Identification and Clinical Characteristics Analysis of HNF-1A Mutations p.I27L, p.S487N and p.G574S in Chinese Patients with MODY3

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Research

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Abstract

Background: Due to the rarity, the type 3 of maturity-onset diabetes of the young (MODY3) has not been explored comprehensively. The study aimed to describe and analyze the molecular and clinical characteristics of MODY3, which could help physicians understand the subtype of diabetes and increase the diagnosis rates in the future.

Methods: Ten unrelated patients with suspected maturity-onset diabetes of the young (MODY) were included in the study based on information on family history and onset age. Sanger sequencing was used to identify cases with mutations in the hepatic nuclear factor 1A gene (HNF-1A).

Results: Five patients were identified with MODY3, three cases (60%) with p.I27L mutation, one case (20%) with p.S487N mutation, and one case (20%) with p.G574S mutation. The average onset age was (23.00±3.00) years and the average age of diagnosis was (28.67±9.29) years. Most patients had typical clinical symptoms (polydipsia, polyuria, polyphagia, and weight loss). The main complications included diabetic ketoacidosis (DKA, 3/5,60%), diabetic macroangiopathy (2/5,40%), diabetic peripheral neuropathy (DPN,3/5,60%), diabetic nephropathy (DN,1/5,20%) and diabetic retinopathy (DR,1/5,20%). Four patients (80%) had fatty liver. The average body mass index (BMI) (26.39±4.67) kg/□, triglyceride (TG 2.95±1.43 mmol/L) and low-density lipoprotein (LDL-C 3.37±0.65 mmol/L) were beyond normal value. The glycosylated hemoglobin A1c (HbA1c 12.45±4.60 %), fasting plasma glucose (FPG 10.10±3.57 mmol/L) and postprandial plasma glucose (PPG 21.88±2.53 mmol/L) also increased dramatically. In addition, islet function examination revealed impaired secretion and slightly poor reserve function, which was similar to the changes inT2DM. All five patients used insulin, three (60%) also using antidiabetic drugs which did not include sulfonylureas.

Conclusions: In brief, five patients were identified with MODY3. The mutation site could influence the onset age, the islet function and the incidence of complications. The age at diagnosis was 4.2 years later than the onset age. The control of diabetes was poor due to the inappropriate treatment. It is vital to make an early diagnosis and provide appropriate treatment for MODY3 patients.

Background

Maturity-onset diabetes of the young (MODY) is a monogenic dominant type of diabetes with the characters of early onset and impaired insulin secretion[1]. It is estimated to account for 1–2% of all patients diagnosed with diabetes, however, due to the similarity of clinical features, it is challenging to distinguish MODY with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM)[2]. Patients with MODY still have some functional beta cells after three to five years of diagnosis while the insulin is at a complete loss in T1DM[2]. It is still controversial whether patients with MODY have positive pancreatic antibodies[3, 4]. Contrary to patients with T2DM, patients with MODY lack insulin resistance symptoms such as hypertension[5]. The contrast is more distinct in adolescents[2]. MODY is divided into more than 10 subtypes based on different mutation sites, of which the type 3 of maturity-onset diabetes of the young (MODY3) is the most common subtype[6].

MODY3 results from mutations in the hepatic nuclear factor 1 A gene (HNF-1A) located on chromosome 12q24[7]. HNF-1A encodes for a transcription factor expressed in liver and pancreas cells in the regulation of glucose transport and metabolism[6, 8]. The onset age and severity of the disease vary within patients with MODY3[9]. Several modifying genes have been identified, which might explain the heterogeneity of MODY3[10]. Environmental factors, such as exposure to diabetes in utero also influence the age at onset of MODY3[1]. It is unclear whether the type of the HNF-1A mutation contributes to the phenotype variability of the disease [9, 11]. At present, sulfonylureas are the

first-line therapies owning to the high sensitivity of MODY3 to sulfonylurea medication[2]. Microvascular and macrovascular complications are observed with the same risk in patients with MODY3 as in T1DM and T2DM[12, 13].

The mutation sites and clinical features of MODY3 in China have not been investigated comprehensively due to the rarity of the disease. Besides, due to the lack of awareness of this subtype of diabetes, MODY3 is often misdiagnosed in the real clinical practice. In this study, we identified patients with MODY3 to analyze the molecular and clinical characteristics, which could help doctors to make a correct diagnosis of MODY3 in the future.

Methods

Subjects

Genetic testing was performed on ten unrelated patients with suspected MODY3 in the endocrinology department of the Affiliated Hospital of Yunnan University/the Second People's Hospital of Yunnan Province from September 2018 to December 2019. The suspected MODY3 were identified based on two criteria as previously reported[14]. (a) autosomal dominant inheritance pattern through at least two generations; (b) diagnosis of diabetes under the age of 25 years in at least one family member. A detailed medical history was quizzed and the peripheral venous blood was collected after obtaining written informed consent from the patients or their guardians. The blood volume was 5ml, it was anticoagulated by EDTA. The institutional review boards of the Second People's Hospital of Yunnan Province.

DNA Extraction

EDTA anticoagulated venous blood samples were collected from all study subjects and the genomic deoxyribonucleic acid (DNA) was isolated from whole blood by proteinase K digestion followed by phenol-chloroform extraction. Subsequently genomic DNA was precipitated in ethanol. Those passed the test were placed at 4℃ or -20℃ for a long-term storage, but those failed passed the extraction would be re-extract. The extracted DNA was measured with an ultraviolet spectrophotometer, and the concentration was ≥ 50ng/ul and 260/280 = 1.7-2.0 as the DNA amplification template.

Sequencing and Sequence Analysis

All exons and flanking intron regions of the HNF-1A gene were amplified from the genomic DNA samples by the polymerase chain reaction (PCR) according to published methods, and primers for amplifying the specific fragments of the promoter region were synthesized based on the human mtDNA cambridge sequence (provided by Kunming Shuo Qing Biotechnology Co. LTD Table 1). To ensure the quality of the DNA sequences, PCR products were sequenced at least twice in both directions. Sanger sequencing technology was used to select the PCR amplified fragment. DNA sequences were edited using DNASTAR's SeqMan software (DNASTAR Inc., Madison, WI, USA). According to the cDNA sequence of the gene provided by NCBI and the amino acid sequence of the encoded protein, the mutation types of HNF-1A gene and its impact on the encoded amino acid were clarified.

Table 1
Primers for specific fragments of HNF-1A gene promoter region.

Gene	Primer-up (5′-3′)	Primer-down(3′-5′)
Exons		
1	GGC AGG CAA ACG CAA CCC ACG	GAA GGG GGG CTC GTT AGG AGC
2	CAT GCA CAG TCC CCA CCC TCA	CTT CCA GCC CCC ACC TAT GAG
3	GGG CAA GGT CAG GGG AAT GGA	CAG CCC AGA CCA AAC CAG CAC
4	CAG AAC CCT CCC CTT CAT GCC	GGT GAC TGC TGT CAC TGG GAC
5	GGC AGA CAG GCA GCT GGC CTA	GCC TCC CTA GGG ACT GCT CCA
6	TGG AGC AGT CCC TAG GGA GGC	GTT GCC CCA TGA TCC CAC
7	GGT CTT GGG CAG GGG TGG GAT	CCC CTG CAT CCA TTG ACA GCC
8	GAG GCC TGG GAC TAG GGC TGT	CTC TGT CAC AGG CCA GGG AG
9	CAG AGC CCC TCA CCC CCA CAT	CGGACA GCA ACA GAA GGG GTG
10	GTA CCC CTA GGG ACA GGC AGG	ACC CCC CAA GCA GGC AGT ACA

Clinical and Biochemical Variables

Clinical data of the patients including: basic patient information (name, ethnicity, gender, age of onset, age of diagnosis, body mass index (BMI) at diagnosis etc.), the BMI was calculated using the formula, weight (kilograms)/height (square meters). Obesity was defined as of 25 kg/m^2 for both males and females according to Asia Pacific World Health Organization guidelines. Lifestyle habits (smoking, drinking, etc.), family genetic information (whether parents, grandparents /grandparents, brothers and sisters had diabetes, other relatives had diabetes), comorbidities (hypertension, hyperlipidemia, cardiovascular and cerebrovascular diseases, etc.), diabetic complications (diabetic ketoacidosis(DKA), diabetic macroangiopathy, diabetic nephropathy(DN), diabetic retinopathy (DR), diabetic peripheral neuropathy(DPN) etc.),fasting plasma glucose(FPG), postprandial plasma glucose(PPG), glycated hemoglobin A1c (HbA1c), pancreatic antibodies(IA-2A-120KD□GADA-65KD□ICA-64KD□ICA-40KD□IAA-5.8KD), insulin and C-peptide release tests, blood biochemical variables(triglyceride(TG), low-density lipoprotein(LDL-C), total cholesterol (CHOL), high-density lipoprotein (HDL-C) ,Alanine transaminase (ALT), glutamic oxalacetic transaminase(AST) and gamma-glutamyl transpeptidase(GGT) etc.) and treatments (oral antidiabetic drugs(OAD), insulin alone, antidiabetic drugs combined with insulin)were collected as well. We organized and analyzed the clinical data and drew pedigree of families.

Statistical analysis

Statistical analysis was performed using SPSS software (version 23). Data were expressed as mean ± standard deviation (SD), and as percentages (%).

Results

The mutations of HNF-1A

A total of 10 unrelated patients with suspected MODY were sequenced by sanger sequencing HNF-1A gene. Five (50%) patients were identified with the mutation sites p.I27L, p.S487N and p.G574S, of which three patients (3/5,60%) had mutations in p.I27L, one (1/5,20%) in p.S487N, and one (1/5,20%) in p.G574S. The mutation type of the five patients was missense mutation (Table 2, Fig. 1and Fig. 2).

Table 2
Mutations identified in HNF-1A.

Patient	Gene	Exon	cDNA	Protein	Status	Type mutation
A-III:4	HNF1A	1	c.79A > C	I27L	Known	missense
B-III:9	HNF1A	9	c.1720G > A	G574S	Known	missense
C-III:7	HNF1A	7	c.1460G > A	S487N	Known	missense
D-III:8	HNF1A	1	c.79A > C	I27L	Known	missense
E-III:8	HNF1A	1	c.79A > C	I27L	Known	missense

Baseline characteristics

We drew 5 genograms (a, b, c, d, e) (Fig. 3), Each family met the minimum diagnostic criteria of MODY, and the basic characteristics of the patients were shown in Table 3. There were 4 males (4/5,80%) and 1 female (1/5,20%). The mean age of onset was (21.00 ± 4.85) years, the mean age of diagnosis was (25.20 ± 9.50) years. The average BMI was (26.39 ± 4.67) kg/□. Among these patients, 3 cases were Han nationality (3/5,60%), 1 case was Yi nationality (1/5,20%) and 1 case was Bai nationality (1/5,20%). All cases had family history of diabetes, negative pancreatic antibodies. Three had typical clinical symptoms (polydipsia, polyuria, polyphagia, and weight loss). The rest of them had no symptoms. Four patients had fatty liver. The main complications included DKA (3/5,60%), diabetic macroangiopathy (2/5,40%), DPN (3/5,60%), DN (1/5,20%) and DR (1/5,20%). All five patients used insulin, three of them also using antidiabetic drugs which not including sulfonylureas.

Table 3
Baseline parameters of MODY3 patients.

Patient ID	A-III:4	B-III:9	C-III:7	D-III:8	E-III:8	$\bar{x} \pm s$
Sex	Male	Female	Male	Male	Male	
Nationality	Yi	Han	Bai	Han	Han	
Age of Onset (age)	20	24	25	23	13	21.00 ± 4.85
Age of Diagnose(age)	21	39	26	27	13	25.20 ± 9.50
Family History	Yes	Yes	Yes	Yes	Yes	
BMI (kg/m^2)	33.95	26.71	30.46	23.71	17.10	26.39 ± 4.67
Smoking	Yes	No	Yes	Yes	No	
Drinking	Yes	No	No	No	No	
Fatty liver	Yes	Yes	Yes	Yes	No	
Pancreatic autoantibody$^+$	No	No	No	No	No	
DKA	No	Yes	Yes	Yes	No	
Hypertension	No	No	No	No	No	
Symptoms	Asymptomatic	Asymptomatic	Polydipsia Polyuria	Polydipsia Polyuria Lose weight	Polydipsia Polyuria Polyphagia Lose weight	
Complications	No	DPN Macroangiopathy	DR DN DPN Macroangiopathy	DPN	No	
Treatment	0AD Insulin	0AD Insulin	0AD Insulin	Insulin	Insulin	

Data of age and BMI were expressed as mean ± standard deviation (SD). BMI: Body mass index. DKA: Diabetic ketoacidosis. OAD: Oral antidiabetic drugs. DPN: Diabetic peripheral neuropathy. DN: Diabetic nephropathy. DR: Diabetic retinopathy. $^+$:Pancreatic autoantibody including IA-2A-120KD、GADA-65KD、ICA-64KD、ICA-40KD、IAA-5.8KD.

Blood biochemical indexes

Table 4 described the biochemical indexes separately in five patients. All five patients had dyslipidemia. It showed that the average TG (2.95 ± 1.43 mmol/L) and LDL-C (3.37 ± 0.65 mmol/L) increased, but the CHOL (5.25 ± 0.49

mmol/L), HDL-C (0.93 ± 0.17 mmol/L) were in normal. ALT, AST and GGT, which reflects the liver function, slightly increased in patient A-III:4 and C-III:7. The HbA1c (12.45 ± 4.60 %), FPG (10.10 ± 3.57 mmol/L) and PPG (21.88 ± 2.53 mmol/L) were also beyond the normal value.

Table 4
Blood biochemical indexes ($\bar{x} \pm s$)

Patient ID	A-III:4	B-III:9	C-III:7	D-III:8	E-III:8	$\bar{x} \pm s$	Normal range+
FPG(mmol/L)	7.4	8.52	9.8	8.5	16.3	10.10 ± 3.57	3.9–6.1
PPG (mmol/L)	21	25.9	22.6	19.4	20.5	21.88 ± 2.53	< 7.8
HbA1c(%)	7.4	12.7	10.02	12.4	19.74	12.45 ± 4.60	4.8–5.9
CHOL (mmol/L)	5.32	5.68	5.07	5.69	4.5	5.25 ± 0.49	< 5.2
TG (mmol/L)	3.54	1.75	4.89	3.23	1.37	2.95 ± 1.43	< 1.7
HDL-C (mmol/L)	0.98	1.18	0.71	0.86	0.9	0.93 ± 0.17	> 1.04
LDL-C (mmol/L)	2.56	4.33	3.08	3.53	3.36	3.37 ± 0.65	< 2.07
ALT(U/L)	93	16	52	19	14	38.80 ± 34.05	5–40
AST(U/L)	47	17	28	15	16	24.60 ± 13.58	8–40
GGT(U/L)	144	15	53	35	9	51.20 ± 54.70	11–50

Data were expressed as mean ± standard deviation (SD). FPG: Fasting plasma glucose. PPG: Postprandial plasma glucose. HbA1c: Glycosylated hemoglobin A1c. CHOL: Total cholesterol. TG: Triglyceride. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol. ALT: Alanine transaminase. AST: Glutamic oxalacetic transaminase. GGT: Gamma-glutamyl transpeptidase. +: normal range reference value of the Affiliated Hospital of Yunnan University.

Islet function

The islet function was shown by the insulin and C-peptide release levels, from best to worst: C-III:7, A-III:4, B-III:9, E-III:8, D-III:8. The basal secretion of insulin and C-peptide was low. The level of insulin and C-peptide reached the peak at 120 minutes. The multiply growth was not enough, and there was no obviously decrease at 180 minutes (Fig. 4).

Discussion

Our study, a population-based investigation, estimates the prevalence of MODY3 and describes clinical features of the disease. Previous studies mainly discussed MODY3 in the European population[15]. Few studies have focused on the incidence and characters of this subtype of diabetes in China[16]. Meanwhile, MODY3 is often misdiagnosed asT1DM orT2DM owning to the similar symptoms[2]. Our study is of great significance for doctors to reduce the frequency of wrong diagnosis and provide appropriate treatment for patients with MODY3 in the future.

Fifty percent clinically suspected MODY cases had missense mutations in HNF-1A, p.I27L, p.S487N and p.G574S. The result showed that patients with mutations located in the transactivation domain (B-III:9 and C-III:7) were diagnosed later than those carrying mutations in the dimerization/DNA-binding domains (A-III:4, D-III:8 and E-III:8), which is consistent with previous studies[9]. Our study showed no negative correlation between the duration of MODY3 and the islet function. Patient B-III:9 had MODY3 for 15 years, the longest period among five patients,

however, the islet function of that patient was better than patient D-III:8 and patient E-III:8 who only suffered from MODY3 for 4 years and 1 year separately. The duration of the disease was the same in patients A-III:4, C-III:7 and E-III:8, but the islet function of patient C-III:7 was obviously the best. The difference might be caused by different mutation sites. Mutations in the transactivation domain may have less effect on the islet function, which need to be verified by future research. Another impact of mutation site is the risk of angiopathy in MODY3. Both patients with mutations in the transactivation domain had angiopathy secondary to MODY3, opposite to patients with mutations in the dimerization/DNA-binding domains. The study indicated patients with mutations in the transactivation domain could have later onset age and better islet function, but could also have higher susceptibility of complications such as angiopathy.

The onset age in the study is similar to the prior literature[5]. Previous research showed that patients with MODY3 lacked clinical features of insulin resistance, such as obesity and dyslipidaemia, which was different from patients with T2DM[2, 5]. However, insulin resistance existed in the five MODY3 patients in the current study. The average BMI, TG and LDL-C was over normal value. All patients had dyslipidemia. Four patients (80%) had fatty liver. As all patients in our study were from Yunnan province, they might carry some similar modifying genes which could be different to genes carried by patients from other districts in China and other parts in the world. The difference of clinical features in the present study might be caused by these specific modifying genes. The overlap of clinical symptoms between MODY3 and T2DM brought the difficulty in making a correct diagnosis. In our study, the average age of diagnosis was 4.2 years later than the average onset age. Before patients being diagnosed correctly, insulin was used in all five patients, of which three patients also used antidiabetic drugs which not including sulfonylureas. The control of diabetes was poor as the average HbA1c, FPG and PPG were still beyond the normal range. Therefore, early diagnosis and appropriate treatment of MODY3 are vital for effective control of blood glucose and decreasing complications related to diabetes.

Genetic testing is specific for MODY3, but due to the high expense, it is not feasible as a routine examination for all diabetic patients[17]. Previous research recommended genetic testing only for young diabetic patients with strong family histories of diabetes, which was also the criteria in our study to select suspected MODY3 patients[18, 19]. However, it was estimated that more than half of MODY cases were missed in the real practice as some patients could not meet these criteria[20]. Therefore, sensitive and specific biomarkers are needed to select proper patients for diagnostic genetic testing. N-glycan profile and high-sensitivity C-reactive protein (hs-CRP) have been reported to have a role in identifying diabetic patients with high risk of carrying HNF-1A mutations, which could improve diagnosis rates of MODY3[21]. At present, low dose sulfonylureas are recommended as first-line therapy for patients with MODY3[2, 22, 23]. Some recent studies reported that nateglinide alone or DPP-4 inhibitor linagliptin as add-on therapy to glimepiride could better control glycemic fluctuations without increasing risk of hypoglycemia in MODY3 patients, which need to be verified by randomized multicenter trials[24, 25].

Limitations

There are some limitations in our study. First, modifying genes inherited independently of MODY were not tested. Thus, the impact of modifying genes on the age at diagnosis could not be analyzed in the study. Second, we did not measure the level of hs-CRP in MODY3 patients and in those without MODY3 mutations. Therefore, we could not evaluate the role of hs-CRP to screen MODY3 patients from diabetic cases. Third, only five patients with MODY3 were identified. Small samples might cause incomplete analysis of the influence of mutation sites on the features of MODY3. The mutation sites and clinical features of MODY3 in Chinese population need more research from other districts in the future.

Conclusion

In conclusion, our study described clinical features of the disease and analyzed the impact of mutation sites on MODY3. Five patients were identified with the disease, three cases carrying p.I27L mutation, one with p.S487N mutation, and one with p.G574S mutation. The mutation site could influence the onset age, the islet function and the incidence of complications. The average age of diagnosis in the study was 4.2 years later than the average onset age. The control of diabetes was poor due to the inappropriate treatment, all five patients using insulin, three (60%) also using antidiabetic drugs which not including sulfonylureas. Therefore, it is vital for doctors to make an early diagnosis and provide appropriate therapy for MODY3 patients.

Abbreviations

ALT: Alanine transaminase; AST: Glutamic oxalacetic transaminase; BMI: Body mass index; CHOL: Total cholesterol; DNA: Deoxyribonucleic acid; DR: Diabetic retinopathy; DN: Diabetic nephropathy; DPN: Diabetic Peripheral neuropathy ;FPG: Fasting plasma glucose; GGT: Gamma-glutamyl transpeptidase; HNF-1A: Hepatic nuclear factor 1A; HbA1c: Glycosylated hemoglobin A1c; HDL-C: High-density lipoprotein; hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein; MODY3: The type 3 of maturity-onset diabetes of the young; MODY: Maturity-onset diabetes of the young; OAD：Oral antidiabetic drugs; PPG: Postprandial plasma glucose; PCR: Polymerase chain reaction; SD: Standard deviation; SGLT2: Sodium-dependent glucose cotransporter 2; TG: Triglyceride; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Declarations

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Authors' contributions

RL and CXY collected the data required for generating the pedigree, analyzed the data and wrote the manuscript; YY and KY was responsible for revising the manuscript for important intellectual content and final approval of the version of the article to be published; HJY and TCZ performed sequencing experiments; LY YYZ and HSLwere responsible for collecting data and helped perform the analysis with constructive discussions; All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Fourth Affiliated Hospital of Kunming Medical University (No.2020112).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

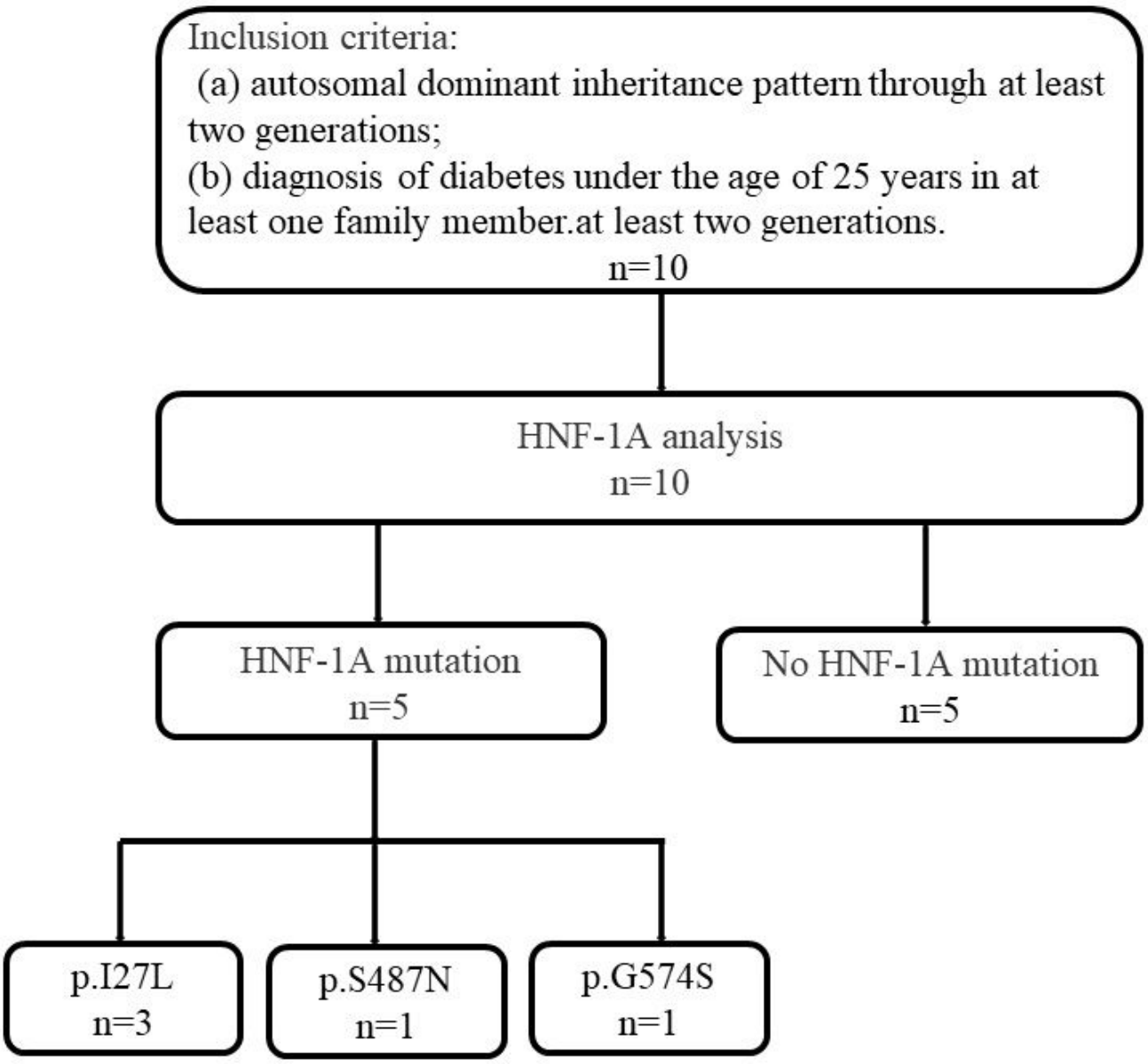

Figure 1

The screening flow chart of HNF-1A mutation.

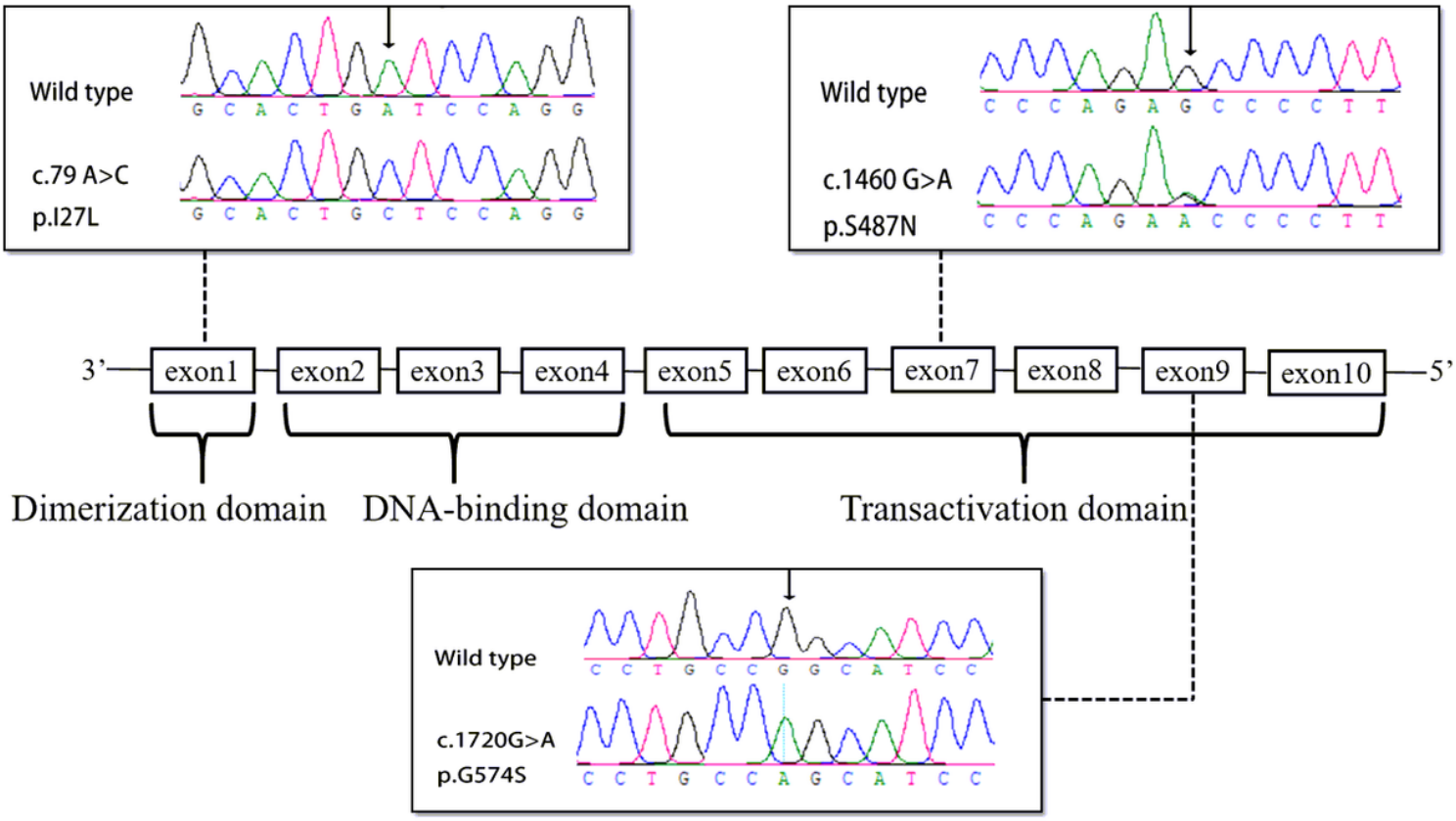

Figure 2

The sequencing chromatogram and position of the HNF-1A mutation. The mutations of HNF1A, p.I27L, p.S487N and p.G574S, are indicated by arrows respectively.

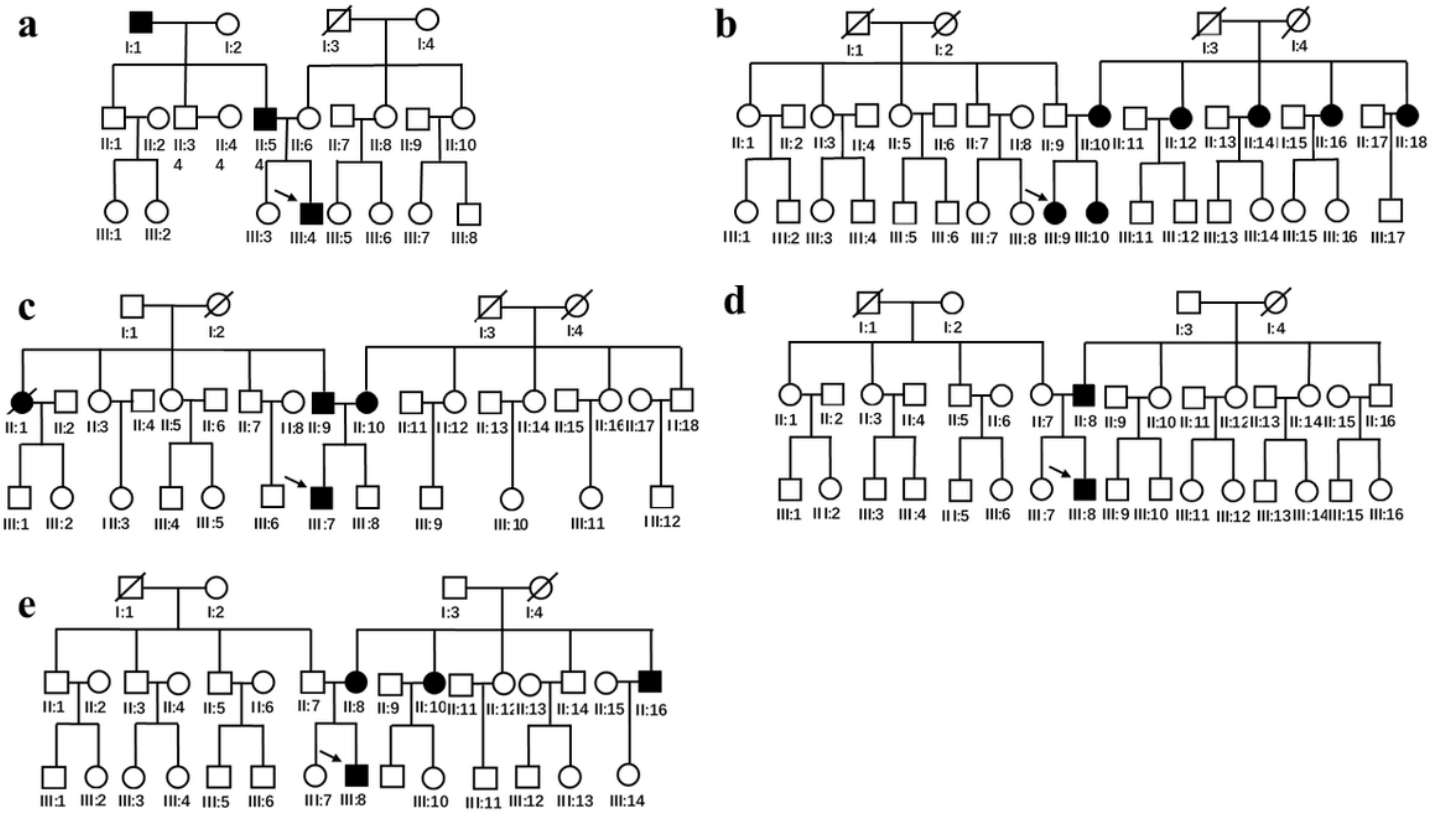

Figure 3

Family Diagrams of MODY3 patients. (a, b, c, d, e). Filled symbols represent patients with diabetes, open symbols represent unaffected individuals. Squares and circles symbols denote males and females, respectively. Oblique lines through symbols represent deceased individuals. Arrows indicate the probands.

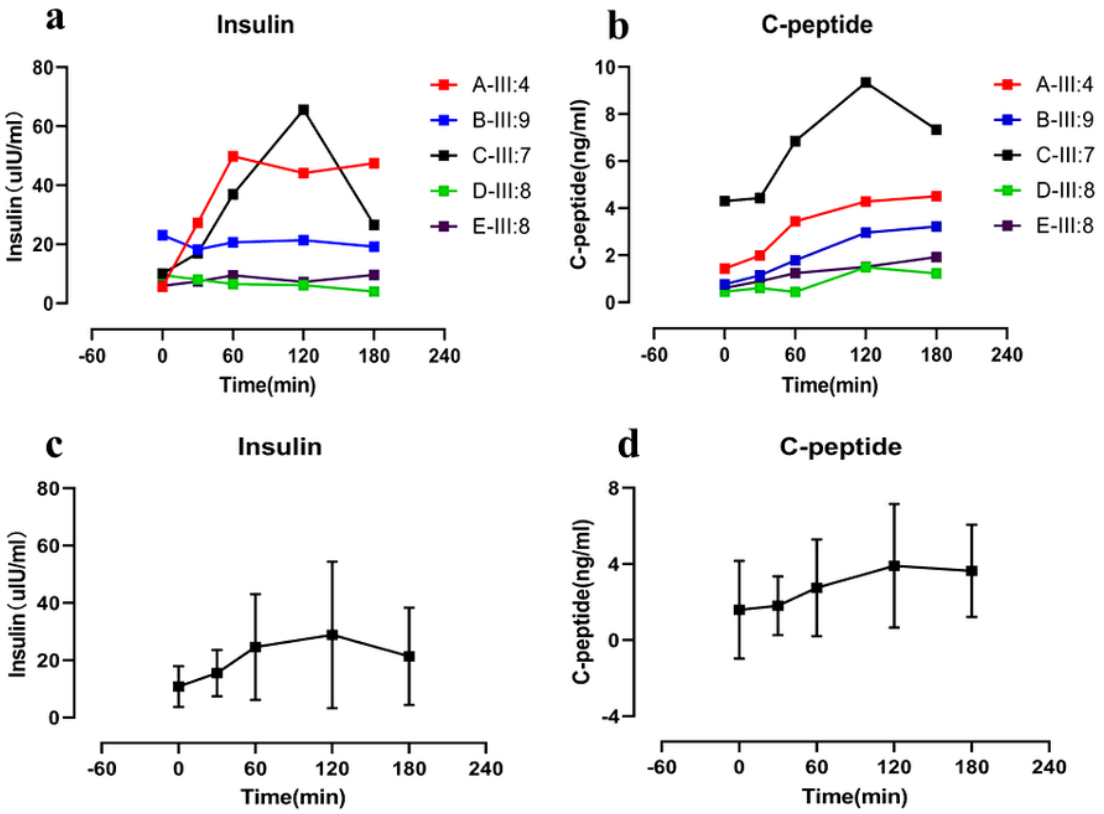

Figure 4

Islet function of patients. a and b show the insulin or C-peptide release levels of the five patients (A-III:4, B-III:9, C-III:7, D-III:8, E-III :8), c and d show the mean insulin or C-peptide release levels of the five patients.