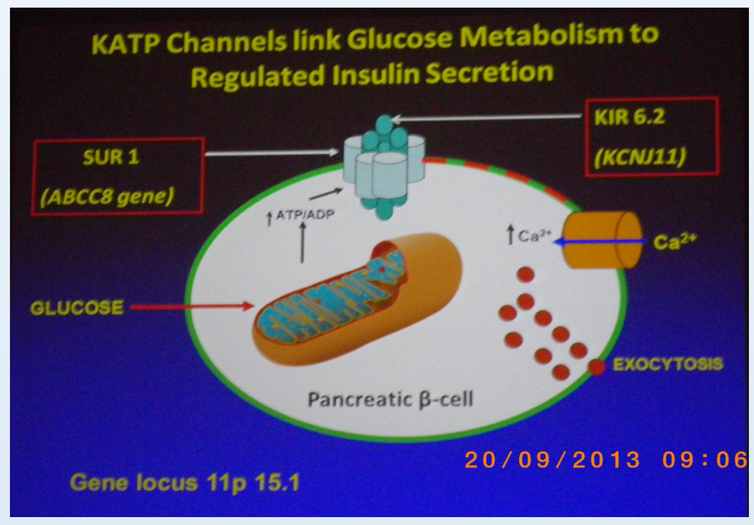
Clinical case of family neonatal diabetes with *KCNJ11* gene mutation

hrp0082P3-D2-714

Chumak S.O.[1], Budreiko O.A.[1], Globa E.V.[2], Hattersley A.T.[3], Ellard S.[3]

[1.]State Institution "Institute of Children and Adolescents Health Care" of NAMS of Ukraine
[2] Ukrainian Center of Endocrine Surgery, Endocrine Organs and Tissue Transplantation, MoH of Ukraine
[3] University of Exeter Medical School, UK.

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.

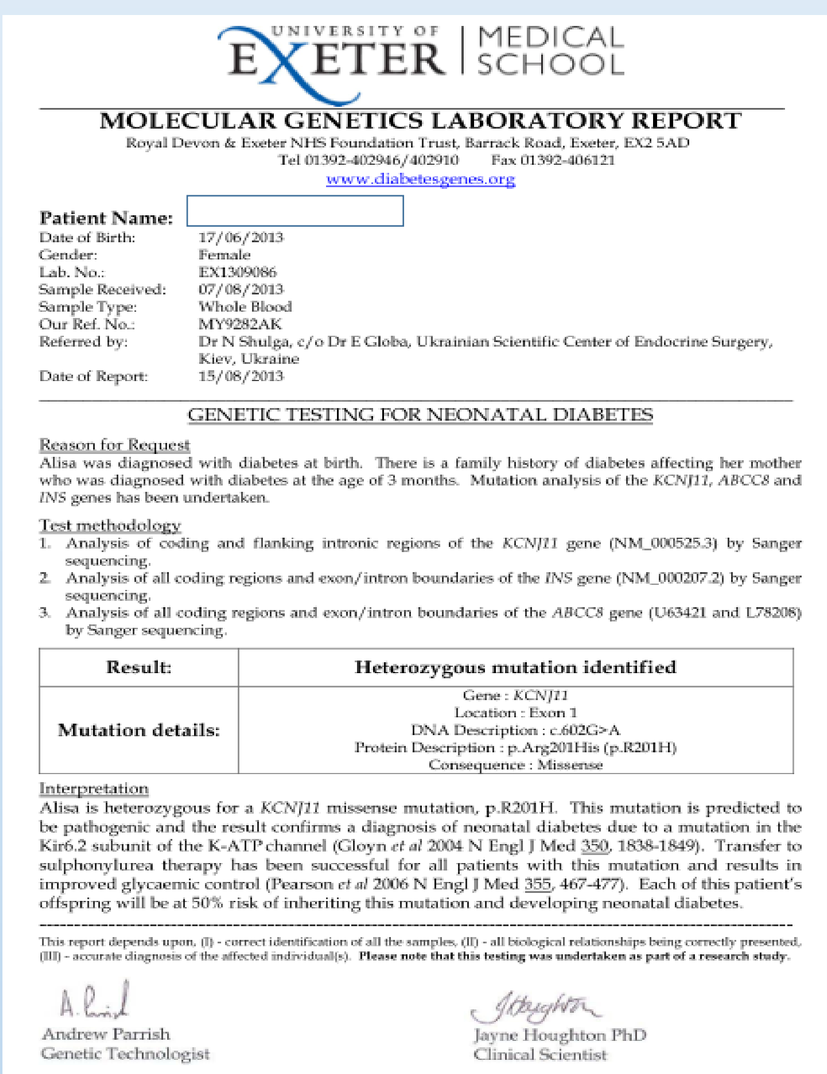
Objective and hypotheses: To determine the dynamic of carbohydrate metabolism in family transferred from insulin to sulphonylureas (SU).

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

Date, time	HвAc1	insulin	C-peptid	Glycaemic	TSH	MAU
03.09.13	13,8	0,5	0,09	13,8 [2,6-28,6]	4,1	
03.03.14	5,15	3,74	1,52	6,0 [3,3-10,2]	3,2	2,5
reference values	5-7 %	2,6-27,5 mkME/ml	0,5-2,5 ng/ml	3,3-5,5 mmol/l	0,5-3,5 mME/L	<30 mg/l

Dynamics targets the child's mother N., 28 years in patients receiving 15 mg / day of glibenclamide

Date, time	HвAc1	Insulin	C-peptid	Glycaemic	TSH	MAU
03.09.13	8,9	0,05	0,009	11,6 [2,8-18]	2,5	12,5
03.03.14	6,5	8,9	2,35	7,8 [5,4-14,5]	2,15	5,6
reference values	5-7 %	2,6-27,5 mkME/ml	0,5-2,5 ng/ml	3,3-5,5 mmol/l	0,5-3,5 mME/L	<30 mg/l



UNIVERSITY OF EXETER | MEDICAL SCHOOL

MOLECULAR GENETICS LABORATORY REPORT

Royal Devon & Exeter NHS Foundation Trust, Barrack Road, Exeter, EX2 5AD
Tel 01392-402946/402910 Fax 01392-406121
www.diabetesgenes.org

Patient Name:
Date of Birth: 17/06/2013
Gender: Female
Lab. No.: EX1309086
Sample Received: 07/08/2013
Sample Type: Whole Blood
Our Ref. No.: MY9282AK
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

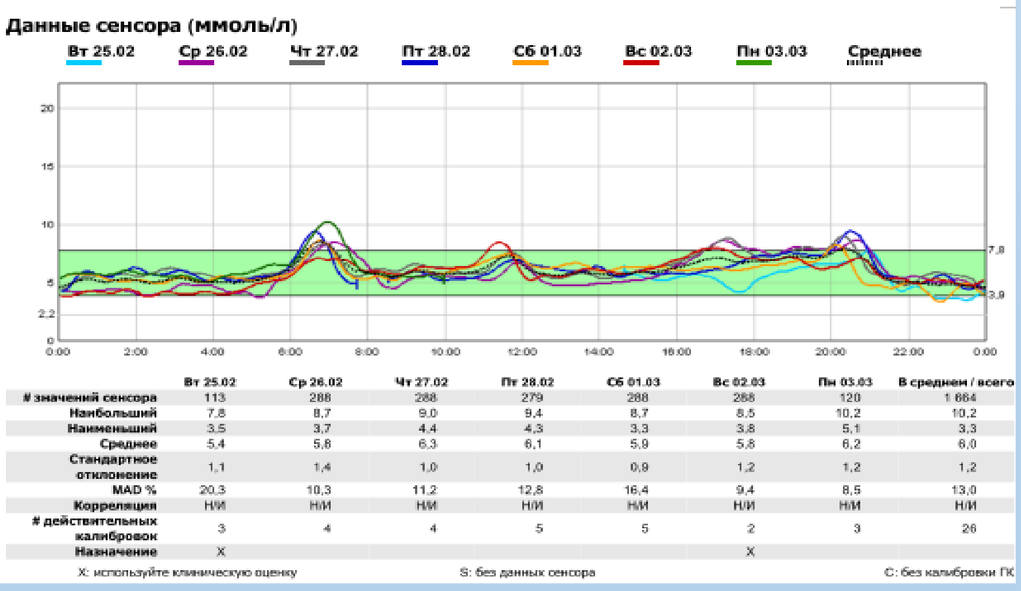
Interpretation
Alisa is heterozygous for a *KCNJ11* missense mutation, p.R201H. This mutation is predicted to be pathogenic and the result confirms a diagnosis of neonatal diabetes due to a mutation in the Kir6.2 subunit of the K-ATP channel (Gloyn *et al* 2004 N Engl J Med 350, 1838-1849). Transfer 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 individuall(s). **Please note that this testing was undertaken as part of a research study.**

Andrew Parrish
Genetic Technologist

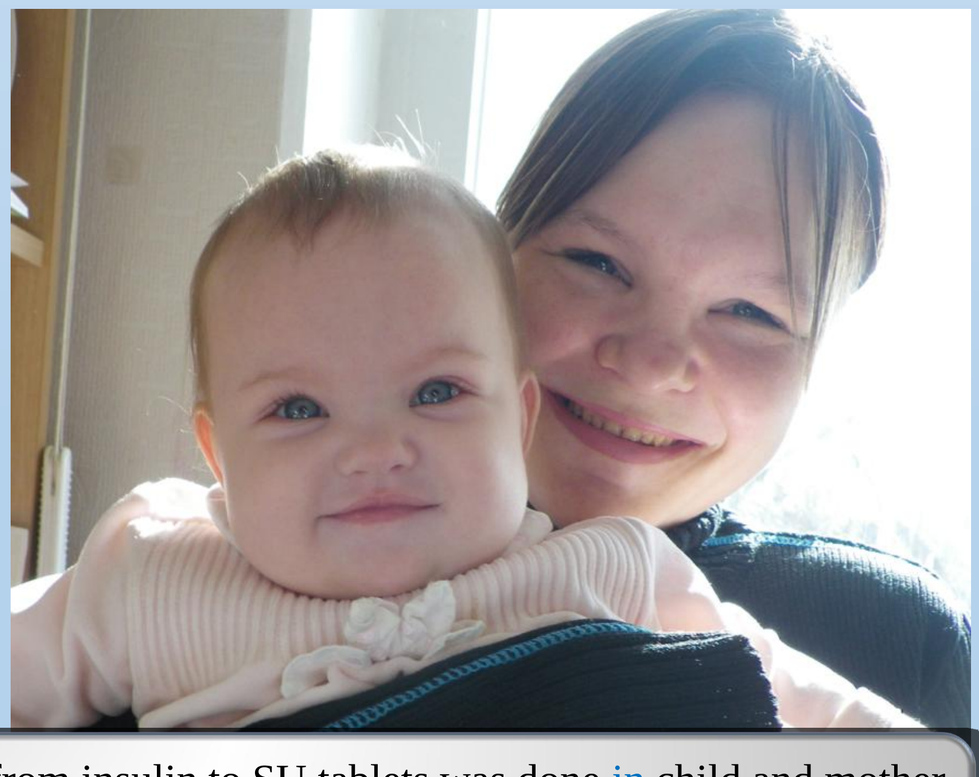
Jayne Houghton PhD
Clinical Scientist

Comparison of daily glycaemia levels during 7 days for patient, received treatment.



	Вт 25.02	Ср 26.02	Чт 27.02	Пт 28.02	Сб 01.03	Вс 02.03	Пн 03.03	В среднем / всего
# значений сенсора	113	288	288	279	288	288	120	1 664
Наибольший	7,8	8,7	9,0	9,4	8,7	8,5	10,2	10,2
Наименьший	3,5	3,7	4,4	4,3	3,3	3,8	5,1	3,3
Среднее	5,4	5,8	6,3	6,1	5,9	5,8	6,2	6,0
Стандартное отклонение	1,1	1,4	1,0	1,0	0,9	1,2	1,2	1,2
MAD %	20,3	10,3	11,2	12,8	16,4	9,4	8,5	13,0
Корреляция	Н/И	Н/И	Н/И	Н/И	Н/И	Н/И	Н/И	Н/И
# действительных калибровок	3	4	4	5	5	2	3	26
Назначение	X					X		

X: используйте клиническую оценку S: без данных сенсора C: без калибровки ГК



Results: A mutation in *KCNJ11*, R201H was identified in both patients. Transfer from insulin to SU tablets was done in child and mother at the age of 2 months and 28 y.o. accordingly. At the start of transfer process in child the daily dose of SU was divided into 6 doses (0,27 mg/kg/day), every feeding, but after 8 months of SU treatment frequency of dosing is reduced to 4 doses with decreasing of SU daily dose (0,17 mg/kg/day). The child's mother at 28 y.o. stopped insulin (45 units/day) and went on to SU in dose 15 mg/day. After 8 months of SU treatment HbA1c improved in both patients (in child 5.15% vs 13.9%, in mother 6,5% vs 8,9%, accordingly). Daily monitoring (iPro- 2) in child showed a marked reduction in the fluctuations as well as an overall lower level of glycaemic control (13,8 [2,6-26,6] mmol/l before SU treatment to 6,0 [3,3-10,2] mmol/l – after). C-peptide level increased from 0,09 ng/ml to 0,5 ng/ml in child, and from 0,009 ng/ml to 0,35 ng/ml in mother after 8 months of SU treatment accordingly.

Conclusion: Patients with diabetes, manifestated within the first 6 months of life have to perform genetic testing for determination of the pathogenetic treatment. Daily dose of SU given for child during 8 months decreased by 37% on a background of improving of carbohydrate metabolism, HbA1c. A good response on SU treatment was observed even after 28 years of insulin therapy