years the dose of the drug increased again to 1.5 mg / day of glibenclamide.



Dynamics of carbohydrate metabolism child A, 8 months and after 6 years follow-up in patients receiving 1.5 mg / day of glibenclamide



Conclusion: with the manifestation of diabetes mellitus during the first 6 months of life, the patient after genetic testing shows the pathogenetic treatment of SU. The daily dose of SU in a child over the course of 5 years of observation decreased on average by 40% from the initial dose due to the stabilization of carbohydrate metabolism. However, a decrease in the level of C-peptide by 20% from the initial **one** was also noted. However, when trying to reduce the dose of the drug, the compensation for carbohydrate metabolism worsened (HbA1c = 10,29%) and the dose again became the same (1.5 mg / day). Further observation required