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A Case Report of MODY 2 with Growth Hormone Deficiency Caused by GCK Mutation

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Abstract: *Objective*: To investigate the clinical and molecular genetic characteristics of Chinese adolescents with maturity-onset diabetes of the young type 2 (MODY 2) and the safety and efficacy of recombinant human growth hormone (r-hGH). *Methods*: The clinical features and laboratory data of a family with MODY 2 combined with partial growth hormone deficiency (pGHD), diagnosed at the Fourth Clinical Medical College of Xinjiang Medical University, were analyzed. DNA was extracted from peripheral blood using the column method, and Sanger sequencing was conducted to analyze the glucokinase (GCK), hepatocyte nuclear factor 1α (HNF1α), and hepatocyte nuclear factor 4α (HNF4α) in the proband and relevant family members. *Results*: A heterozygous mutation in GCK (Reference sequence: NM_000162, location: Exon 10) c.1340G > A (p.R447Q)) was detected in three family members (the proband, the proband's younger brother, and their mother). The proband also had pGHD. *Conclusion*: GCK mutations causing MODY 2 exist in the Chinese population, and the combined treatment with r-hGH is safe and effective.

Keywords: MODY; GCK; Gene mutation; GHD

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1. Introduction

Maturity-onset diabetes of the young (MODY) in adolescents is a monogenic disease with genetic heterogeneity, primarily caused by impaired function or development of the islets (including insulin-secreting pancreatic β-cells). MODY could cause insulin secretion deficiency in the absence of obesity. The most common form of monogenic diabetes is MODY, which may account for 0.5%–5% of patients diagnosed with non-autoimmune diabetes, with a prevalence of approximately 100 cases per 1 million people among European Caucasians [1]. In a study from Hong Kong, China, targeted sequencing of 33 genes associated with monogenic diabetes was conducted on 1021 Chinese

patients diagnosed with type 1 diabetes at ≤ 40 years of age, and a total of 22 patients (2.2%) were found to have monogenic diabetes. Among patients diagnosed with diabetes before the age of 30, the prevalence of monogenic diabetes was 4.1%, and among those diagnosed before the age of 20, the prevalence was 10.6%. The pathogenic mutations are distributed as follows: hepatocyte nuclear factor 1α (HNF1α) 40.9%, glucokinase (GCK) 27.3%, and hepatocyte nuclear factor 1β (HNF1B) 13.6%, followed by peroxisome proliferator-activated receptor γ (PPARγ) 9.1%, hepatocyte nuclear factor 4α (HNF4α) 4.6%, and perilipin 1 (PLIN1) 4.6% [2]. However, the true prevalence of monogenic diabetes remains unclear and may be significantly underestimated in many countries due to limited access to or unavailability of genetic testing, lack of provider awareness, and the overlap of clinical characteristics with more common forms of diabetes. In fact, even in most affluent countries, genetic testing is not widely accessible: for example, in the UK, >80% of MODY cases may go undiagnosed [3]. Currently, over 40 subtypes of monogenic diabetes have been identified, with the most common being MODY 2 caused by GCK mutations, MODY 3 caused by HNF1α mutations, and MODY 1 caused by HNF4α mutations. This study focuses on MODY 2 caused by GCK mutations, with clinical analysis and genetic testing performed on some family members.

2. Case presentation

A 14-year-old male of Han ethnicity is the second child of the first pregnancy, born at full term via spontaneous vaginal delivery, without any asphyxia at birth. His birth length was 48 cm, and his weight was 2.8 kg. There were no significant issues in his birth history. He was breastfed and experienced no feeding difficulties. He reached developmental milestones such as teething, sitting, crawling, and walking at the same age as his peers, although he has consistently been shorter than his contemporaries. In June 2020, at the age of 13, he sought medical attention at the referring hospital due to short stature, where his height was recorded at 148.0 cm (P3%–P10%), and his weight was unspecified; fasting blood glucose ranged from 6.8 to 7.1 mmol/L, and glycated hemoglobin (HbA1c) was 7.40%. During this period, no definitive diagnosis was made, and he was placed on dietary control while monitoring his blood glucose levels, with a random blood glucose reading of 6.4 mmol/L and an HbA1c of 6.70%. In July 2021, he was hospitalized at the referring hospital, where his HbA1c was found to be 7.1%, and fasting blood glucose was 6.8 mmol/L. Tests for IAA, ICA, and GAD were negative, and he was diagnosed with "diabetes" (without classification). Therefore, dietary control was recommended. After discharge, on July 15, he visited the hospital, having received a 3.75 mg injection of Triptorelin every 28 days for 6 months at the referring hospital (with a height increase of 4.8 cm over nearly one year). Physical examination revealed a height of 152.8 cm (P3%–P10%), a weight of 37 kg (P3%–P10%), and testicular volume (R/L) of 10–12 ml. The calculated target height based on genetic potential was 166.5 ± 5 cm. His medical history was otherwise unremarkable. Family history includes a grandmother with type 2 diabetes.

Laboratory data showed that the routine blood, urine, and stool tests, as well as liver and kidney function tests and blood lipid profiles, showed no significant abnormalities; 25-hydroxyvitamin D: 22.33 ng/ml, alkaline phosphatase: 287 U/L, glycosylated hemoglobin: 7.13%; adrenocorticotropic hormone: 22.75 pg/ml, cortisol: 7.07 μg/dl; FT3: 5.92 pmol/L, FT4: 16.89 pmol/L, TSH: 2.5 μIU/mL; luteinizing hormone: 0.15 mIU/ml, follicle-stimulating hormone: 0.77 mIU/ml, testosterone: < 0.10 ng/ml; GH: 0.34 ng/mL, IGF-1: 338 ng/mL. **Table 1** shows the proband's glucose tolerance test results, with fasting blood glucose consistently elevated (6.67–7.34 mmol/L). **Table 2** reveals a suboptimal growth hormone peak (5.83 ng/mL) in response to levodopa stimulation, supporting pGHD diagnosis. **Figure 1** demonstrates his delayed bone age (14y-), consistent with growth hormone

deficiency while **Figure 2** confirms no pituitary abnormalities on MRI.

Table 1. Glucose tolerance test

Time (min)	0	30	60	120	180
Blood glucose (mmol/L)	6.67	7.99	7.18	7.07	7.34
Insulin (pmol/L)	60.2	272.66	115.82	197.33	82.34
C-peptide (nmol/L)	0.629	1.96	1.32	1.85	1.13

Table 2. Stimulation test of growth hormone in response to levodopa

Time (min)	0	30	60	90	180
Growth hormone (ng/ml)	0.34	5.83	5.32	3.44	1.25

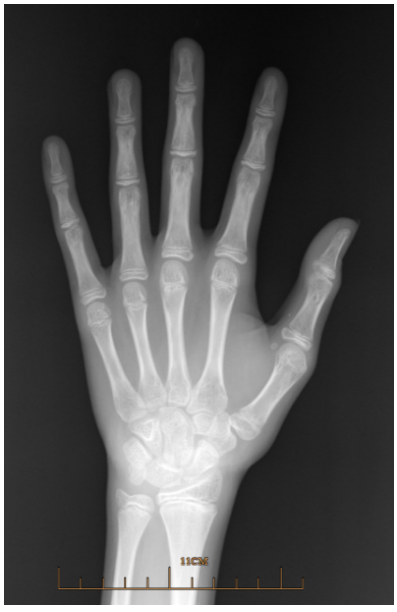

Figure 1. Bone age assessment: 14y-

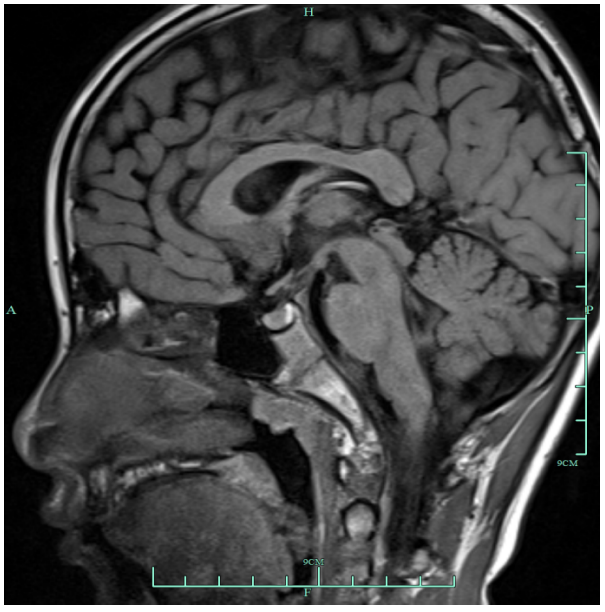

Figure 2. Pituitary MRI: No significant abnormalities observed

The proband's younger brother is 12 years and 6 months old, the third child from the second pregnancy, born full term via spontaneous vaginal delivery, with no history of asphyxia at birth. He was born measuring 50 cm in length and weighing 3.23 kg, and there were no notable circumstances during the birth. He was breastfed and experienced no feeding difficulties, and his milestones for teething, sitting, crawling, and walking were consistent with those of his peers, although he has always been shorter than them. In June 2020, he sought treatment at an external hospital for short stature, where his height was measured at 148.0 cm (P25%–P50%), and his weight was not specifically recorded (**Figure 3**). His fasting blood glucose ranged from 6.05 to 6.58 mmol/L, with a HbA1c of 6.49%. During this period, no definitive diagnosis was made, and he was advised to control his diet and monitor his blood glucose. Random blood glucose was 6.29 mmol/L, and HbA1c was 6.59%. In July 2021, he was hospitalized at a referring hospital, where his HbA1c was 7.1% and fasting blood glucose was 6.8 mmol/L. Tests for IAA, ICA, and GAD were

negative, and he was diagnosed with "diabetes" (without classification). Therefore, dietary control was recommended. After discharge, he visited the hospital on July 15, and by that time, he had been receiving monthly injections of 3.75 mg triptorelin for the past 6 months, during which his height increased by 4.7 cm. Physical examination revealed a height of 152.7 cm (P25%–P50%), weight of 40 kg (P25%–P50%), and testicular volume (R/L) of 10–12 ml. The target height was calculated to be 166.5 ± 5 cm, and his medical history was otherwise unremarkable. **Table 3** and **Table 4** detail the younger brother's glucose tolerance and GH stimulation tests, showing similar metabolic patterns. **Figure 3** (bone age: 13y+) and **Figure 4** (normal pituitary MRI) further corroborate findings.

Table 3. Glucose tolerance test

Time (min)	0	30	60	120	180
Blood glucose (mmol/L)	6.17	10.31	8.47	7.73	7.08
Insulin (pmol/L)	53.46	674.9	406.12	353.39	274.43
C-peptide (nmol/L)	0.606	3.03	2.86	2.53	2.21

Table 4. Stimulation test of growth hormone in response to levodopa

Time (min)	0	30	60	90	180
Growth hormone (ng/ml)	1.25	4.54	5.63	13.55	14.71

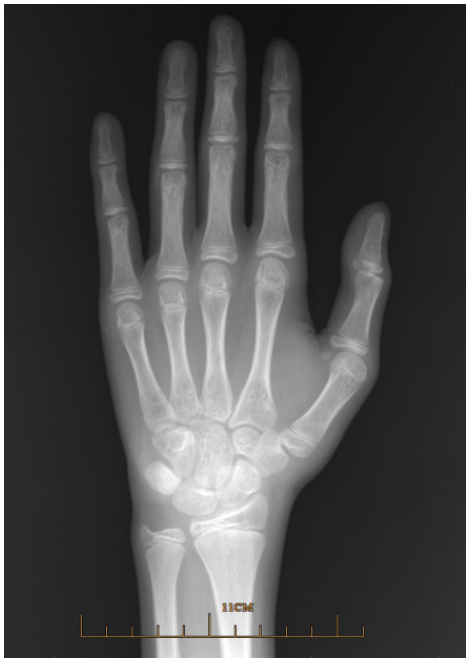

Figure 3. Bone age assessment: 13y+

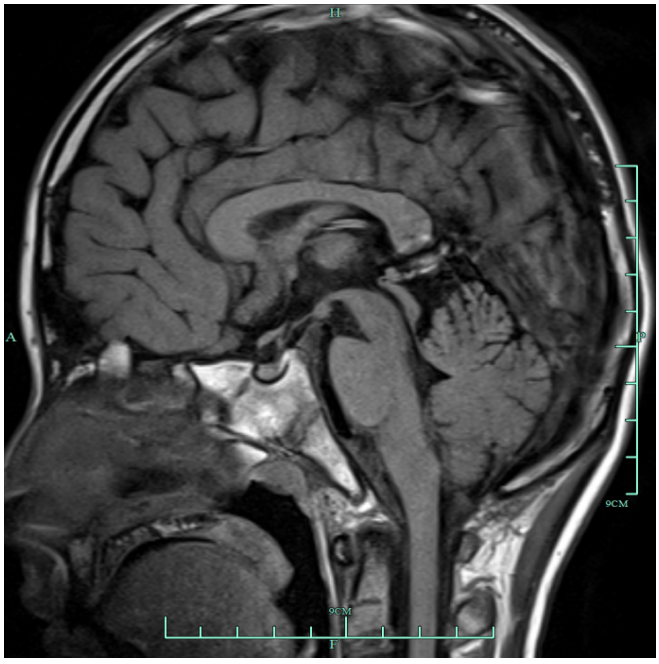

Figure 4. Pituitary MRI: No significant abnormalities observed

Proband's mother has glycated hemoglobin of 6.33%, while fasting blood glucose is 7.05 mmol/L, as shown in **Table 5**. The father's glucose tolerance test (**Table 6**) demonstrates normal glycemic regulation, with appropriate insulin and C-peptide responses. Proband's father had HbA1c value of 5.48%. The mother's OGTT

confirms GCK-MODY with fasting hyperglycemia and delayed insulin secretion, while the father's results indicate preserved pancreatic β-cell function, corroborating autosomal dominant inheritance of the GCK mutation from the maternal side.

Table 5. Proband's mother glucose tolerance test

Time (min)	0	30	60	120	180
Blood glucose (mmol/L)	7.05	10.52	11.35	8.21	6.25
Insulin (pmol/L)	42.29	236.94	331.42	342.29	94.74
C-peptide (nmol/L)	0.61	1.76	2.75	3.27	1.64

Table 6. Proband's father glucose tolerance test

Time (min)	0min	30min	60min	120min	180min
Blood glucose (mmol/L)	5.02	7.02	5.57	4.6	5.43
Insulin (pmol/L)	85.97	580.37	318.27	133.14	243.09
C-peptide (nmol/L)	0.922	3.34	2.94	2.41	2.87

2.2. Genetic testing results

Based on **Figure 5** to **Figure 8**, the proband, his younger brother, and their mother all carry a variant in GCK (reference sequence: NM_000162, location: Exon 10) c.1340G > A (p.R447Q). This variant results in a heterozygous mutation at nucleotide 1340 in the coding region of GCK, where guanine (G) is replaced by adenine (A) (c.1340G > A), causing a change in the 447th amino acid from arginine to glutamine (p.R447Q), which is classified as a missense mutation. Based on the available evidence, this variant is defined as pathogenic. According to Sanger validation, this variant was inherited from the mother.

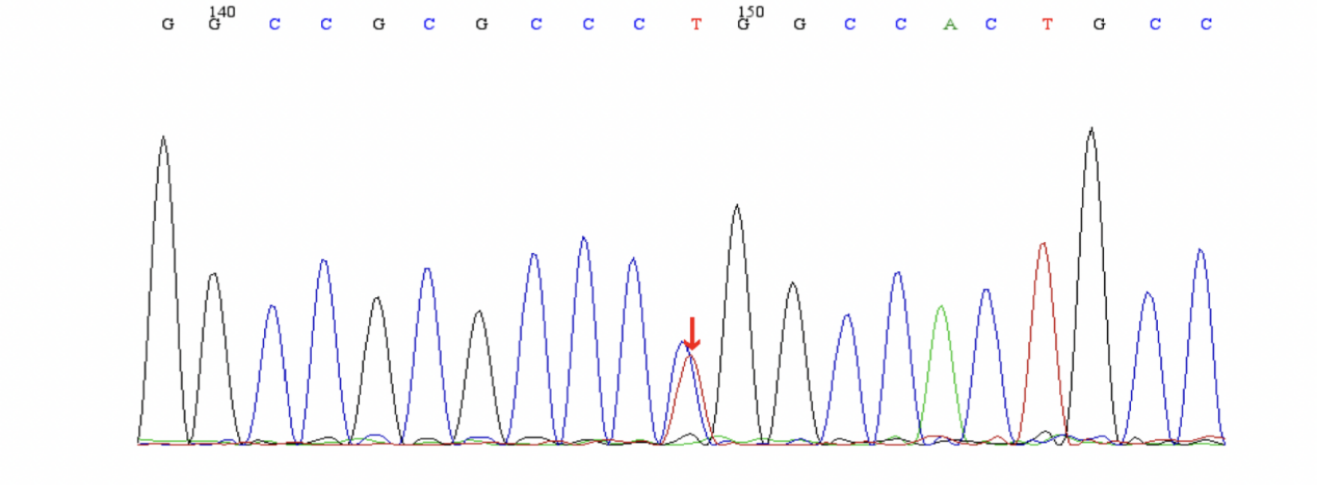

Figure 5. The proband

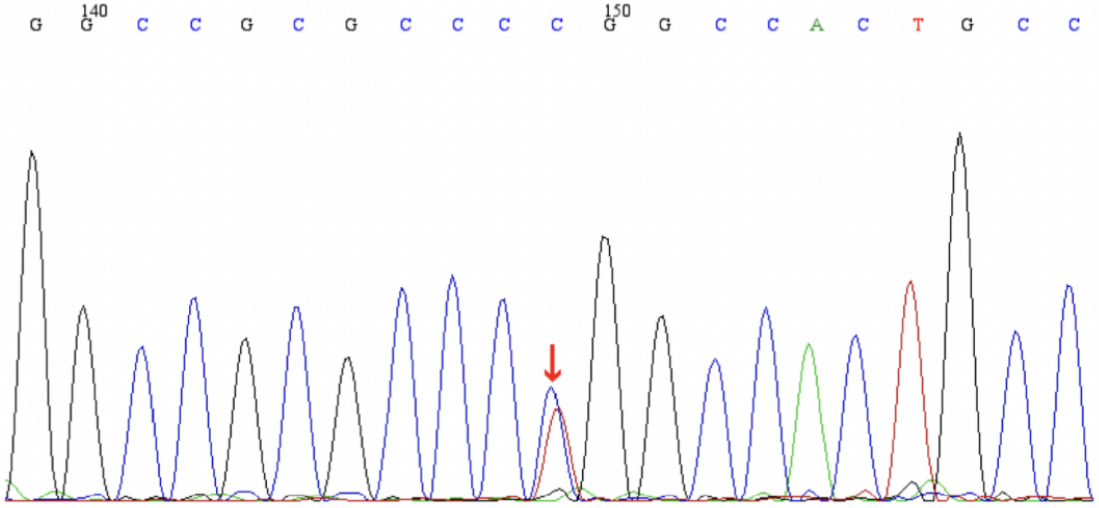

Figure 6. The proband's younger brother

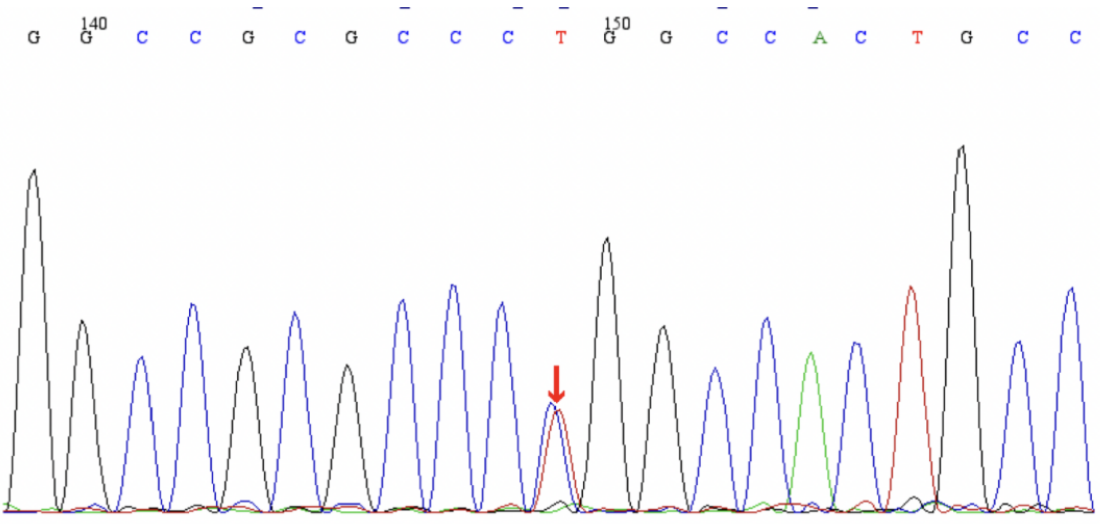

Figure 7. The proband's mother

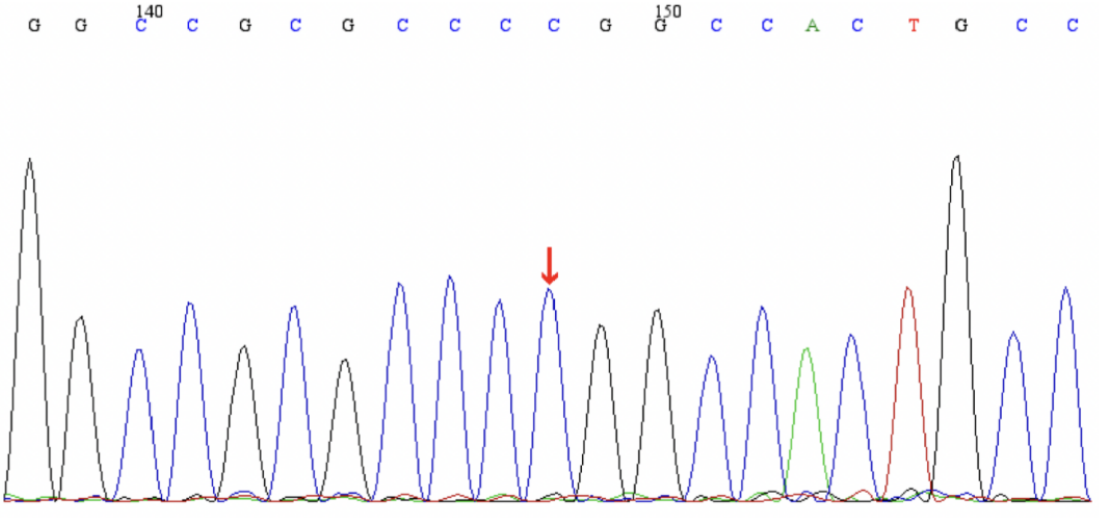

Figure 8. The proband's father

3. Treatment outcome of conversion therapy

The proband and his younger brother were both diagnosed with MODY 2, which can be managed through diet and exercise without the need for pharmacological intervention. Considering the predicted short stature of the proband and his younger brother, and the strong request from the patient and his mother for treatment, they were informed of the risk of increased blood glucose due to growth hormone therapy. Close monitoring of blood glucose was advised during treatment, along with regular follow-up visits. Informed consent was obtained before initiating combined therapy with gonadotropin-releasing hormone analogue (GnRHa) injections and recombinant human growth hormone (r-hGH). This intervention was intended to suppress bone age advancement while supplementing growth hormone. The treatment plan also included dietary, exercise, and sleep guidance.

3.1. Treatment plan

3.1.1. The proband

For the first 3 months, GnRHa injections were used for intensive treatment, with monthly monitoring of LH/FSH. After that, regular follow-ups were conducted every 3 months to monitor LH/FSH, fasting blood glucose, fasting insulin, and thyroid function. IGF-1 and GH levels were also monitored. The dosage of growth hormone was adjusted based on the treatment response and changes in body weight. As shown in **Table 7**, the proband's height increased from 152.8 cm to 168.5 cm over 25 months.

Table 7. Proband's treatment response and monitoring data during GnRHa + r-hGH therapy

Age	H/cm	W/kg	BA	LH	FSH	GH	IGF-1	FBG	INS	TSH	rhGH/IU/kg.d	GnRHa/mg
14y3m	152.8	37	14y-	2.5	0.77	0.34	338	6.67	60.23	1.74	0.15	3.75/28d
14y4m	153.4	37	-	0.28	1.07	-	-	-	-	-	0.15	3.75/28d
14y5m	153.6	38.5	-	0.28	0.82	-	-	7.19	-	-	0.15	3.75/28d
14y8m	157.0	40	-	0.1	1.64	4.21	364	6.38	63.29	1.17	0.15	3.75/28d
14y11m	158.1	40	14y	0.1	0.90	2.69	390.1	6.42	40.93	2.04	0.15	3.75/28d
15y6m	161.2	43	15y-	0.07	0.73	4.36	401	7.14	87.79	1.43	0.15	3.75/28d
15y9m	163.3	43	-	0.44	0.76	12.7	402	6.63	42.87	1.23	0.2mg (PEG-rhGH)	DC
16y4m	168.5	48	15y-	2.93	9.45	9.12	327	6.39	23.92	2.01	DC	DC

3.1.2. The proband's younger brother

For the first 3 months, GnRHa injections were used for intensive treatment, with monthly monitoring of LH/FSH. After that, regular follow-ups were conducted every 3 months to monitor LH/FSH, fasting blood glucose, fasting insulin, and thyroid function. IGF-1 and GH levels were also monitored. The dosage of growth hormone was adjusted based on the treatment response and changes in body weight. **Table 8** highlights a 17.3 cm height gain (152.7 cm to 170.0 cm) without significant glucose deterioration.

Table 8. Younger brother's treatment outcomes with combined therapy

Age	H/cm	W/kg	BA	LH	FSH	GH	IGF-1	FBG	INS	TSH	rhGH/IU/kg.d	GnRHa/mg
12y5m	152.7	40	13y	0.41	0.99	1.25	396	6.37	53.46	1.21	0.15	3.75/28d
12y8m	153.2	40	-	0.51	1.3	-	-				0.15	3.75/28d
12y9m	154.2	41	-	0.23	0.99	-	-				0.15	3.75/28d
13y	155.7	43	-	0.17	1.78	2.71	329	6.89	75.53	1.06	0.15	3.75/45d
13y3m	158.3	44	13y+	0.4	1.97	1.47	382	6.51	53.05	1.44	0.15	3.75/45d
13y11m	163.1	49	14y	0.29	0.89	2.12	342	6.5	45.5	1.24	0.15	15/3m
14y1m	165.1	54	-	0.3	1.33	0.15	242	6.37	55.77	1.28	0.15	DC
14y6m	170	62	14y+	4.03	8.57	8.47	291	6.22	47.33	1.51	DC	DC

Figure 9 and **Figure 11** show the proband's and his younger brother's bone age assessment, while **Figure 10** and **Figure 11** show their pituitary MRI. After 25 months of treatment, the proband's height increased by 15.7 cm, and the height of the proband's younger brother increased by 17.3 cm. The treatment was safe and effective. During the 6-month follow-up, it was found that the Proband's height was 170.0 cm, while the proband's younger brother's height was 172.0 cm.

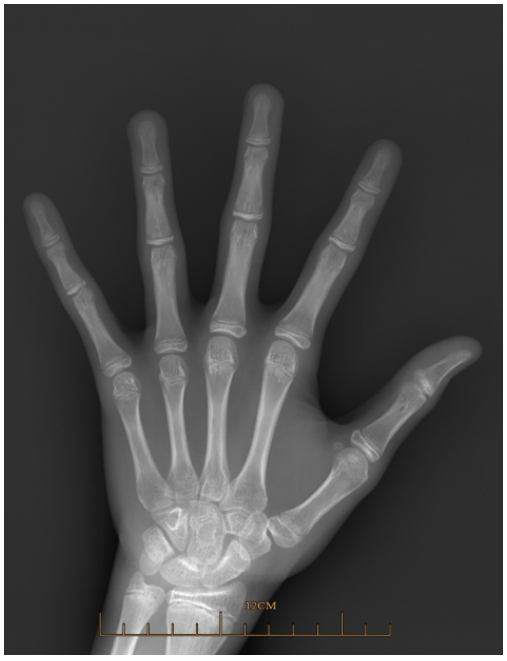

Figure 9. The proband's bone age assessment: 15y —

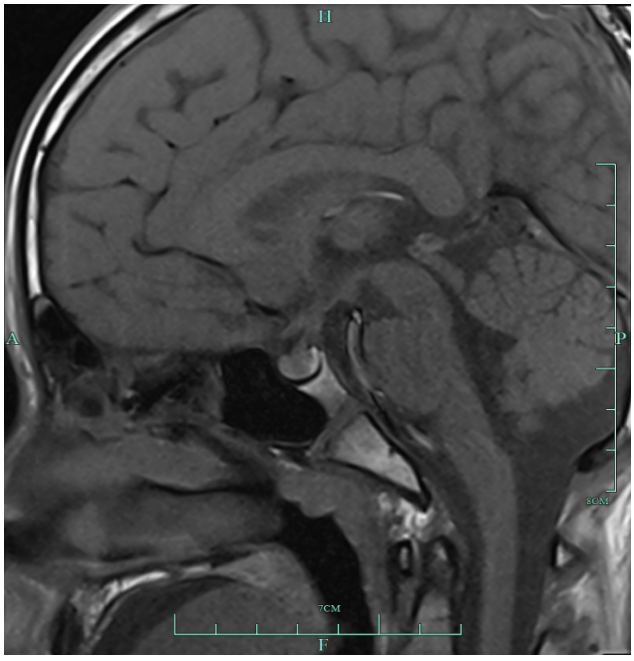

Figure 10. The proband's pituitary MRI

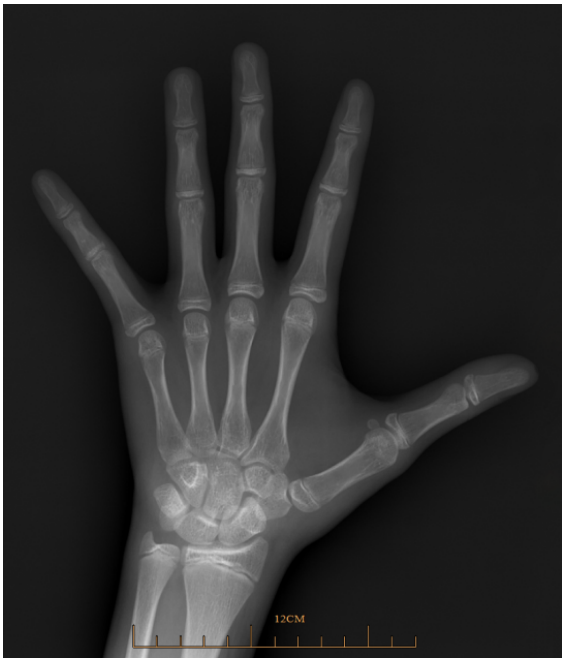

Figure 11. Bone age assessment of the proband's younger brother: 14y ＋

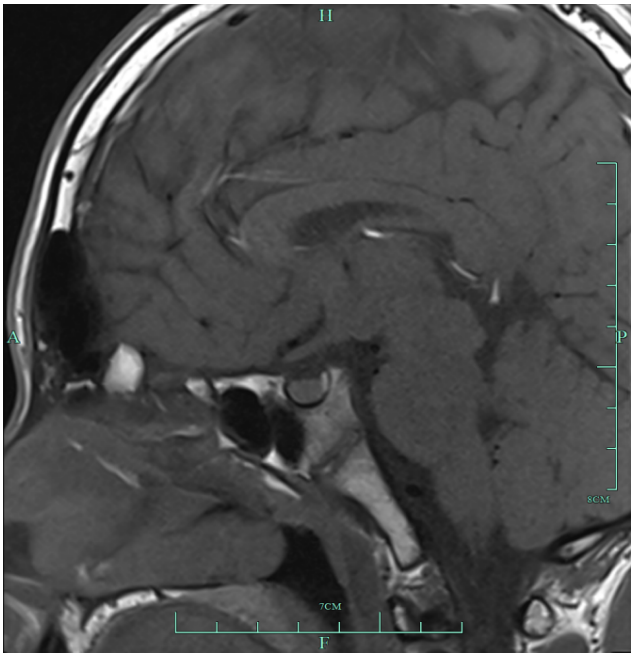

Figure 12. Pituitary MRI of the proband's younger brother

4. iMDT discussion

MODY is an autosomal dominant form of early-onset diabetes, accounting for about 1%–2% of all diabetes cases. It typically manifests in childhood or early adulthood (usually before the age of 25, although diagnosis may occur later in life). The initial presentation primarily involves insulin secretion deficiency and frequent insulin resistance. Genetic pathways specific to β-cells lead to impaired insulin secretion, but there is little to no defect in insulin action (in the absence of obesity). In most cases, MODY is inherited in an autosomal dominant manner. Due to its phenotypic overlap with type 1 and type 2 diabetes, it is often misdiagnosed. One of the most common forms is MODY 2, which is caused by mutations in GCK, thus also called GCK-MODY. GCK-MODY typically exhibits no significant clinical symptoms, presenting with persistently mild fasting hyperglycemia (5.4–8.3 mmol/L) from birth and mildly elevated HbA1c. For patients under the age of 40 years, HbA1c ranges from 5.6%–7.3% (in this case, the proband had an HbA1c of 7.13%, and the proband's younger brother had an HbA1c of 6.72%); for those over 40, it ranges from 5.9%–7.6% (the proband's mother had an HbA1c of 6.33%) [4, 5]. Individuals with GCK mutations can live relatively healthy lives long-term with proper dietary control, without the need for medication, except in specific cases like pregnancy [6]. Compared to treated individuals, untreated GCK-MODY patients show no significant differences in HbA1c or in the incidence of microvascular and macrovascular complications. Among long-term complications, non-proliferative retinopathy is the only microvascular complication, and its occurrence is only slightly higher in GCK-MODY patients than in healthy individuals [7]. Therefore, treatment is generally unnecessary unless the patient also develops type 1 or type 2 diabetes, obesity (extremely rare), or becomes pregnant [8, 9].

Growth hormone is synthesized, stored, and secreted in pulses by somatotropic cells. Its synthesis and release are regulated by various hormones, including growth hormone-releasing hormone (GHRH), somatostatin, ghrelin, insulin-like growth factor-1 (IGF1), thyroid hormones, gonadal steroids, and glucocorticoids. The growth hormone

levels are higher during the fetal, neonatal, and pubertal periods compared to adulthood and increase in response to chronic malnutrition, exercise, trauma, and sepsis [10]. In children and adolescents, the growth hormone promotes increased bone length and bone density while it also plays a crucial role in increasing muscle mass, regulating lipid and carbohydrate metabolism, and maintaining body water balance. Studies suggest that growth hormone antagonizes insulin action through unclear mechanisms [11]. An analysis of data from 19 studies involving 913 patients showed that growth hormone significantly increases fasting insulin, glucose, and HbA1c [12]. However, many studies found no changes in HbA1c [13, 14]. This emphasizes the need for close blood glucose monitoring during treatment with r-hGH for both the proband and his younger brother.

Growth hormone deficiency (GHD) refers to a condition characterized by impaired secretion of growth hormone from the anterior pituitary gland, resulting in growth disorders. This condition can be either congenital or acquired and may occur alone or in conjunction with multiple pituitary hormone deficiencies (MPHD). Early diagnosis and treatment are essential, as initiating r-hGH therapy promptly can help individuals achieve their genetically determined height. Currently, the most commonly used tests for evaluating growth hormone secretion include clonidine, arginine, and insulin-induced hypoglycemia stimulation. There is still no consensus on the diagnosis of GHD, and the threshold for diagnostic peak growth hormone levels remains a topic of debate. In China, the diagnostic standard for GHD, based on stimulation tests, is defined as a peak value of < 10 μg/L, with a peak value of < 5 μg/L for complete GHD, and severe GHD is typically defined as < 3 μg/L [15]. However, most European countries and nations such as Japan recommend adjusting the diagnostic threshold to < 7 μg/L based on clinical trials and literature data [16]. In this case, the peak growth hormone level of the MODY 2 patient was 5.83 μg/L, which meets the diagnostic criteria set by both domestic and international standards and results in a diagnosis of partial GHD.

Additionally, because growth hormone reduces insulin sensitivity, patients diagnosed with diabetes may require increased insulin. However, due to impaired body composition (a reduced proportion of lean body mass), GHD may alter glucose metabolism, while growth hormone treatment can reverse this effect. Therefore, patients with concurrent diabetes or at risk of diabetes should not discontinue rhGH treatment. After initiating r-hGH therapy, blood glucose control may deteriorate, and the beneficial effects on glucose metabolism will only become evident over time as body composition improves. For these patients, it is advisable to start with a low dose of r-hGH treatment [17]. Blood glucose should be closely monitored to ensure that the treatment is safe and effective. In this case, both the proband and his younger brother were diagnosed with GCK-MODY. They underwent GnRHa + r-hGH treatment under strict blood glucose monitoring for 25 months, during which the proband grew 15.7 cm, and his younger brother grew 17.3 cm, with no significant changes in blood glucose. The treatment was safe and effective. Therefore, accurate diagnosis, timely administration of appropriate treatment, assessment of complications and prognosis, and implementation of personalized therapy are particularly important.

5. Conclusion

The findings of this study confirm the presence of GCK mutations associated with MODY 2 in the Chinese population. Furthermore, combination therapy with recombinant human growth hormone (r-hGH) demonstrates safety and efficacy, supporting its potential clinical application in this patient group.

Disclosure statement

The authors declare no conflict of interest.

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