Birth weight in offsprings of mothers with gestational diabetes mellitus due to mutations in *GCK* gene.

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Background. The prevalence of MODY2 in the gestational diabetic population has been estimated to be approximately 2%. Risk of macrosomia in *GCK*/GDM cases depends on maternal glycemic control and fetal mutation status. However, the fetal genotype is unknown before birth.

Objective and hypotheses: To assess effects of insulin therapy on the birth weight of children born to mothers with *GCK* mutations.

Subjects: The study included 38 patients with GDM due to *GCK* gene mutations (Fig.1) and their 38 offsprings (22 affected children and 16 unaffected). All participants were divided into 2 groups: 1. *GCK+/*Mother and *GCK*+/Child ("M+Ch+"); 2. *GCK+/*Mother and *GCK*-/Child ("M+Ch-") depending on offspring's genotype. All women during pregnancy were treated with insulin.
The Mann-Whitney U test was applied to analyze the results of the study.

Methods: To define molecular basis of GDM in pregnant women we used a targeted NGS (Ion Ampliseq™ technology). Custom "DM/hyperinsulinism" gene panel (*GCG, GLUD1, WFS1, HNF1A, GCK, INS, HNF1B, ABCC8, HNF4A, RFX6, PTF1A, NEUROD1, AKT2, ZFP57, INSR, EIF2AK3, PPARG, PAX4, PDX1, GLIS3, KCNJ11, SLC16A1, FOXP3, BLK, CEL, KLF11, SCHAD, GCGR).* PGM semiconductor sequencer (Ion Torrent, Thermo Fisher, USA). Carrier status of *GCK* mutations in the offsprings was analyzed by Sanger sequencing.
Bioinformatics: Torrent Suite Software (Ion Torrent); ANNOVAR (Openbioinformatics.org)
Pathogenicity Interpretation, ACMG guidelines [1].

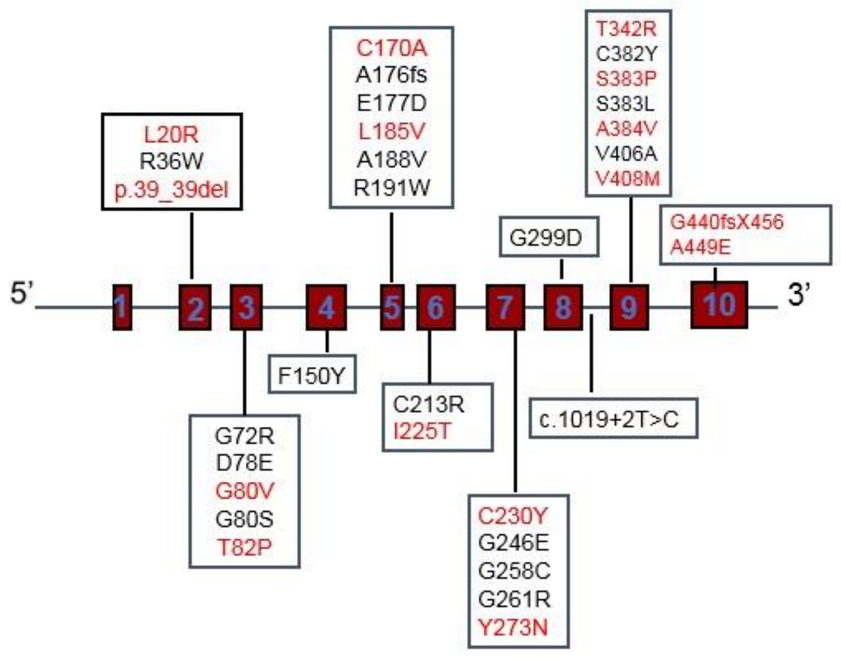

Fig. 1 *GCK* mutations
(novel = 14)

Results: The baseline characteristics of these subjects are summarized in Table 1.
The median birthweight in affected children was 3125 g [2800; 3300], in unaffected 3550 g [2930; 3890], p=0.036, nevertheless the weight remained in the normal range for gestational age
Among unaffected children diabetic fetopathy was observed in 6 (37.5%) newborns, including one child born at week 31 with weight +2.3 SD. Two affected children had low birth weight. Insulin therapy in these cases was started early (5-7 weeks) with achievement of strict glycemic control and episodes of hypoglycemia.

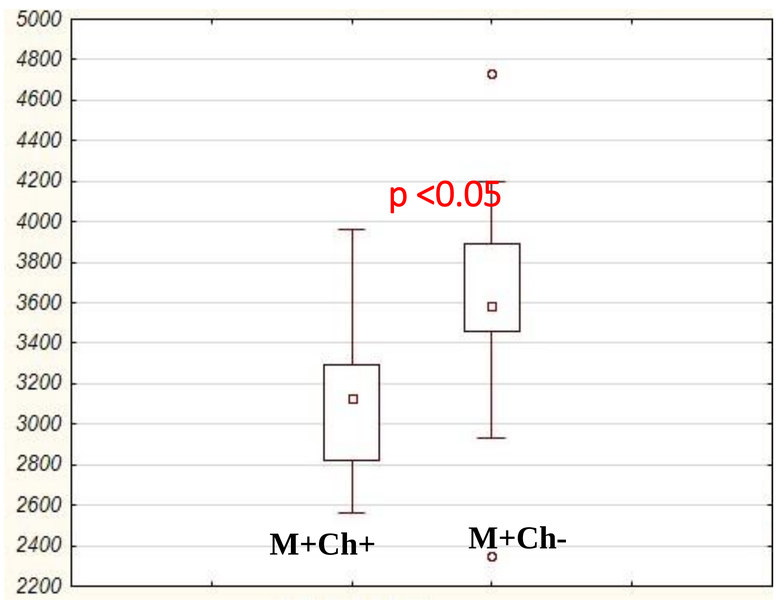

Fig. 2 Birthweight, gr

Table 1. Clinical date

Parameters	M+Ch+ (n=22)	M+Ch- (n=16)
Sex (Male/Female)	10/12	10/6
Gestation, week	38.7±1.2	37.7±2.2
Birthweight, gr	3125 [2800; 3300]	3550 [2930; 3890]
Birthweight, SD	-0.51 [-1.17; 0.17]	0.66 [0.48;1.92]
24-hour glycemia, mmol/l	6.3 [2.1;11.3]	6.18 [2.7;12]
Start Insuline, week	12.5 [6;30]	14.5 [5;34]
Insulin, U/kg	1.2 [0.8;1.4]	0.7 [0.5;0.8]
Diabetic fetopathy	No	37.5% (n=6)

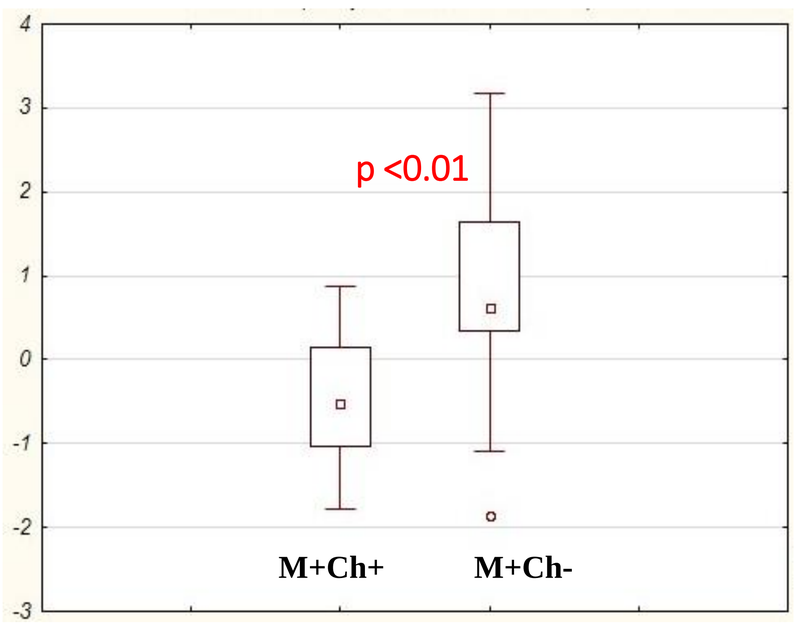

Fig. 3 Birthweight, SDS

Conclusions: Since prenatal diagnostics in mothers with *GCK* gene mutations is not always justified we recommend insulin therapy in order to prevent fetal macrosomia, which, however, should be less aggressive than in GDM due to other causes.

Acknowledgements. This study was supported by the Grant 16-15-10408 of the Russian Science Foundation

References:.
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