Clinical, Laboratory and Genetic Characteristics of Children with GCK-MODY (MODY2): Report of Four Novel Variants in GCK Gene

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ABSTRACT

Objective: *Maturity-Onset Diabetes of the Young (MODY) is the most common type of monogenic diabetes. Heterozygous inactivating variants in glucokinase (GCK) gene are related to MODY2 (GCK-MODY). In this study, we aimed to investigate the phenotype and genotype characteristics of patients with GCK-MODY.*
Methods: *Anthropometric and clinical characteristics (age, gender, weight, height and body mass index, complaints, family history), laboratory data (glucose, insulin, glycated hemoglobin, lipid levels) and molecular analysis of the GCK gene were collected from the hospital records.*
Results: *The median age was 9.50 y (1.0-16.0), weight SDS -0.27 (-1.50-2.50), height SDS -0.09 (-2.20-1.60), and body mass index SDS -0.10 (-1.30-2.40). The median level of fasting blood glucose was 121 mg/dL (101-143), insulin was 9.50 mIU/mL (1.80-21.0), and HbA1c was 6.35% (6.20-6.60) at the time of diagnosis. Fourteen patients (78%) were diagnosed incidentally with asymptomatic hyperglycemia, while 4 patients (22%) had symptoms of polyuria and polydipsia. Ten different variants were detected in the GCK gene of 18 cases; one variant was nonsense, one variant was deletion, and the rest of the variants were missense mutations. Exon 7 was the most common location in coding regions and missense was the primary mutation type. The most common variant was c.802G>T (p.Glu268Ter) and detected in 5 (28%) patients. Four (22%) of the variants were novel; seven missense (p.Asp132Gly, p.Arg191Gln, p.Met238Thr, p.Met238Ile, p.Leu243Pro, p.Arg250Cys, p.Arg275Cys), one deletion (p.Pro153del) and one splice site mutation (c.863+3A>G).*
Conclusion: *Since there is no specific treatment for GCK–MODY, GCK gene mutation screening should be considered in cases with early onset mild hyperglycemia, family history of impaired fasting glycemia and negative beta-cell antibodies to avoid unnecessary use of insulin or oral antidiabetic drugs. In this study, ten different variants were detected in the GCK gene of the 18 cases, four of which were novel.*

INTRODUCTION

Maturity-Onset Diabetes of the Young (MODY), is a group of monogenic defects in β cell functions characterized by autosomal dominant inheritance and non-insulin dependent form of diabetes. Classically, patients with MODY have a family history of diabetes at two or three generations and the diagnosis is made before the age of 25 years [(1)].

MODY is the most common form of monogenic diabetes in Europe and accounts for 1-2% of all cases of diabetes. The prevalence of MODY is 21-45/1,000,000 in children and 100/1.000.000 in adults [(2–4)]. The most common causes of MODY are MODY2 and MODY3, due to variants in glucokinase (GCK) and hepatocyte nuclear factor 1-alpha (HNF1A) genes, respectively [(1)]. The prevalence of GCK-MODY is higher in countries such as Germany, France, Spain and Italy, where glucose screening in asymptomatic children is a routine procedure [(1)]. Similar to these countries, GCK-MODY is the most common form of MODY in Turkey [(5)].

GCK-MODY is characterized by stable, mild and non-progressive hyperglycemia, low glycosylated hemoglobin (HbA1c) levels with good prognosis that does not require specific treatment [1]. Considering that MODY patients often misdiagnosed with type 1 or type 2 diabetes mellitus (DM), correct molecular diagnosis of MODY is crucial for choosing the optimal treatment and identifying at-risk family members [6].

In this study, we aimed to describe (i) the molecular spectrum of GCK gene, (ii) clinical and laboratory characteristics of these children, and (iii) to present 4 novel variants.

MATERIALS and METHODS

Patient Data

Children with a clinical diagnosis of GCK-MODY and available molecular results for GCK gene were enrolled in the study. Demographic, clinical and laboratory characteristics of the subjects were collected from the hospital records. Inclusion criteria were: (i) stable and mild hyperglycemia (fasting plasma glucose 100-144 mg/dL), (ii) family history of diabetes with autosomal dominant inheritance, and (iii) absence of beta-cell autoantibodies [6]. Patients with type 1 or type 2 DM, and HbA1c level greater than 7.5% were excluded from the study. Patients were classified and compared in two groups: Subjects with documented variant in GCK gene were classified as GCK-MODY (+) and subjects that exhibit typical characteristics of GCK-MODY but without any variant in GCK gene were classified as GCK-MODY (-).

Genetic Analysis

Genomic DNA was extracted from peripheral blood using standard techniques (QIAGEN® (Hilden, Germany) were used following the manufacturer's instructions. All coding GCK (NM_000162) exons and their flanking regions were amplified by PCR. The amplicons were cleaned up with Sephadex (GE Healthcare). ABI PRISM 3100 DNA analyzer (Applied Biosystems) and Big Dye Terminator Cycle Sequencing V3.1 Ready Reaction Kit (Life Technologies) were used to elucidate the DNA sequence. Variants were evaluated according to the reference genome of GRCh37(h19) [RefSeqIDs: GCK (NM_000162.5)]. Novel variants in the GCK gene were analyzed in three different bioinformatics tools that examine functional effects of variants: PolyPhen-2 (http://genetics.bwh.harvard.edu/pph/), Mutation Taster (http://www.mutationtaster.org) and SIFT (Sorting Intolerant From Tolerant) (http://sift.jcvi.org/www/SIFT_enst_submit.html) [7-9]. The CADD and DANN scores of the single nucleotide variants as well as the insertion/deletion variants detected in the analysis were calculated by reference to PubMed publications [10,11].

Statistical Analysis

Statistical Package for Social Sciences (SPSS) software (version 25.0, SPSS Inc., Chicago, IL, USA) was used for the statistical. Data from groups with and without variants were compared using Mann-Whitney U-test. The results of non-parametric tests were given as median (minimum-maximum). A p value less than 0.05 were defined as statistically significant.

RESULTS

Table 1. Demographic, clinical and laboratory characteristics of children with GCK–MODY*

Characteristics	n=18
Age (year)	9.50 (1.0-16.0)
Female/Male	8/10
Weight SDS	-0.27 (-1.50-2.50)
Height SDS	-0.09 (-2.20-1.60)
BMI SDS	-0.10 (-1.30-2.40)
Glucose 0 min (mg/dL)	121 (101-143)
Glucose 120 min (mg/dL)	152 (99-249)
Insulin 0 min (mIU/mL)	9.50 (1.80-21.0)
Insulin 120 min (mIU/mL)	29.30 (2.20-109.30)
HbA1c (%)	6.35 (6.20-6.60)
C peptide (mg/dL)	0.69 (0.40-4.30)
Total Cholesterol (mg/dL)	190 (101-232)
LDL- Cholesterol (mg/dL)	106 (26-153)
HDL- Cholesterol (mg/dL)	53 (46-90)
Triglyceride (mg/dL)	70 (33-180)

**Data were given as median (min-max)*
BMI, body mass index; SDS, standard deviation score; LDL, low-density lipoprotein; HDL, high-density lipoprotein

Molecular analysis of the GCK gene was performed in 29 patients and variant was detected in 18 cases [10 male, 56%] from 15 different families [GCK-MODY (+)], and no variants were detected in 11 cases [6 male, 55%] [GCK-MODY (-)].

The median age was 9.50 y (1.0-16.0), weight SDS -0.27 (-1.50–2.50), height SDS -0.09 (-2.20-1.60), and body mass index SDS -0.10 (-1.30-2.40) in children with GCK-MODY (+). The median level of fasting blood glucose was 121 mg/dL (101-143), insulin was 9.50 mIU/mL (1.80-21.0), and HbA1c was 6.35% (6.20-6.60) at the time of diagnosis (Table 1). Fourteen patients (78%) were diagnosed incidentally with asymptomatic hyperglycemia, while 4 patients (22%) were symptomatic (polyuria and polydipsia). According to the oral glucose tolerance test (OGTT) the increase in blood glucose level was <83 mg/dL except for one case who had high postprandial glucose level (249 mg/dL).

There was no significant difference between the GCK-MODY (+) and GCK-MODY (-) groups with respect to age, gender, anthropometric measurements, and laboratory tests (Table 2).

Ten different variants were detected in the GCK gene of 18 cases; one variant was nonsense, one variant was deletion, and the rest of the variants were missense mutations. The variants were evaluated according to American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines recommendations [12]. The most common variant was 802G>T (p.Glu268Ter) and detected in 5 (28%) patients. Four (22%) of the variants were novel; 7 missense (p.Asp132Gly, p.Arg191Gln, p.Met238Thr, p.Met238Ile, p.Leu243Pro, p.Arg250Cys, p. Arg275Cys), one deletion (p.Pro153del) and one splice site mutation (c.863+3A>G) (Table 3). In addition, targeted next-generation sequencing analysis of other genes in the MODY etiology was planned in cases with no mutation.

Table 2. Comparison of GCK–MODY (+) and GCK–MODY (-) groups*

Characteristics	GCK–MODY (+) n= 18	GCK–MODY (-) n= 11	p**
Age (year)	9.5 (1.0-16.0)	10.0 (1.0-17.0)	0.63
Female/Male	8/10	5/6	1.000
Weight SDS	-0.27 (-1.50–2.50)	0.65 (-3.90–1.40)	0.46
Height SDS	-0.09 (-2.20–1.60)	0.60 (-2.40–1.50)	0.61
BMI SDS	-0.10 (-1.30–2.40)	0.05 (-3.30–1.20)	0.92
Glucose 0 min (mg/dL)	121 (101–143)	121 (104–142)	0.88
Glucose 120 min (mg/dL)	152 (99–249)	146 (99–218)	0.64
Insulin 0 min (mIU/mL)	9.5 (1.8–21.0)	6.4 (3.3–21.6)	0.52
Insulin 120 min (mIU/mL)	29.30 (2.20–109.30)	35.1 (8.8–137.0)	0.82
HbA1c (%)	6.35 (6.20–6.60)	6.05 (5.00–6.40)	0.26
C peptide (mg/dL)	0.69 (0.40–4.30)	1.20 (1.0–1.50)	0.43
Total Cholesterol (mg/dL)	190 (101–232)	142 (126–178)	0.06
LDL-Cholesterol (mg/dL)	106 (26–153)	78 (60–105)	0.23
HDL-Cholesterol (mg/dL)	53 (46–90)	49 (31–55)	0.07
Triglyceride (mg/dL)	70 (33–180)	87 (41–129)	0.49

**Data were given as median (min-max), **Mann-Whitney U test*
BMI, body mass index; SDS, standard deviation score; LDL, low-density lipoprotein; HDL, high-density lipoprotein

Table 3. The characteristics of the variants in GCK gene and prediction tools scores

Nucleotide changes	Location	Aminoacid changes	dbSNP number	Mutation Taster score	Polyphen-2 score	SIFT score	DANN score	CADD score	ACMG 2015 Criteria	Reported
c.395A>G	Exon 4	p.Asp132Gly	-	0.9999	0.53 possibly damaging	0.006 damaging	0.9964	24.6	PM1, PM2, PP2, PP3	Novel
c.457_459 delCCT	Exon 4	p.Pro153del	-	1	N/A	0.894 damaging	N/A	N/A	PM1, PM2, PM4, PP3	Novel
c.572G>A	Exon 5	p.Arg191Gln	rs886042610	1	1 probably damaging	0.001 damaging	0.9995	32	PM1, PM2, PM5, PP2, PP3	Massa 2001 (22)
c.713T>C	Exon 7	p.Met238Thr	-	1	0.1 benign	0.276 tolerated	0.9906	24.2	PM1, PM2, PP2, PP3	Novel
c.714G>A	Exon 7	p.Met238Ile	-	1	0.48 possibly damaging	0.053 tolerated	0.9941	23.6	PM1, PM2, PP2, PP3	Novel
c.728T>C	Exon 7	p.Leu243Pro	rs1470562535	1	1 probably damaging	0.028 damaging	0.9989	31	PM1, PM2, PP2, PP3	Borowiec, 2012 (23)
c.748C>T	Exon 7	p.Arg250Cys	rs1057524904	1	1 probably damaging	0.001 damaging	0.9994	32	PM1, PM2, PP2, PP3	Pinterova, 2006 (24)
c.802G>T	Exon 7	p.Glu268Ter	-	1	N/A	N/A	0.9977	42	PVS1, PM2, PP3	Pruhova, 2003 (25)
c.823C>T	Exon 7	p.Arg275Cys	rs556436603	1	0.99 probably damaging	0.002 damaging	0.9991	26.4	PM1, PM2, PM5, PP2, PP3	Gloyn, 2003 (26)
c.863+3A>G	Intron 7	Non coding variant	rs193922334	1	-	-	0.9178	22.5	PM2, BP4	No publication

N/A: Not available. PM1: Mutation hotspot. PM2: Absent from controls. PM4: Change in protein length. PM5: Other aminoacid change in same codon. PP2: Rare benign missense. PP3: In silico pathogenic evidence. PVS1: Loss of function. BP4: In silico benign evidence.

DISCUSSION

GCK-MODY is the most common form of MODY in some countries with the highest prevalence in southern European countries [13-15]. According to the three recent studies from Turkey, the frequency of GCK-MODY in Turkish children with MODY was 24-64% [5,16,17].

GCK-MODY is an autosomal dominant disease characterized by mild hyperglycemia and mild elevation of HbA1c [1]. The glucose threshold for insulin secretion has increased in GCK–MODY and mild fasting hyperglycemia is present from birth [6]. The characteristic biochemical features of GCK-MODY are, (i) mild fasting hyperglycemia (100-145 mg/dL), (ii) HbA1c lower than 7.5%, and (iii) increment of glucose at 2h in OGTT lower than 83 mg/dL [1]. In the present study, the inheritance pattern was compatible with autosomal dominant, fasting glucose levels of the patients were between 100-145 mg/dL, HbA1c levels ≤7.5% and increment of glucose level in OGTT <83 mg/dL in accordance with the literature data. Classical symptoms of diabetes are rare in patients with GCK-MODY. Patients with GCK-MODY are usually asymptomatic and the majority of the patients are discovered during routine screening or accidental discovery of elevated blood glucose [18]. In our study, most of the patients were referred for accidental discovery of elevated blood glucose compatible with the literature data.

Glucokinase which encoded by the 50Kb ten-exon

GCK gene, phosphorylates glucose [19]. More than 700 GCK variants have been reported in different populations with no common variants or hotspots [20]. In the present study, the missense variants (n=1/10: 1 known), nonsense variants (n=7/10, 3 novel and 4 known), deletions (n=1/10, 1 novel) and splice site variants (n:1/10, 1 known) were distributed throughout the protein: 3/10 (30%) in the small domain and 7/10 (70%) in the large domain of the protein.

Missense variants of GCK gene are the most frequent causes of GCK-MODY [20]. Exon 7 was the most common location in coding regions and missense was the primary mutation type.

Clinical and laboratory characteristics of patients with molecularly proven GCK-MODY were similar with the patients with suspicion of GCK-MODY but without mutation. This suggested that there may be variants in the GCK gene that we could not detect with existing methods, or unknown genes that cause the GCK-MODY phenotype.

There are some limitations in our study. Firstly, functional studies could not be performed for novel variants. Secondly, we may not be able to detect all variants, such as large deletions and duplications that account for up to 3.5% of disease-causing variants in the GCK gene [21]. In addition to other limitations, other genes in MODY etiology were not studied in cases with no mutation in the GCK gene.

Since there is no specific treatment in GCK-MODY, the correct diagnosis is essential for optimal management of patients to prevent unnecessary use of insulin or oral antidiabetic medications. This study revealed 4 novel heterozygous variants in the GCK gene that caused GCK-MODY disease and showed that the phenotypic properties of the novel variants are similar.

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