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CASE REPORT

HNF1A mutation in a Thai patient with maturity-onset diabetes of the young: A case report

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Abstract

BACKGROUND

Maturity-onset diabetes of the young (MODY) is the most common form of monogenic diabetes. The disease is transmitted in autosomal dominant mode and diabetes is usually diagnosed before age 25 year. MODY 3 is caused by mutation of hepatocyte nuclear factor (*HNF*) *1A* genes and is the most common MODY subtype. Diagnosis of MODY 3 is crucial since glycemic control can be accomplished by very low dose of sulfonylurea. In this report we described a Thai MODY 3 patient who had excellence plasma glucose control by treating with glicazide 20 mg per day and insulin therapy can be discontinued.

CASE SUMMARY

A 31-year-old woman was diagnosed diabetes mellitus at 14 years old. The disease was transmitted from her grandmother and mother compatible with autosomal dominant inheritance. Sanger sequencing of proband's DNA

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identified mutation of *HNF1A* at codon 203 which changed amino acid from arginine to cysteine (R203C). This mutation was carried only by family members who have diabetes. The patient has been treated effectively with a combination of oral hypoglycemic agents and must include a very low dose of glicazide (20 mg/d). Insulin therapy was successfully discontinued.

CONCLUSION
We demonstrated a first case of pharmacogenetics in Thai MODY 3 patient. Our findings underscore the essential role of molecular genetics in diagnosis and guidance of appropriate treatment of diabetes mellitus in particular patient.

Key words: Oral sulfonylureas; Maturity-onset diabetes of the young; *HNF1A*; Case report

Core tip: Maturity-onset diabetes of the young (MODY) is the most common form of diabetes in patients diagnosed under the age of 25. In addition, MODY is characterized by autosomal dominant inheritance. We report a R203C mutation in the *HNF1A* causing MODY type 3. The genetic diagnosis is implicated to alter SU treatment. This study revealed that excellent glycemic control in this patient could be achieved by very low dose SU. Furthermore, this is the first report of exceptional response to treatment with SU in Thai MODY3.

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INTRODUCTION

Maturity-onset diabetes of the young (MODY) is the most common type of monogenic diabetes, it is inherited in an autosomal dominant manner, and it is normally diagnosed before 25 years of age. To date, at least 15 subtypes of MODY caused by mutations of 15 different genes have been identified[1,2]. Thus, the clinical heterogeneity of MODY is explained by its genetic heterogeneity[3]. MODY3 is caused by mutation of hepatocyte nuclear factor 1A (*HNF1A*), which encodes a transcription factor that regulates functions of several proteins, including amylin, insulin, GLUT2, and L-pyruvate kinase, that are important for glucose metabolism and insulin secretion. *HNF1A* dysfunction are leading to Diabetes development and imbalance of insulin in patients. More than 350 mutations of *HNF1A* have been identified, and MODY3 is the most common MODY subtype among Caucasians[4]. In contrast, Asians most commonly have MODY-X or MODY subtype without identified genetic cause[5-10]. Identification of MODY3 is very important, because pancreatic β-cells exhibited hyperexcitability in this subtype in response to treatment with sulfonylurea (SU)[11]. The Siriraj Center of Research Excellence for Diabetes and Obesity (SiCORE-DO) discovered 3 different *HNF1A* mutations, including R203C, G554fsX556, and P475L, in 3 unrelated MODY pedigree[12-14]. Here, we report a Thai MODY3 patient carrying *HNF1A* R203C mutation that exhibited outstanding diabetes control with low-dose glicazide, which is a short-acting second-generation SU. Rapid deterioration of her glycemic control was observed after withdrawal of SU. The purpose of this report is to present alteration of drug treatment in patient by genetic diagnosis.

CASE PRESENTATION

Chief complaints

A 31-year-old Thai woman came to Siriraj Diabetes Center, Siriraj Hospital, Bangkok, Thailand for her diabetes management.

History of present illness

The patient has been following up every 3 months at the Siriraj Diabetes Center, Siriraj Hospital, Bangkok, Thailand. Currently, she was 44 years old and treated with glicazide 20 mg/d. She has excellence glycemic control without diabetic complications. Laboratory assessment included fasting plasma glucose (FPG) 78 mg/dL, hemoglobin A1c (HbA1c) 6.7%, serum creatinine (0.56 mg/dL), total cholesterol (TC) 173 mg/dL, high-density lipoprotein (HDL) 99 mg/dL, low-density lipoprotein (LDL) 62.6 mg/dL, and triglycerides (TG) 57 mg/dL.

History of past illness

The patient was first seen at Siriraj Diabetes Center when she was 31 years old and diabetes was diagnosed at age 14.

Personal and family history

Her mother and brother were diagnosed with diabetes at age 17 and 13, respectively. There was no history of diabetic ketoacidosis, and glycemic control could be achieved without insulin treatment for more than 5 years after diabetes diagnosis in all 3 patients.

Physical examination upon admission

The patient's body mass index (BMI), waist-to-hip ratio, and blood pressure was 19.43 kg/m^2, 0.83, and 120/70 mmHg, respectively (Table 1).

Laboratory examinations

Laboratory assessments at her first visit to Siriraj Diabetes Center included FPG 126 mg/dL, HbA1c 9.5%, serum creatinine (0.6 mg/dL), TC 156 mg/dL, HDL 71 mg/dL, LDL 90 mg/dL, and total TG 55 mg/dL.

Sequencing profile and timeline of patient's glycemic control with and without SU

Sanger sequencing of her DNA revealed heterozygous mutation of *HNF1A* at codon 203 in exon 3 that caused substitution of cysteine for arginine (R203C) (Figure 1). This mutation was also identified in all diabetic family members, but not in non-diabetic family members whose DNA were available for sequencing (Figure 2). The patient's glycemic control profile (with and without SU) is shown in Figure 3. The results of our analysis revealed that excellent glycemic control could only be achieved when our patient was taking SU. Interestingly – when SU treatment was withdrawn, severe hyperglycemia eventually developed, even when insulin was given. The optimal dose of glicazide in this case was 20 mg per day. This patient continues to do well with no observed diabetic complications.

FINAL DIAGNOSIS

SU hyperresponsiveness in MODY subtype 3 due to *HNF1A* mutation.

TREATMENT

The patient has been successfully treated with glicazide 20 mg/d, metformin 2000 mg/d and sitagliptin 100 mg/d.

OUTCOME AND FOLLOW-UP

The patient's glycemic control has been excellence and without hypoglycemic episodes during the last 4 years of follow up. No diabetic complications have developed.

DISCUSSION

MODY3 is one of the best examples of precision medicine in diabetes. Studies in animal models showed that total deletion of *HNF1A* resulted in decreased SU uptake by hepatocytes and decreased excretion[2,12,15,16]. Clinical studies in humans demonstrated that MODY3 patients treated with SU exhibited excellent glycemic control, and withdrawal of SU led to severe hyperglycemia – even with insulin treatment. However, dosage adjustment is essential since inappropriate SU dose can lead to hypoglycemia[11]. The current recommendation for treatment of MODY3 patients is to

Table 1 Demographic, anthropometric, and clinical characteristics of the case profiled in this report

Characteristics	Values
Age (yr)	31
Age at onset (yr)	14
Duration (yr)	17
BMI (kg/m^2)	19.43
Waist circumference (cm)	77
Waist-to-hip ratio	0.83
Systolic BP (mmHg)	120
FPG (mg/dL)	126
HbA1c (%)	9.5
Serum creatinine (mg/dL)	0.6
Total cholesterol (mg/dL)	156
Total triglycerides (mg/dL)	55
LDL (mg/dL)	90
HDL (mg/dL)	71.0

BMI: Body mass index; BP: Blood pressure; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol.

use a very low dose of SU. Caution should be exercised if SU is to be withdrawn from the treatment plan since a deterioration in the patient's glycemic status can be anticipated. Our MODY3 patient exhibited exceptional plasma glucose control using a very low dose of glicazide, and severe hyperglycemia developed after glicazide was discontinued, even though she was treated with metformin, sitagliptin, and insulin glargine. Moreover, her glicazide dosage was titrated to 20 mg/d to avoid hypoglycemia, even though the usual dose is up to 80 mg/d for treatment of type 2 diabetes. Upon reaching her maintenance dosage and after stabilization of her blood sugar, insulin therapy could be discontinued and the durability of glycemic control has been almost 4 years (Figure 3). To our knowledge, this is the first report of exceptional response to treatment with SU in Thai MODY3. Our findings are in agreement with those from previous reports in MODY3 patients from different ethnicities, including Caucasian, Saudi Arabian, and Tunisian[17-19]. A study from the United Kingdom reported lower HbA_{1c} and lower BMI at genetic diagnosis, and shorter duration of diabetes to be factors that significantly influence treatment success after treatment with SU in MODY3 patients[20]. However, this finding has not yet been investigated or confirmed in Asian population due to the relatively lower prevalence of MODY3 in this ethnicity.

CONCLUSION

In this report, we presented and described a 31-year-old Thai MODY3 patient with a heterozygous mutation of *HNF1A* at R203C who demonstrated excellent diabetic control with a very low dose of SU. To our knowledge, this is the first report of exceptional response to treatment with SU in Thai MODY3. Our findings emphasize the critical role of correct genetic diagnosis, especially in patients with early-onset diabetes.

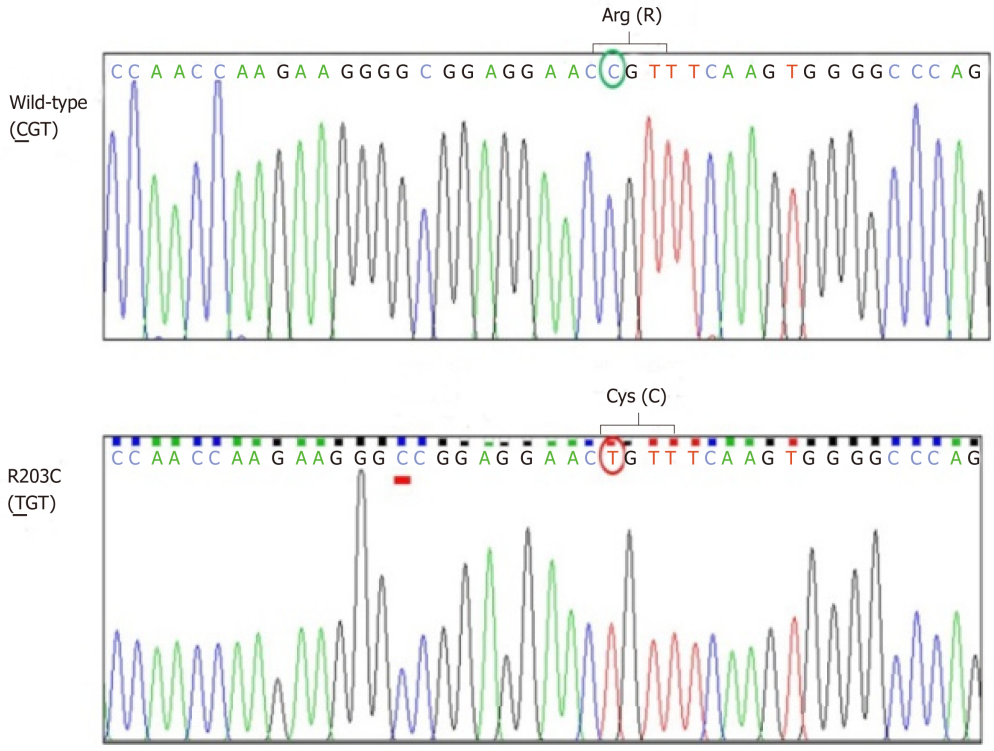

Figure 1 Sequencing profile of exon 3 of *HNF1A* in the mutation region (R203C). The green circle indicates the location of C in wild-type, and the red circle indicates the location of T substitution in heterozygous.

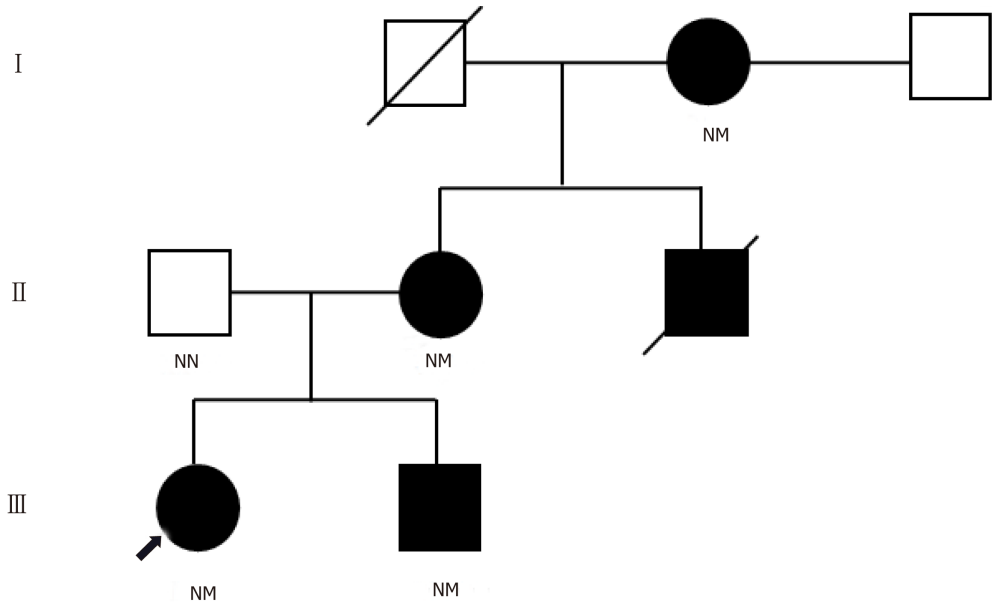

Figure 2 Pedigree showing autosomal dominant inheritance of diabetes associated with a hepatocyte nuclear factor-1-alpha mutation. Symbols and abbreviations: Circles: Females; squares: Males; Darkened circles or squares: Diabetes; NM: Heterozygous *HNF1A* R203C; NN: *HNF1A* wild-type genotype.

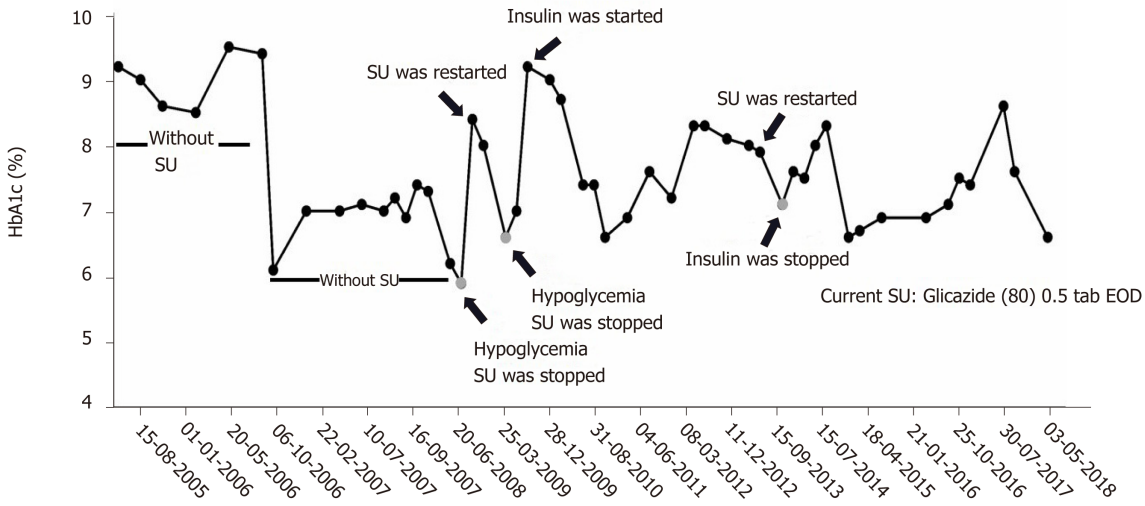

Figure 3 Timeline of patient's glycemic control with and without sulfonylurea.

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