Клиническая и молекулярно-генетическая характеристика случаев MODY1—3 в Российской Федерации, выявленных по результатам NGS

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Цель исследования — изучить клинические и молекулярно-генетические характеристики наиболее частых подтипов MODY (1—3), выявленных с помощью NGS.

Материал и методы. В исследование включены 312 пациентов (162 мальчика, 150 девочек) в возрасте от 3 мес до 25 лет с подозрением на MODY. Критерии включения: нарушения углеводного обмена различной степени выраженности, отрицательный титр аутоантител к ICA, IA2 и GAD, сохранная секреция эндогенного инсулина. Для молекулярно-генетического исследования использована технология NGS. Применялась авторская панель праймеров (Custom DNA Panel) для мультиплексной ПЦР и секвенирования с использованием технологии Ion Ampliseq. Авторская панель «Сахарный диабет» включала 28 генов (13 генов-кандидатов MODY и другие гены, ассоциированные с сахарным диабетом). Неописанные ранее несинонимичные мутации считались «вероятно патогенными» при частоте минорного аллеля менее 0,1% и «патогенными» при оценке по базе данных ANNOVAR.

Результаты. У 178 (57,1%) пробандов выявлены мутации в генах-кандидатах MODY. Из них в гене *GCK* выявлено 99 мутаций у 129 (41,4%) пробандов и 77 родственников, в гене *HNF1A* — 20 мутаций у 19 (6,1%) пробандов и 14 родственников, в гене *HNF4A* — 8 мутаций у 9 (2,9%) пробандов и 3 родственников. Все мутации выявлены в гетерозиготном положении. Подтип MODY1 описан в РФ впервые.

Выводы. В российской популяции преобладает подтип MODY2. Только для MODY2 характерна типичная клиническая картина. Метод NGS является высокоэффективным в диагностике MODY.

Ключевые слова: MODY, NGS, GCK, HNF1A, HNF4A, гестационный сахарный диабет.

Clinical and molecular genetic characteristics of MODY1—3 cases in the Russian Federation as shown by NGS

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Objective — the research was aimed at studying clinical and molecular genetic characteristics of the most common subtypes of MODY (1—3) detected by NGS.

Material and methods. The study included 312 patients (162 boys and 150 girls) aged 3 months to 25 years with suspected MODY. Inclusion criteria were as follows: carbohydrate metabolism disorders of varying severity, negative titer of ICA, IA2, and GAD autoantibodies, preserved secretion of endogenous insulin. NGS technique was used for molecular genetic studies. Custom DNA Panel was used for the multiplex PCR and sequencing using the Ion Ampliseq technique. Custom Diabetes Panel included 28 genes (13 MODY candidates genes and other diabetes-associated genes). Non-synonymous mutations that were not previously described were rated as «probably pathogenic» if they had minor allele frequency of <0.1% and «pathogenic» when assessed against the ANNOVAR database.

Results. Mutations in MODY candidate genes were detected in 178 (57.1%) probands. Of these, 99 mutations in *GCK*99 gene were found in 129 (41.4%) probands and 77 relatives, 20 mutations in *HNF1A* gene were found in 19 (6.1%) probands and 14 relatives, 8 mutations in *HNF4A* gene — in 9 (2.9%) probands and 3 relatives. All detected mutations were heterozygous. MODY1 subtype was not previously described in the Russian Federation.

Conclusions. The Russian population is dominated by MODY2 subtype. Only MODY2 is characterized by typical clinical presentation. NGS is a highly effective method in the diagnosis of MODY.

Keywords: MODY, NGS, GCK, HNF1A, HNF4A, gestational diabetes mellitus.

Abbreviations

DM — diabetes mellitus
NGS — next generation sequencing
PG — pancreatic gland
CMD — carbohydrate metabolism disorder
BFH — borderline fasting hyperglycemia
HbA_{1c} — glycated hemoglobin
OGTT — oral glucose tolerance test
IR — insulin resistance
IGT — impaired glucose tolerance
MGT — molecular genetic test
IT — insulin therapy
SU — sulfonylurea
NG — normoglycemia
GDM — gestational diabetes mellitus
GU — glycosuria
DPN — distal polyneuropathy
MF — Metformin
OHGT — oral hypoglycemic therapy

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Topicality

MODY ranks first among monogenic forms of diabetes mellitus (DM), being detected in 2—5% of all DM cases. MODY (maturity-onset of diabetes of the young) is a heterogeneous group of diseases caused by gene mutations leading to dysfunction of β-cells of the pancreatic gland (PG). MODY is characterized by an autosomal dominant type of inheritance, manifestation at a young age, and a mild course. This term was first used by R.Tattersall and coworkers in 1975 to define hereditary non-progressive or low-progressive insulin-independent DM in young people [1, 2]. The first MODY candidate gene (*GCK*) was verified in 1992 [3]. To date, 13 candidate genes have been known (*HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *ABCC8*, and *KCNJ11*) and, respectively, 13 MODY subtypes. Subtypes 1—3 are the most common ones in all studies conducted in the world, but their occurrence in different countries is different. For example, MODY2 prevails in Italian [4] and Polish families [5]; MODY3 is more often detected in English [6] and American families [7], accounting for about 50—55% of all MODY subtypes. MODY1 ranks third among all conducted studies in the rate of occurrence.

The prevalence of MODY and its different subtypes in Russia is currently unknown. The first literature review on MODY in Russia was published by I.I. Dedov et al. [8] in 2000. To date, a number of studies of the most frequent MODY subtypes (2 and 3) have been published in Russia [9—14].

The «gold standard» for diagnosing MODY is molecular genetic testing (MGT). In all domestic studies, direct sequencing was used for MGT. Currently, new-generation sequencing (NGS) is extensively used worldwide, which greatly simplifies genetic verification of monogenic diseases. This technology enables simultaneous analysis of several candidate genes. Several studies of the MODY structure using this technology have been carried out [15—19]. For the first time in Russia, we used NGS for genetic diagnosis of hereditary carbohydrate metabolism disorders (CMDs), which enabled identification of a rare variant of DM, MODY6 [20], in Russia as well as cases of MODY with digenic and oligogenic inheritance [21]. In this paper, we present the clinical and molecular genetic characteristics of patients with the most common subtypes of MODY (1—3), which were identified by NGS.

AIM

The study aim was to investigate the clinical and molecular genetic characteristics of the most common subtypes of MODY (1—3) detected by NGS.

Material and methods

MGT was conducted in 312 patients (162 boys and 150 girls) aged 3 months to 25 years and 93 their relatives (MGT of relatives was performed by Sanger sequencing). MGT of mothers was financed by a Russian Science Foundation grant (project No. 16-15-10408). The median age of patients at the time of the study was 10.9 years. The inclusion criteria were as follows: CMDs of varying severity, a negative titer of ICA, IA2, and GAD autoantibodies, and preserved secretion of endogenous insulin. MGT was performed by NGS. The technique of high-throughput parallel sequencing was earlier described in detail [20]. All identified mutations were confirmed by Sanger sequencing.

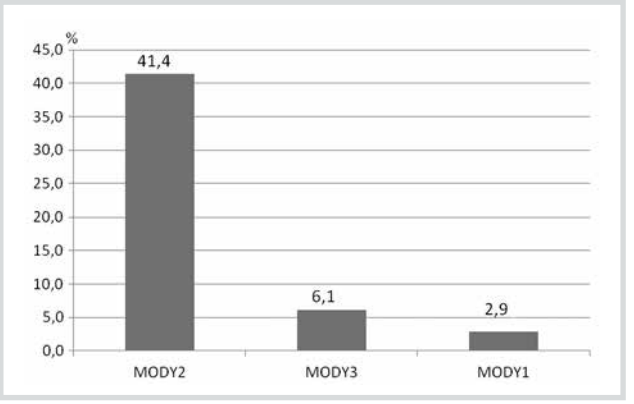

Figure 1. **A NGS-based rate of occurrence of MODY1—3 among all MODY forms in the Russian population.**

Results

Mutations in MODY candidate genes were identified in 178 (57.1%) probands. Of these, 99 mutations were detected in the *GCK* gene in 129 (41.4%) probands, 10 siblings, 57 parents, 7 2nd degree relatives, 23rd degree relatives, and 14th degree relative; 20 mutations were detected in the *HNF1A* gene in 19 (6.1%) probands, 10 parents, 33rd degree relatives, and 14th degree relative; 8 mutations were identified in the *HNF4A* gene in 9 (2.9%) probands, 1 sibling, and 2 parents **(Fig. 1)**. All mutations were found in the heterozygous state.

Mutations in the *GCK* gene (MODY2)

Ninety nine mutations were detected in the *GCK* gene in 129 (41.4%) probands; of these, 37 mutations were new **(Table 1)**. Among the latter, 6 mutations were identified in unrelated probands. Of 62 previously described mutations, missense mutations p.F150Y and p.C213R (n=5), p.E256K and p.G258C (n=4), p.R191W and p.Y273N (n=3), and p.L20R, p.G80S, p.E157K, p.L185V, p.R186L, and p.C382R (n=2) were most common. One patient was detected with two mutations in the *GCK* gene: a new mutation (p.E265D) and a previously described one (p.C213R). Apart from missense mutations (n=80, 80.8%); there were identified frameshift deletions (n=4) and non-frameshift deletions (n=3), splice site mutations (n=5), nonsense mutations (n=4), non-frameshift insertions (n=2), and one mutation with a change in the stop codon (p.X446S). Most often mutations were localized in exons 7 (n=18), 9 (n=13), 5

Table 1. **A spectrum of new mutations in the *GCK* gene (MODY2)**

Nucleotide substitution	Amino acid substitution	Mutation	Exon/ Intron	N
c.85G>T	p.D29Y	Missense	Exon 2	1
c.110T>C	p.M37T	Missense	Exon 2	1
c.115_117delAAG	p.K39del	Non-frameshift deletion	Exon 2	2
c.138delG	p.R46SfsX10	Frameshift deletion	Exon 2	1
c.171G>A	p.M57I	Missense	Exon 2	1
c.317delA	p.Q106RfsX10	Frameshift deletion	Exon 3	1
c.424A>T	p.K142X	Nonsense	Exon 4	1
c.434C>T	p.P145L	Missense	Exon 4	2
c.452_4delCCT	p.S151del	Non-frameshift deletion	Exon 4	2
c.475A>T	p.I159F	Missense	Exon 4	1
c.478G>T	p.D160Y	Missense	Exon 4	1
c.479A>G	p.D160G	Missense	Exon 4	1
c.488T>A	p.I163N	Missense	Exon 5	1
c.488T>G	p.I163S	Missense	Exon 5	1
c.574A>G	p.R192G	Missense	Exon 5	1
c.509G>C	p.G170A	Missense	Exon 5	1
c.542T>A	p.V181D	Missense	Exon 5	1
c.632T>A	p.I211N	Missense	Exon 6	1
c.674T>C	p.I225T	Missense	Exon 6	2
c.725A>G	p.E242G	Missense	Exon 6	1
c.689G>A	p.C230Y	Missense	Exon 7	1
c.850_851insTGGTGGACGAGAGCT CTGCAAACC	p.P248insLVDESSANP	Non-frameshift insertion	Exon 7	1
c.767A>G	p.E256G	Missense	Exon 7	3
c.771G>A	p.W257X	Nonsense	Exon 7	1
c.795G>C	p.E265D	Missense	Exon 7	1
c.884G>T	p.G295V	Missense	Exon 8	1
c.946C>T	p.L316F	Missense	Exon 8	1
c.1019G>A	p.S340N	Missense	Exon 8	2
c.1024delA	p.T342RfsX11	Frameshift deletion	Exon 8	1
c.1019+2_3insG	—	Splice-site mutation	Intron 8	1
c.1154_1155insGCTGGCGGG	p.S383_A384insAGL	Non-frameshift insertion	Exon 9	1
c.1130_1138delGCTCTGCGC	p.R377_A379del	Non-frameshift deletion	Exon 9	1
c.1142T>A	p.M381K	Missense	Exon 9	1
c.G1154A	p.G385E	Missense	Exon 9	1
c.1120G>T	p.V374L	Missense	Exon 9	1
c.1346C>A	p.A449E	Missense	Exon 10	1
c.1397G>C	p.X466S	Nonstop	Exon 10	1

n is the number of probands with a mutation.

(*n*=13), 2 (*n*=11), 4 (*n*=11), and 8 (*n*=9). No mutations were detected in exons 1, 11, and 12.

Clinical characterization

Boys (62.8%) predominated among the patients. At birth, the median body weight was 3,149 g, and the height was 50.7 cm. The median age of CMD diagnosis was 7.0 years (0.1; 17.1). The diagnosis was established occasionally in 79 (61.2%) cases; in 42 (32.6%) cases, diabetes was diagnosed based on a hereditary history of CMDs; 8 (6.2%) probands had clinical manifestations of DM (polyuria, polydipsia) in onset. Eight (6.2%) patients were overweight (SDS BMI, +1.5—1.9) in onset, and 2 (1.6%) patients were obese (SDS BMI, +2.68 and +2.32). The median fasting glucose level at diabetes manifestation was 6.9 mmol/L (5.7; 9.2; in some cases, capillary blood glucose was measured; the normal value <5.6 mmol/L). In only 3 (2.3%) cases, there was no borderline fasting hyperglycemia (BFH), but basal normoglycemia (NG) was detected in the presence of elevated HbA_{1c} levels; these patients underwent examination due to a hereditary history of CMDs. The median HbA_{1c} level at manifestation was 6.4% (4.8; 8.2), with the HbA1c level being <6.0% in 13 (10.1%) cases. In onset, glycosuria (GU) was detected in 4 (3.1%) patients. None of the patients had ketoacidosis in onset. Ten (7.7%) patients receved insulin therapy (IT) at a dose of 0.2 U/kg/day (0.07; 0.4); 13 (10.1%) patients received Metformin (MF) at a dose of 500—2,000 mg/day; a diet was recommended to the remaining patients (82.2%). MF was recommended mainly to patients with overweight and obesity at the time of CMD diagnosis. The data of a standard oral glucose tolerance test (OGTT) during diagnosing are presented in **Table 2**. After 2

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Table 2. **OGTT indicators in patients with MODY2**

Indicator	0 min	30 min	60 min	90 min	120 min
Glucose, mmol/L	6.6 (4.2; 9.2)	10.7 (6; 14.4)	10.1 (6.0; 15.1)	9.9 (6.5; 14.6)	8.5 (5.07; 13.5)
C-peptide, ng/mL	1.3 (0.2; 5.6)	4.9 (2.9; 6.3)	5.1 (1.29; 8.5)	5.2 (3.2; 6.3)	5.0 (1.5; 11.2)
Insulin, μIU/mL	4.83 (0.29; 76.94)	40.1 (6.6; 73.42)	32.3 (3;77.1)	36.1 (7.9; 74.7)	25.1 (4.1; 76.8)

h, the glucose concentration was normal in 29 (22.5%) cases and reached the diabetic level (11.9—13.5 mmol/L) in 4 (3.1%) cases. Impaired glucose tolerance (IGT) was diagnosed most often (n=96, 74.4%).

Two patients with CMD diagnosed in the setting of obesity had insulin resistance (IR) in onset (HOMA index, 25.3 and 10.3; the normal value <3.2). Both patients were diagnosed with T2DM. The patient with high IR (HOMA index, 25.3) was prescribed with MF at a dose of 1,300 mg/day; the other was recommended adhering to a diet. Six months later, both patients had normal body weight, but a decrease in IR (HOMA index, 8.66) occurred only in the MF-treated patient. The second patient after the second examination was also recommended taking MF, which led to a decrease in the HOMA index to 5.36 after 6 months.

At the time of MGT, the median age of patients was 10.6 years (0.11; 18.2); the disease duration was 3.0 years (0.1; 13). The median HbA_{1c} level was 6.4% (4.5; 7.7) and did not differ from that detected at the time of CMD diagnosis. After molecular genetic confirmation of a mutation in the *GCK* gene, therapy was ceased in all patients, and they were recommended adhering to a diet.

Family history

A hereditary history of CMDs was present in 110 (85.3%) families: 73 (56.6%) families had a maternal history of CMDs, and 36 (27.9%) families had a paternal history of CMDs. In 20 (15.5%) cases, there was no hereditary history, or the data were not available. In most cases, examination of relatives was actively initiated after diagnosing CMD in a child. Sanger sequencing revealed similar mutations in 10 siblings, 57 parents, 72nd degree relatives, 23rd degree relatives, and 1 4th degree relative, with each of them having CMD. Twenty eight mothers had a history of gestational diabetes mellitus (GDM).

Mutations in the *HNF1A* gene (MODY3)

Twenty mutations were detected in the *HNF1A* gene (MODY3) in 19 (6.1%) probands **(Table 3)**. In 1 case, a proband, a parent, and 4 relatives had 2 mutations in the *HNF1A* gene. Of the identified mutations, 3 mutations were not previously described: 2 missense mutations (c.508C>G p.Q170E, c.1813A>C p.N605H) and 1 frameshift duplication (c.1012dupG p.G339RfsX80). Mutations occurred most often in exon 4 (n=6). No mutations were detected in exons 7, 8, and 9.

Clinical characterization

Girls predominated (78.9%) among the patients. At birth, the median body weight was 3,234 g, and the median height was 51.9 cm. The median age of CMD diagnosis in probands was 10.6 years (0.1; 15 years). In 11 (57.8%) cases, the diagnosis was established occasionally during examination for another disease (for obesity in 2 cases) or during clinical examination; in 4 (21.1%) cases, diabetes was diagnosed due to a hereditary history of CMDs; 4 (21.1%) children had a clinical picture of diabetes (polyuria, polydipsia). At the disease onset, 11 (57.9%) patients had GU, with 6 of them having NG, which was the cause for further examination. In medical history of 3 children, GU was periodically observed for a long time (1—5 years), which was considered as transient, and no specific examination was performed. Three (15.8%) patients with classical signs of diabetes and high hyperglycemia had ketosis in onset.

In patients with the clinical picture of diabetes (n=4), the median glucose level at manifestation was 19.5 mmol/L (10; 33 mmol/L), and the HbA_{1c} level was 10.5% (7.7; 12.4%). Among patients with occasionally diagnosed diabetes, the median glycemic level was 10.7 mmol/L (4.1; 18.5 mmol/L), and the HbA_{1c} level was 7.0% (5.1; 10.4%). At the disease onset, 8 (42.1%) patients started IT at a dose of 0.6 U/kg/day (0.06; 3); of these, the highest doses (1.1 and 3 U/kg/day) were used in two young children who manifested with a typical clinical picture of diabetes and high hyperglycemia; during treatment, insulin was discontinued in one patient because of hypoglycemia. MF at a dose of 500—1,000 mg/day was prescribed to 4 (21.1%) patients; a diet was recommended to 7 (36.8%) patients.

At the disease onset, OGTT was performed in 8 patients **(Table 4)**. Two hours after carbohydrate load, glycemia reached the diagnostic level of DM (>11.1 mmol/L) in 4 (21.1%) patients; IGT was diagnosed in 1 (5.3%) case; NG was detected in 3 (15.7%) cases. Of these, 2 patients had obesity (SDS BMI, +2.32 and +2.65); one patient was overweight (SDS BMI, +1.85); but only one female patient without overweight was detected with IR (Matsuda index, 0.75; the normal level >2.5—3) and hyperinsulinemia (130.2 μIU/mL). This patient was examined for polycystic ovary syndrome (PCOS).

At the time of MGT, the median age of patients was 12.7 years (0.9; 18); the disease duration was 2.3 years (0.2; 9). During follow-up (2.6 years (0.6; 6 years), OGTT was performed in 9 patients in whom therapy was terminated. The data are presented in **Table 5.** Despite the preserved level of endogenous insulin, NG after 2 h was detected only in 1 patient; IGT was detected in 3 patients; hyperglycemia more than 11.1 mmol/L was found in 5 patients.

Thus, there was deterioration of the glycemic profile indicators over time despite preserved secretion of insulin **(Fig. 2)**.

Table 3. **A spectrum of mutations identified in the *HNF1A* gene (MODY3)**

Nucleotide substitution	Amino acid substitution	Mutation	Exon	D/N	n
c.51delC	p.E18SfsX4	Frameshift deletion	Exon 1	D	1
c.391C>T	p.R131W	Missense	Exon 2	D	1
c. 476G>A	p.R159Q	Missense	Exon 2	D	1
c.508C>G	p.Q170E;	Missense	Exon 2	N	1
c.512G>A	p.R171Q	Missense		D	
c.526+5G>A	–	Splicing impairment	Exon 2	D	1
c.607C>T	p.R203C	Missense	Exon 3	D	
c.685C>T	p.R229X	Nonsense	Exon 3	D	1
c. 693G>A	p.T231T	Synonimous mutation (splicing impairment)	Exon 3	D	1
c.788G>A	p.R263H	Missense	Exon 4	D	1
c. 798C>A	p.N266K	Missense	Exon 4	D	1
c. 815G>A	p.R272H	Missense	Exon 4	D	1
c.824_826delAAG	p.E275del	Nonframeshift deletion	Exon 4	D	1
c.862delG	p.P291QfsX51	Frameshift deletion	Exon 4	D	1
c.865dupC	p.G292RfsX25	Frameshift duplication	Exon 4	D	1
c.1012dupG	p.G339RfsX80	Frameshift duplication	Exon 5	N	1
c.1061C>T	p.T354M	Missense	Exon 5	D	1
c.1136_1137delCT	p.P379RfsX39	Frameshift deletion	Exon 6	D	1
c.1137delT	p.V380SfsX4	Frameshift deletion	Exon 6	D	1
c. 1813A>C	p.N605H	Missense	Exon 10	N	1

n is the number of probands with a mutation; N is a new mutation; D is a previously described mutation.

By the time of MGT, 9 patients received IT at a dose of 0.48 U/kg/day (0.2; 1.2); 5 patients received MF at a dose of 500—2,000 mg/day; 5 patients had no treatment. After molecular genetic confirmation of the diagnosis, 7 patients receiving IT and 5 patients receiving MF were successfully switched to pathogenetic therapy with sulfonylurea (SU) drugs: 4 patients received Glibenclamide at a dose of 5.25—7.5 mg/day, and 8 patients received Gliclazide at a dose of 30—60 mg/day. IT was continued in 2 patients with an early diagnosis of diabetes due to high insulin requirements (1.1—1.2 U/kg/day) and a low level of endogenous insulin. At the time of MGT, 5 patients had no need in treatment due to compensation of diabetes.

Family history

A hereditary history of CMDs was present in 15 (78.9%) families: in 7 cases in 2 generations, in 5 cases in 3 generations, and in 4 cases in 4 generations. In 2 families, there was no hereditary history; in 1 case, hereditary history was unavailable. GSD was present in 5 (26.3%) mothers; of these, 3 patients received IT.

Similar mutations were detected in 10 parents, 33rd degree relatives, and 14th degree relative.

In this group of patients, of interest was a 10-year-old proband with two mutations in the *HNF1A* gene, one of which was new (c.508C>G p.Q170E). After establishing the diagnosis, IT was ceased, and the patient was successfully switched to Gliclazide at a dose of 60 mg/day. Given the high concentration of diabetes in the family (mother, 6 mother's sisters, grandmother, and cousin), 5 family members underwent direct sequencing for similar mutations, and all were detected with these mutations.

Mutations in the *HNF4A* gene (MODY1)

Eight mutations were detected in the *HNF4A* gene (MODY1) in 9 (2.9%) probands: 1 new splicing site mutation (c.50—3delC) and 7 previously described mutations **(Table 6)**. A mutation c.439G>A p.V147I was detected in two unrelated probands and one parent with CMD. A mutation in the 5'-untranslated region was detected in a proband as well as in a sibling and a parent who also had CMD. Most mutations were found in exon 1 (*n*=3); no mutations were found in exons 3 and 6 to 12.

Table 4. **OGTT indicators in 8 patients with MODY3 at the disease onset**

Indicator	0 min	120 min
Glucose, mmol/L	6.73 (3.87; 12.6)	9.4 (4.9; 13.4)
C-peptide, ng/mL	1.7 (0.3; 3.9)	2.92 (2.3; 3.5)
Insulin, μIU/mL	7.4 (0.5; 15.1)	36.4 (1.48; 130.2)

Clinical characterization

Girls predominated (77.8%) among the probands. One (10%) patient had macrosomia at birth (height, 62 cm; weight, 5,600 g); the others had average statistical weight-height indicators. The median age of CMD diagnosis was 11 years (4.7; 18). An occasional diagnosis was made in 5 (55.6%) cases; in 2 (22.2%) cases, there were clinical manifestations of diabetes in onset; in 2 (22.2%) cases, diabetes was diagnosed due to a hereditary history of CMDs. In one case at the disease onset, hyperglycemia (14 mmol/L) was discovered within one day in the presence of clinical manifestations of diabetes; in other cases, the median fasting glucose level was 9.4 mmol/L (6; 14); the median HbA1c level was 7.0% (6.3; 8). GU occurred only in 3 (30%) patients with glycemia in a range of 8.2—14 mmol/L in onset. Diabetes was detected in in 3 (30%) patients with obesity (SDS BMI, +2.2—2.8) (which was initially considered as T2DM) and in 1 (11.1%) patient with overweight. At the disease onset, intensive IT was prescribed to 4 patients; IT with prolonged insulin was prescribed to only 1 patient (0.5 U/kg/day

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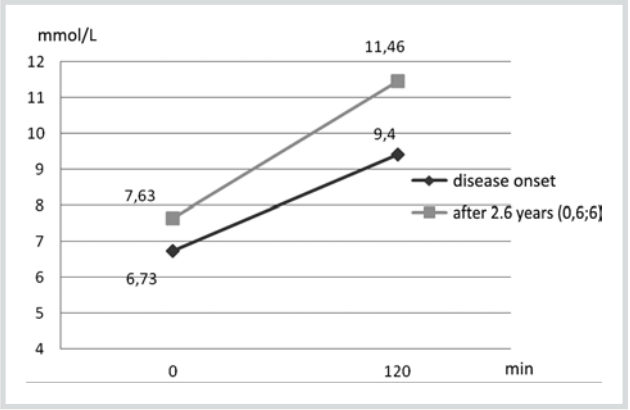

Figure 2. **Glycemic indicators of OGTT in MODY3 patients at the disease onset and follow-up.**

(0.1; 1)). MF at a dose of 1,000 mg/day was prescribed to 1 patient with obesity; a diet was recommended to 3 patients. A patient with a 7.9-year disease history was diagnosed with distal diabetic polyneuropathy (DPN) 3 years after detection of CMD, despite satisfactory compensation of diabetes (HbA1c, 6.4%).

According to the OGTT data, 3 patients at the disease onset had different grade CMDs: NG (3.5—4.9 mmol/L), IGT (4.6—8.4 mmol/L), and DM (6.67—11.85 mmol/L).

The median age of patients at the time of MGT was 13.8 years (8.2; 25.9); the disease duration was 2.9 years (0.3; 7.9).

Changes in OGTT over time (3.9 years (1.5; 7) were analyzed in 4 patients, three of whom received IT at a dose of 0.2—0.3 U/kg/day (the test was performed in the setting of ceased IT) **(Table 7)**. IGT was revealed in two cases; in 1 case, glycemia reached the diabetic level; in another case, NG was detected.

After molecular genetic confirmation of the diagnosis, 1 patient (25.9-year-old, 7.9-year history of diabetes) was successfully switched from IT to oral hypoglycemic therapy (OHGT) with Novonorm at a dose of 1.5 mg/day. An attempt to switch one patient from IT (0.17 U/kg/day) to OHGT was unsuccessful.

Family history

Seven (87.5%) patients had a hereditary history of CMDs: 2 patients in two generations, 4 patients in 3 generations, and 1 patient in 4 generations. Similar mutations were found in 1 sibling and 2 parents.

Discussion

MODY 2 is associated with heterozygous mutations in the glucokinase (*GCK*) gene. Mutations impair the ability of glucokinase to phosphorylate glucose, which increases the minimum glucose concentration necessary to stimulate insulin release. To date, more than 600 mutations have been identified in the *GCK* gene. Most of the mutations occur in exons 7 and 8. In this study, mutations prevailed in exon 7. Two frequent mutations, p.F150Y and p.C213R, were identified.

At the time of MGT and a disease duration of 3 years (0.1; 13), the median HbA_{1c} level was 6.4% (4.5; 7.7), i.e. it did not differ from the median HbA_{1c} level at disease manifestation, which again confirms the absence of CMD progression in MODY2.

One of the characteristic features of MODY2 is moderate fasting hyperglycemia caused by an increase in the threshold glycemia level necessary to stimulate the release of insulin. At the time of CMD diagnosis, all our patients with MODY2 had elevated fasting glycemia (5.7—9.2 mmol/L), but during OGTT (venous plasma), the basal glycemia level was below 6.1 mmol/L in 32 (24.8%) patients. This largely depended on intake of carbohydrates that was significantly reduced after discovery of CMD. During OGTT, glycemia after 2 hours was normal in 29 (22.5%) cases and reached the diabetic level (11.9—13.5 mmol/L) in 4 (3.1%) cases; IGT was diagnosed in most cases (n=96, 74.4%). Therefore, moderate fasting hyperglycemia and IGT, which are pathognomonic for MODY2, were also the main CMD types in these patients in the present study.

In recent years, there have been often reports of the onset of MODY2 in the setting of obesity and IR that are considered as signs of T2DM. The widespread prevalence of obesity in the children's population changes the common criteria for MODY2. There is a need for differentiating MODY from T2DM, and the only reliable diagnostic technique is MGT. For example, in our study, 2 patients with obesity and high IR in onset were initially followed-up for T2DM. Changes in the clinical picture in both patients over time were the basis to suspect a monogenic variant of DM and to substantiate the reasonability of MGT despite the T2DM phenotype at the time of CMD diagnosis.

MODY3 is associated with mutations in the hepatocyte nuclear factor 1 alpha (*HNF1A*) gene, which lead to impaired insulin secretion and/or a decrease in the number of pancreatic β-cells [22]. More than 400 different mutations in the *HNF1A* gene (both in the coding sequence and in the promoter) have been identified [23]; more than 50% of them are missense mutations. The most common mutation is a frameshift mutation p. P291fs (exon 4) that leads to synthesis of a truncated 315 amino acid protein [24]. This mutation is widespread in

Table 5. **Changes in OGTT indicators in 9 patients with MODY3 over time**

Indicator	0 min	30 min	60 min	90 min	120 min
Glucose, mmol/L	7.63 (4.6; 17.49)	9.55 (8.5; 10.6)	13.38 (9.6; 19.8)	14.4 (13.2; 15.6)	11.46 (6.2; 15.4)
C-peptide, ng/mL	1.82 (1.4; 2.7)	4.1 (3.6; 4.6)	4.8 (3.6; 6.7)	6.5 (5.7; 7.3)	4.12 (2.4; 6.1)
Insulin, μIU/mL	7.9 (0.9; 15.1)	31.55 (29.9; 33.2)	33.9 (7.5; 44.5)	40.3 (33.3; 47.3)	20.75 (4.1; 41.4)

Table 6. **A spectrum of mutations detected in the *HNF4A* gene (MODY1)**

Nucleotide substitution	Amino acid substitution	Mutation	Exon	D/N	n
c.37_38insGA	p.E13GfsX92	Frameshift insertion	Exon 1	D	1
c.12_16delGAACG	p.N5AfsX50	Frameshift deletion	Exon 1	D	1
c.128A>G	p.D43G	Missense	Exon 1	D	1
c.199C>T	p.R67W	Missense	Exon 2	D	1
c. 335G>A	p.R112Q	Missense	Exon 4	D	1
c. 439G>A	p.V147I	Missense	Exon 5	D	2
c.50-3delC	–	Splicing site mutation	Intron 1	N	1
chr.20:43029938_43029944delGGAGGC	–	5'-untranslated region mutation	5'UTR	D	1

n is the number of probands with a mutation; N is a new mutation; D is a previously described mutation

Table 7. **Changes in OGTT indicators in patients with MODY1 over time**

Indicator	0 min	60 min	120 min
Glucose, mmol/L	5.27 (5.19; 6.6)	9 (12.5; 15.9)	9.9 (7.73; 14.5)
C-peptide, ng/mL	1.84 (1.33; 2.5)	5 (4.47; 5.6)	5.02 (4; 6.5)
Insulin, μIU/mL	9.5 (7.74; 11.6)	32.34 (19.7; 47.3)	37.9 (18.8; 63.53)

Japan, Great Britain, Germany, and Finland, which is the basis to consider codon 291 as a «hot spot» of mutagenesis. It is interesting that this mutation was not detected in our study, whereas in a study by E.A. Sechko et al. [11], who analyzed 18 cases of MODY3 in Russian patients, this mutation was predominant (27.8%).

According to the literature data, mutations in the *HNF1A* gene are more common in exons 2 and 4 [23]. In our study, mutations in these exons also prevailed.

Patients with MODY3 are characterized by a reduced renal threshold for glucose, which manifests as asymptomatic GU, often in combination with NG. This symptom is caused by a defect in the sodium-dependent glucose transporter SGLT2 (transcription of the *SGLT2* gene is controlled by the HNF1A protein) [25]. In 11 (57.9%) our patients with MODY3, this symptom was present in a medical history (in the setting of NG in 6 patients). In this regard, it is important to emphasize that this is the combination of GU with NG or BFH in patients without kidney diseases that should be the reason to visit the endocrinologist and initiate a diagnostic search.

Ketosis is generally believed to be untypical of monogenic forms of DM. However, several studies (in particular, the first description of MODY3 in Russia [10, 26]) have demonstrated that the presence of ketosis in onset does not exclude MODY. Indeed, three our patients who manifested with a clinical picture of diabetes and high hyperglycemia had ketosis in onset. This should be taken into account to avoid overdiagnosing T1DM in patients with the MODY phenotype.

Mutations in the *HNF1A* gene are characterized by progressive insulin secretion deficiency, which worsens the glycemic profile over time, as noted in our patients. Early manifestation of diabetes in MODY3 patients leads to rapid depletion of endogenous insulin. For example, one of our patients with early onset diabetes (at the age of one month) had a high need for insulin (1.1—1.2 U/kg/day) despite residual secretion of the C-peptide.

While MODY2 is characterized by fasting hyperglycemia in a range of 5.6—8.3 mmol/L, fasting glycemia in MODY3 can vary in a wide range, as demonstrated in our study. Of interest are the OGTT data in MODY3: in onset, the fasting glycemia level in 5 our patients was within normal limits and reached a diabetic value after 2 h. Therefore, the normal level of basal glycemia is not a sufficient criterion for exclusion of MODY3; if this diabetes form is suspected, OGTT should be performed. In particular, a glucose concentration curve in one of our patients with a basal glycemia level of 3.87 mmol/L was detected occasionally during OGTT for PCOS. Impairments of OGTT in the setting of baseline fasting NG as well as the absence of diabetes signs and a negative titer of autoantibodies served the reason for considering monogenic diabetes.

MODY1 is associated with heterozygous mutations in the hepatocyte nuclear factor 4 alpha (*HNF4A*) gene. This subtype accounts for about 10% of all MODY variants. To date, more than 100 mutations in the *HNF4A* gene have been described in 173 families [23], with missense and nonsense mutations being predominant (n=52). This subtype is characterized by a pronounced variability of clinical manifestations, from the absence of symptoms to severe diabetes with ketosis. Often, CMDs are discovered in the setting of obesity. Patients with MODY1 can have the entire spectrum of vascular complications of diabetes. For example, one of our MODY1 patients developed distal neuropathy as early as 3 years after a diagnosis of CMD.

Heterozygous mutations in the *HNA4A* gene can cause significant fetal macrosomia (a mean weight gain of 790 g) due to increased intrauterine insulin secretion, which can lead to transient or prolonged neonatal hypoglycemia [27]. The time and causes for further transition of hyperinsulinemia to diabetes have not been established yet [28]. Among our patients, only one child had macrosomia at birth; however, no episodes of hypoglycemia oc-

curred at an early age. In Russia, this MODY subtype was described for the first time.

Conclusion

The most common MODY subtype in the Russian population is MODY2.

Only MODY2 is characterized by a typical clinical picture. In the case of *HNF1A/HNF4A*-MODY, the clinical picture varies considerably even in patients with the same mutation. This variability of the clinical course dictates the need for molecular genetic confirmation of MODY.

The timely correct diagnosis is the key to choosing adequate therapy, evaluating the disease prognosis, and providing medical and genetic counseling to the family, while a high efficiency of NGS supports widespread introduction of this technology.

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