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ORIGINAL RESEARCH

GCK Mutation Analysis and Clinical Profiles of Chinese Pediatric Patients with MODY2: Insights into Screening and Diagnosis

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Objective: To investigate the clinical and genetic features of maturity onset diabetes of the young type 2 (MODY 2) in Chinese pediatric patients and optimize the screening strategy.

Methods: A total of 11 Chinese pediatric patients diagnosed with MODY2 were enrolled in this study. Detailed clinical data and follow-up outcomes were retrospectively collected and summarized. Genetic testing was conducted using next-generation sequencing (NGS), and all identified variations were verified by Sanger sequencing.

Results: All cases carried heterozygous mutations in the *GCK* gene. 9 pathogenic variations were identified, including 8 missense mutations, 1 frameshift mutation, and 1 splice-site mutation. Among these, the mutation c.456T>G was novel. The mean age at diagnosis was 8.1±2.7 (years). 10 of 11 cases had a family history of hyperglycemia or diabetes. 2 cases were overweight. Patients exhibited mild hyperglycemia. The median HbA1c was 6.3% (interquartile range [IQR]: 6.3%–6.4%). Glucose increment in OGTT was 1.68±0.95 mmol/L. Mean triglyceride level was 0.62±0.15 mmol/L. Two cases were positive for insulin antibodies. All cases were treated with a balanced diet after diagnosis. The follow-up period was 1.5–7 years, and the median HbA1c was 6.3% (IQR: 6.2%–6.4%).

Conclusion: MODY2 typically manifests with mild, stable fasting hyperglycemia and is predominantly caused by missense mutations in the *GCK* gene. Our findings support the inclusion of triglyceride levels as a screening marker and highlight that features like overweight status and autoantibody positivity may coexist in MODY2, warranting comprehensive evaluation to prevent misdiagnosis.

Keywords: maturity onset diabetes of the young type 2, monogenic diabetes, *GCK* gene, gene mutation

Introduction

Maturity-Onset Diabetes of The Young (MODY) is a type of monogenic diabetes with autosomal dominant inheritance. The prevalence is approximately 1–5% of the adult diabetic patients[1] and 1–6% of the pediatric diabetic patients.[2] It is characterized by early-onset (ranging from 6 months to 25 years), absence of autoimmune-antibodies, non-insulin-dependent. MODY is currently categorized into 14 subtypes (MODY1-14) according to the type of mutated genes. MODY11, MODY7, MODY9 are controversial.[3] The age of onset, clinical features, treatment, and prognosis vary greatly among different subtypes.

MODY2 (also known as GCK-MODY) is an autosomal dominant disease caused by heterozygous inactivating mutations in the *GCK* (glucokinase) gene and first reported in 1992 by Froguel, P.[4] There are racial differences in the prevalence of MODY2. A multicenter real-world study from Germany showed a prevalence of MODY2 in MODY cases was 57.4%,[5] but about 12% in Norwegian.[6] A recent single-center cohort study involving Chinese children revealed that MODY2 accounted for the highest proportion, reaching 55.4%.[7]

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The *GCK* gene is located on chromosome 7p15•3-p15•1 and contains 10 exons of 2745 bp. The gene encodes glucokinase (GCK), a protein consisting of 465 amino acids.[8] Glucokinase is expressed mainly in pancreatic β-cells and liver and acts as a glucose sensor by controlling glucose phosphorylation.[9] Reduced glucokinase function results in decreased pancreatic β-cell sensitivity to glucose and a higher glucose threshold for insulin secretion, ultimately leading to hyperglycemia.

MODY2 was characterized by asymptomatic, lifelong nonprogressive mild fasting hyperglycemia and rare complications of microvascular disease. Early and precise diagnosis of MODY2 is critical which helps to avoids unnecessary pharmacotherapy. However, it is easily misdiagnosed due to overlapping features with T1DM and T2DM. It is estimated that 80% of MODY patients remain undiagnosed and receive unnecessary treatment.[10] The comprehensive clinical screening criteria (CSC) can enhance the early diagnosis rate of genetic diseases.[11] In 2008, MODY Group of the European Molecular Genetics Quality Network (EMQN) proposed a practice guideline on MODY,[12] which suggests that the following characteristics are indicative of a *GCK* gene mutation: 1. Fasting hyperglycemia (≥5.5 mmol/1) that persists (at least three times) and stabilizes over months or years. 2. HbAlc is slightly increasing but rarely exceeds 7.5%. 3. Glucose increments of 2-hour OGTT were <3 mmol/1. 4. One parent may have mild fasting hyperglycemia (5.5–8 mmol/L) or type 2 diabetes without complications unless the mutation is de novo. Recent studies have shown that triglycerides can help identify MODY2 in patients with a primary diagnosis of type 2 diabetes.[13,14] However, previous studies have mostly focused on adults or used meta-analyses to investigate mixed populations.

Most previous studies focus on adults or mixed-age cohorts,[5,15,16] leaving lacking detailed characteristic analysis on Chinese pediatric MODY2. This scarcity arises from insufficient clinician awareness and limited routine access to genetic testing. Notably, Chinese pediatric MODY2 patients require targeted study due to their population-specific characteristics.

In this study, we systematically analyzed the clinical manifestations and genetic variants of pediatric patients with MODY2 of Chinese descent to advance the comprehensive understanding of its phenotype-genotype correlations. The secondary objective is to provide clinical practice insights to help clinicians identify MODY2 early, complete genetic testing promptly, and inform optimized clinical screening criteria.

Materials and Methods

Subjects

A retrospective analysis was performed to select a total of 11 MODY2 cases admitted to the Department of Endocrinology, Beijing Children's Hospital from November 2017 to August 2024. Clinical suspicion of MODY2 was initially raised in these patients in accordance with the practice guidelines proposed by the MODY Group of the European Molecular Genetics Quality Network (EMQN).[12] Subsequently, the definitive diagnosis of MODY2 was confirmed through genetic testing.

Clinical Data and Genetic Analysis

Details of clinical data were obtained from medical records. The clinical data of the participants were retrospectively summarized, including gender, age, clinical manifestations, laboratory test results, treatments and follow-ups.

For molecular analysis, genomic DNA was analyzed by next-generation sequencing after informed consent. The genetic variants that were clearly or potentially associated with the clinical phenotypes of the subjects were verified by Sanger sequencing.

Statistical Analysis

All statistical analyses were performed with GraphPad Prism 10. Parametric continuous variables are presented as mean ±SD, and non-parametric continuous variables are presented as median±IQR (25%−75%). Continuous variables between the two groups were compared using Student's *t*-test for parametric variables or the Wilcoxon signed-rank test for non-parametric variables.

Ethics Consideration

This is a retrospective case analysis. The study protocol was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University. The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the legal guardians of all minor participants in the study at the first visit. In alignment with the hospital's established practice, informed consent for the use of patient identifiers in Table 1 data (excluding patient names) was obtained, too. In addition, all patient data were anonymized and de-identified to protect patient privacy.

Result

Clinical Characteristics and Biochemical Data

A total of 11 patients with MODY2 were included in this study, all from non-consanguineous families. Their genotypic and phenotypic characteristics are summarized in Table 1.

The mean age at diagnosis was 8.1± 2.7 (years). All cases presented with asymptomatic mild hyperglycemia. A positive family history of hyperglycemia or diabetes was observed in 10 patients: 6 cases had a 3-generation affected pedigree, while 4 cases had a 2-generation affected pedigree. The mean body mass index (BMI) was 16.8±1.3 kg/m². Among the patients, 2 were classified as overweight, with BMIs of 17.2 kg/m² and 18.5 kg/m², respectively.

The median HbA1c level was 6.3% (IQR: 6.3%–6.4%). Glycosuria was negative. The mean fasting blood glucose (FBG) and postprandial 2-h blood glucose (2hPBG) in OGTT were 6.8±0.51 mmol/L and 8.49±1.00 mmol/L, respectively. The 2-h blood glucose increment in OGTT (calculated as 2hPBG-FBG) was 1.68±0.95 mmol/L. The fasting c-peptide level was 1.95± 0.93 ng/mL. The triglyceride (TG) level was 0.62±0.15 mmol/L. Additionally, insulin antibodies were positive in 2 patients.

Genetic Analysis Results

All patients carried heterozygous mutations in the *GCK* gene. A total of 9 distinct pathogenic mutations were identified, including eight missense mutations, one frameshift mutation, and one splice-site mutation.

Notably, the mutation c.456T>G was novel. The missense mutation is located in exon 4, causing a change of amino acid 152 from phenylalanine to leucine (p. Phe152Leu). This mutation site is not present in the normal population databases. Sanger sequencing validation showed that the patient's father carried the same heterozygous variant, while the mother had the wild-type *GCK* genotype. No prior literature reports or entries in the ClinVar database have documented this mutation. The result of the protein prediction software, REVEL, was deleterious. According to the ACMG guideline, this mutation was classified as pathogenic (PS1+PM2_Supporting+PM5_Strong +PP3_Strong).

Treatment and Long-Term Follow-up

All these patients are managed with a balanced diet regimen without any pharmacological treatment. The duration of follow-up was 1.5–7 years. The median HbA1c was 6.3% (IQR: 6.2%–6.4%) at the last follow-up, with no statistically significant difference compared to the baseline. No diabetic complications were observed.

Discussion

In our study, gene analysis identified 9 mutations, including 8 missense mutations, 1 frameshift mutation, and 1 splice-site mutation. Missense mutations were the most common types. To date, more than 900 mutation sites have been included in the HGMD (Human Gene Mutation Database), and the types of variants contain missense mutations, nonsense mutations, frameshift mutations, insertion deletion mutations, duplications, and splice site variants. Missense mutations were the most common, accounting for 62%. The mutation sites were distributed over all exons (most frequently detected in exons 7 and 9) and no hotspot mutations were found in the previous study.[17] However, the p. T206P was identified in six unrelated families of Jewish-Ashkenazi descent, suggesting an ethnogenesis correlation.[18] Most of the mutation sites in this study were in exon 7. No hotspot mutations were identified. Further large data studies remain necessary.

Table 1 Molecular and Clinical Features of the Childhood-Onset Patients with MODY2

	Gender	Age at Diagnosis	cDNA Variants	Amino Acid Change	BMI (percentile)	HbA1c (%)	Fasting Glucose (mmo/L)	2-h Glucose (mmo/L)	Glucose Increments in OGTT (mmo/L)	Fasting c-peptide (ng/mL)	Autoantibodies	Triglyceride (mmo/L)	Treatment	Follow-up Years (y)	HbA1c (%)
Case 1	F	10y	c.1142T>C	p.M381T	17 (53.6%)	6.5	7.64	8.3	0.66	1.06	–	1.01	Diet	3	6.3
Case 2	F	9y	c.971T>C	p.L324P	15.8 (40.1%)	6.2	7	9.4	2.4	0.52	–	0.7	Diet	3	6.2
Case 3	M	5y2m	c.790G>A	p.G264S	16.1 (71.6%)	6.3	6.83	9.7	2.87	2.78	–	0.43	Diet	2	6.2
Case 4	M	8y	c.775G>A	p.A259T	16.6 (38.2%)	6.4	6.44	9.64	3.2	3.64	IAA+	0.54	Diet	3.5	6.2
Case 5	F	6y	c.683C>T	p.T228M	17.2 (86.4%)	6.2	6.87	8.47	1.6	1.26	–	0.61	Diet	4	6.2
Case 6	F	10y	c.683C>T	p.T228M	17 (52%)	6.8	7.52	8.4	0.88	2.47	IAA+	0.72	Diet	1.5	6.4
Case 7	F	8y	c.680–2A>C	Splice-site	18.5 (86.4%)	6.3	6.89	8.5	1.61	2.2	–	0.54	Diet	4	6.3
Case 8	F	9y	c.680–2A>C	Splice-site	18.5 (80.5%)	6.4	6.97	8.6	1.63	2.4	–	0.56	Diet	4	6.3
Case 9	F	8y	c.661G>A	p.E221K	14.6 (23.6%)	6.4	5.87	6.8	0.93	1.4	–	0.59	Diet	3.5	6.4
Case 10	M	13y	c.456T>G	p.F152L	18.1 (44.8%)	6.4	6.4	6.67	0.27	1.16	–	0.64	Diet	3.5	NA
Case 11	M	3y2m	c.452_c.454delCCT	p.S151_F152delinsF	15.1 (18.9%)	6.3	6.4	8.9	2.5	2.57	–	0.56	Diet	7	6.4

Abbreviations: HbA1c glycated hemoglobin; BMI Body Mass Index; IAA insulin autoantibodies; NA, Not available.

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Previous functional analyses have shown that mutations in the *GCK* gene can attenuate the glucose-binding ability of the enzyme by directly affecting kinetic parameters, post-translational structural stability of the protein, post-translational regulation, or cysteine S-nitrosylation.[17,19–21] Some of the mutations in this study have been validated in functional or modeling studies. The M381T mutant led to a decrease in the stability of the three-dimensional structure of *GCK*.[20] The G264S mutant caused a slight decrease in the thermal stability of the *GCK*.[22] M. Stoffel et al have shown that the T228M mutation affects the affinity for ATP by using computer-aided modeling.[23] Enzyme kinetic studies have shown that the E221K mutant is kinetically inactivated, with decreased catalytic rate, decreased affinity for glucose, and decreased affinity for ATP.[15]

In this study, we identified a novel missense mutation in the *GCK* gene: c.456T>G, which results in the amino acid substitution p. Phe152Leu. Notably, a distinct nucleotide variant within the same codon (c.454T>C) that also leads to the p. Phe152Leu substitution has been previously reported as pathogenic in studies from Belgium and Luxembourg. Functional hypotheses suggest this variant may impair the enzyme's glucose-binding site.[24] Additionally, Gozlan et al described a 16-year-old Moroccan MODY2 patient with another pathogenic *GCK* variant in this codon: c.455T>C, which causes the amino acid change p.Phe152Ser.[18] These findings indicate that codon 152 of the *GCK* gene can be affected by diverse pathogenic variants, providing contextual support for the potential pathogenicity of our newly identified c.456T>G (p. Phe152Leu) mutation.

MODY2 is characterized by early onset of hyperglycemia. 86.4% of cases were childhood onset,[5] mostly at pre-school or school age. The mean age of onset in this study was 8.1±2.7 (years), consistent with results from Italian and Spanish studies.[25,26] MODY2 patients presented with mild asymptotic hyperglycemia. The mild hyperglycemia remains below the renal threshold. As a result, glycosuria and its associated symptoms of polyuria, polydipsia, and weight loss are rarely observed.[27] In our study, all children presented with incidentally elevated glucose, and glycosuria was negative. According to the literature, MODY2 patients usually exhibit blood glycemic abnormalities as slightly elevated fasting blood glucose (FBG), ranging from 5.5 to 8.5 mmol/L, and elevated HbAlc levels, ranging from 5.6 to 7.6%.[28] Our study showed the blood glucose levels of the patients were in accordance with the results of a single-center study in Italy.[25]

Although non-obesity is a classic feature of MODY, a subset of patients may still present with overweight or obesity. For instance, epidemiological data from Spain showed that 6.6% of MODY2 cases were obese.[26] Additionally, in a cohort of overweight/obese children and adolescents initially diagnosed with T2D, 4.5% were later confirmed to have monogenic diabetes.[29] In our own study, two patients (18.1% of the total cohort) were overweight, with BMIs of 17.2 kg/m² and 18.5 kg/m² respectively. While this overweight rate appears higher than reported in other countries, it is likely attributed to the overall small size of our sample or reflect the rising background rates of childhood overweight in China. Our primary aim is to emphasize that overweight/obese status should not be used as a basis to rule out the possibility of MODY2 in patients with hyperglycemia and avoids misdiagnosis as T2DM.

Insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA), protein tyrosine phosphatase-like protein antibodies (IA-2A), islet cell antibodies (ICA), and β-cell-specific zinc transporter 8 antibodies (ZnT8A) are widely recognized as immunological markers associated with T1DM. However, Over-reliance on diabetic autoantibody positivity as a diagnostic marker risks misclassifying MODY2 cases as T1DM. We found that two cases were positive for IAA in our study. Nevertheless, the levels of fasting blood glucose, insulin, and C-peptide in these children, as well as their long-term prognosis, did not support the diagnosis of T1DM. Thus far, evidence has demonstrated that patients with MODY2 may exhibit positivity of diabetes autoantibodies, accounting for 5.4%-17%.[5,25,30] This phenomenon may stem from either coincidental genetic overlap or non-specific immune activation induced by chronic mild hyperglycemia. Additionally, existing evidence indicates that autoantibody positivity can occur in the general population, with a prevalence of approximately 1%.[31] These findings collectively suggest that diabetic autoantibody positivity should not be an absolute exclusion criterion for MODY2. Clinically, this implies that for patients with mild, stable hyperglycemia and autoantibodies—particularly those with a family history of diabetes, clinicians should recommend *GCK* gene testing and long-term β-cell function monitoring, rather than immediately diagnosing T1DM and initiating insulin therapy.

Regarding the clinical screening strategy, the fasting blood glucose, HbAlc level, family history, and blood glucose increment in OGTT of our cases were basically in accordance with the clinical practice guideline proposed in 2008. It

helped with timely cost-effective genetic testing to make a correct diagnosis. Notably, recent studies have highlighted triglycerides as a potential supplementary screening indicator for MODY2. Jing Liu et al found that triglyceride levels were much lower in MODY2 compared with the T2DM.[14] Yumin Ma et al further demonstrated that in adults, a triglyceride level of ≤1.43 mmol/L could distinguish MODY2 from T2DM with a sensitivity of 100% and a specificity of 68.4%.[13] This observation can be accounted for by the common presence of hypertriglyceridemia in T2DM patients. Heterozygous inactivating variants of the *GCK* gene may account for the reduced triglyceride levels. In fact, previous studies have demonstrated an association between common *GCK* variants and triglyceride (TG) levels.[32] In our pediatric cohort, the mean triglyceride level was 0.62±0.15 mmol/L—consistent with findings from a large Chinese pediatric MODY2 study.[7] Triglyceride levels exhibited potential screening marker for MODY2, though this requires validation with larger samples from multiple centers.

Medications such as insulin and oral hypoglycemic agents are not recommended for MODY2 except during pregnancy when there is excessive fetal growth. Previous studies have confirmed drug therapy had no significant reduction in blood glucose or HbA1c levels.[5,16,33] Dorzagliatin is a novel, dual-acting variant of the GCK activator that has been identified to directly increase the enzyme activity of *GCK* mutants[34] and reduce HbA1c levels.[35] In MODY2, the long-term risk of microvascular complications is low.[36] In our study, all cases were treated with dietary control after diagnosis and were followed up for 1.5 to 7 years, and long-term glycemic control remained stable No complications of diabetic microangiopathy were observed.

Our study summarizes the clinical and genetic characteristics of 11 pediatric patients, providing preliminary insights into the disease's phenotypic spectrum in Chinese children, but key limitations exist. The small sample size arises from the retrospective design (relying on limited historical records) and pediatric MODY2's rarity. This limited sample size directly impacted the study's statistical robustness: we just focused solely on descriptive statistics instead of inferential analyses. The generalizability of our findings to broader pediatric MODY2 populations is restricted. Nevertheless, descriptive findings such as coexistent overweight/autoantibody positivity still guide clinicians in identifying this rare disease. Future multicenter, large-sample prospective studies are needed to validate observations and confirm genetic-clinical correlations.

Conclusion

In this study, we characterized the clinical phenotypes, genetic profiles, and outcomes of Chinese pediatric MODY2 patients, identifying a novel *GCK* mutation (c.456T>G, p. Phe152Leu) that expands the genetic spectrum of MODY2 in Chinese populations and underscores codon 152's relevance to glucokinase function. Our findings confirm pediatric MODY2 typically presents with asymptomatic mild fasting hyperglycemia, is mainly caused by *GCK* missense mutations, and can be managed with diet alone, with low microvascular risk. Genetic testing is pivotal for diagnosis, and we recommend screening in children with mild fasting hyperglycemia, HbA1c ≤7.5%, positive family history, and OGTT 2h increment <3mmol/L. Triglyceride levels showed potential associations with MODY2 in our pediatric cohort, and future large-sample prospective studies with comparison groups is necessary. In addition, factors such as obesity/overweight and positive autoantibodies should not be used as a basis to rule out the possibility of MODY2.

Acknowledgments

Chang Su and Yurong Piao have contributed equally to this work and share the first authorship.

Disclosure

The authors declare no conflicts of interest.

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