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Case Report

Treatment strategy for maturity-onset diabetes of the young 3 (MODY3): Experience with two sisters and their mother

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Highlights

- Three MODY3 cases; a mother and her two sisters, found at the same time to have HNF1A gene mutation but diagnosed with diabetes at different ages.
- Even for MODY3 patients with the same genetic mutation, treatment should be tailored to individual patients depending on medical, social, and personal preferences, as well as type 2 diabetes, without limiting sulfonylureas and insulin.

Abstract. Maturity onset diabetes of the young (MODY) is a relatively young-onset diabetes mellitus with an autosomal dominant inheritance. Among these phenotypes, MODY3, caused by mutations in HNF1A, is one of the most frequent. Although MODY3 is known to respond markedly to sulfonylureas (SU), many cases require insulin therapy. However, there are no clear guidelines for factors to consider when introducing antidiabetic drugs and insulin. This report describes a familial case in which an older sister was diagnosed with diabetes and subsequently with MODY3, followed by the onset of diabetes in the younger sister and mother. The elder sister initially denied insulin treatment and exhibited a suboptimal response to SU but finally agreed to insulin use. The mother initially selected insulin therapy because of the challenges associated with adherence to strict dietary therapy. Conversely, the younger sister responded positively to SU and maintained effective glycemic control. The management of MODY3, even though they have the same single-gene mutation and similar residual insulin secretion at diagnosis, should be flexibly individualized for each family member to ensure long-term adherence and appropriate glycemic control.

Key words: maturity-onset diabetes of the young 3 (MODY3), HNF1A gene mutation, multiple daily insulin injections, sulfonylurea drug, shared decision making

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Introduction

The treatment selection of appropriate indications for any type of diabetes has become more complex due to the wide variety of choices, from oral antidiabetic medications, such as sulfonylurea agents (SU), to injection therapy, including insulin pumps and GLP-1 receptor agonists. Maturity onset diabetes of the young (MODY) is caused by mutations in an autosomal dominant gene that disrupts insulin production. MODY reflects impaired glucose tolerance due to non-obesity insulin deficiency. The severity of impaired glucose tolerance and treatment modalities vary according to the 14 types of MODY (MODY1-14) (1–3). MODY3, caused by mutations in HNF1A, is one of the most frequently diagnosed types. Due to the associated low renal threshold for glucose, a urine glucose screening program in schools is often the most common simple test to identify children with MODY3 in Japan (4). Although SU is considered effective in most cases, some patients eventually require insulin and show poor prognoses associated with microvasculopathies (5). There are no clear treatment guidelines for MODY3 regarding when and which oral antidiabetic agents and insulin injections should be administered.

Although several national and international studies have investigated MODY3 families (6–10), no solid studies have provided details on the clinical course, glycemic control, and long-term treatment plans for first-degree relatives and siblings. Many details remain unavailable, such as the main differences between individuals on a long-term diet only and those requiring the early introduction of insulin.

Here, we report three MODY3 cases of a mother and her two daughters, who were simultaneously diagnosed with HNF1A mutations and developed diabetes mellitus at different ages. The family members adopted a combination of multiple drug therapies without limiting the use of SU or insulin therapy because of MODY3, according to their clinical course, lifestyle, and philosophy, to maintain good adherence and appropriate glycemic control.

Case Presentation

The proband (Case 1) was a 12-yr-old Japanese girl referred to our hospital for treatment of hyperglycemia. A non-fasting blood test revealed a plasma glucose level of 162 mg/dL and an HbA1c level of 8.7%. She refused insulin injections and was investigated to determine the exact type of diabetes and the most appropriate treatment plan. The maternal grandfather had insulin-dependent diabetes since his 40s, the maternal great-grandmother had retinopathy (details unknown), and the paternal grandmother had insulin-dependent diabetes. A right axillary subcutaneous abscess was excised while the patient was in elementary school, with no recurrence. Height was 160 cm, body weight 43.7 kg, and BMI 17.0 kg/m^2. No skin pigmentation was observed. Tanner stage was breast 4th grade and pubic hair 4th grade. She had not attained menarche at the first hospital visit. Blood tests on admission showed fasting plasma glucose of 160 mg/dL, fasting immunoreactive insulin (IRI) 22.7 μU/mL, and serum C-peptide 2.36 ng/mL. The calculated HOMA-β was 52.3 (30% above the normal control). Islet-specific autoantibodies, including anti-glutamic acid decarboxylase (GAD), anti-insulinoma-associated antigen-2, and insulin antibodies were negative. The glucagon test revealed a peak plasma glucose level of 160 mg/dL, with a serum C-peptide 3.52 ng/mL (**Table 1**). Based on these findings, the provisional diagnosis was type 2 diabetes mellitus.

The patient had a family history of juvenile-onset diabetes. However, the younger sister and mother had not yet developed diabetes. Therefore, we thoroughly explained the need for genetic testing and obtained informed consent. All three patients provided informed consent for the test. Sequence analysis identified a known heterozygous frameshift mutation, c.872dupC (p.Gly292Argfs*25), in HNF1A in all three family members. As this mutation is considered pathogenic in MODY3, referred to as ClinVar (11), and was consistent with the clinical course of the older sister, the diagnosis of MODY3 was considered valid.

Figure 1 shows the patient's clinical course after discharge. Due to the absence of significant hyperglycemia and the refusal of insulin infusion, 500 mg/d of metformin was started. Continuous glucose monitoring using Libre Pro® showed persistent hyperglycemia after breakfast (**Fig. 2**). Accordingly, 25 mg of miglitol was added before breakfast to control postprandial hyperglycemia. After the diagnosis of MODY3, 1 mg/d of glimepiride was administered based on the reported effectiveness in MODY3 (1); however, due to complaints of abdominal pain and diarrhea, miglitol was discontinued. The glimepiride dose was increased to 2 mg/d, followed by a gradual escalation of metformin to 1000 mg/d. However, metformin was discontinued due to worsening abdominal discomfort. After an extensive discussion about the need for and importance of insulin therapy in supplementing the endogenous insulin secretion capacity, the patient grudgingly agreed to insulin therapy. Accordingly, insulin degludec/aspart combination at 0.6 units/kg body weight/d in the morning and ipragliflozin at 50 mg/d were selected to minimize the number of injections. HbA1c levels gradually improved to 6.6–7.2%. The insulin degludec/aspart was titrated up to 0.8 units/kg/d with increased food intake and decreasing activity. At that point, she complained about the complexity of the oral treatment and desired a switch to insulin. Accordingly, oral medications were replaced with an insulin pump following increased snacking, which was associated with clinical improvement.

Nevertheless, the HbA1c levels worsened to a maximum of 13.2% due to poor adherence to insulin infusion. After discussing the condition with the patient and her mother, she resumed aspart 50 mix twice in the morning and evening at 1.0 units/kg/d, glimepiride 2

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Table 1. Laboratory data of the elder sister on admission

		Reference values
[blood cell count]		
WBC (/μL)	6900	4300–8000
RBC (×10⁴/μL)	484	395–465
Hemoglobin (g/dL)	14	11.3–14.9
Hematocrit (%)	43.4	36.0–47.0
Platelet (×10⁴/μL)	23.9	18.0–34.0
[Biochemistry]		
CRP (mg/dL)	< 0.01	0–0.40
Blood glucose (mg/dL)	162	73–109
AST (U/L)	11	13–30
ALT (U/L)	8	6–27
LD (U/L)	160	124–222
γ-GT (U/L)	8	9–32
Total bilirubin (mg/dL)	0.3	0.2–1.0
Total protein (g/dL)	7.6	6.6–8.1
Albumin (g/dL)	4.8	3.5–5.0
BUN (mg/dL)	13	8–20
Creatinin (mg/dL)	0.45	0.40–0.90
Na (mEq/L)	139	138–145
K (mEq/L)	4.1	3.6–4.8
Cl (mEq/L)	102	101–108
[Endocrine]		
F-T3 (ng/mL)	3.46	2.30–4.00
F-T4 (pg/ml)	1.28	0.90–1.70
TSH (μIU/mL)	0.789	0.500–5.000
Fasting plasma glucose (mg/dL)	160	73–109
Fasting immunoreactive insulin (μU/mL)	22.7	< 18.8
Serum C peptide (ng/mL)	2.36	0.80–2.50
Anti GAD antibody (mg/dL)	< 5.0	< 5.0
Anti IA-2 antibody (U/mL)	< 0.4	< 0.4
Insulin antibody (U/mL)	< 0.4	< 0.4
[Urinalysis]		
pH	5	5–7.5
Specific gravity	1.032	1.002–1.030
Sugar	(3+)	–
Protein	(1+)	–
Blood	(–)	–
Nitrite	(–)	–
[Glucagon tolerance test]		
Blood glucose peak (mg/dL)	160	
Serum C-peptide (ng/mL)	3.52	
[Calculated data]		
HOMA-β (%)	52.3	> 30

WBC, White blood cell; RBC, Red blood cell; F-T4, Free thyroxin; F-T3, Free triiodothyronine; TSH, Thyroid-stimulating hormone; CRP, C-reactive protein; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; LD, Lactic Acid Dehydrogenase; BUN, Blood urea nitrogen; Na, Serum sodium; K, Serum potassium; Cl, Serum Chloride; GAD, Glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; HOMA-β, Homeostatic Model Assessment of beta cell function. HOMA-β = fast Immunoreactive insulin (μU/ml) * 360/ (fast blood glucose (mg/dL) – 63).

mg/d, and ipragliflozin 50 mg during hospitalization. The preprandial plasma glucose level gradually decreased from 310 mg/dL before hospitalization to 94–116 mg/dL after four days without hypoglycemia following the start of the new treatment regimen. One month after the resumption of oral glucose-lowering therapy, the HbA1c level decreased to approximately 10%. At the last clinical visit at the age of 16 yr, the patient continued

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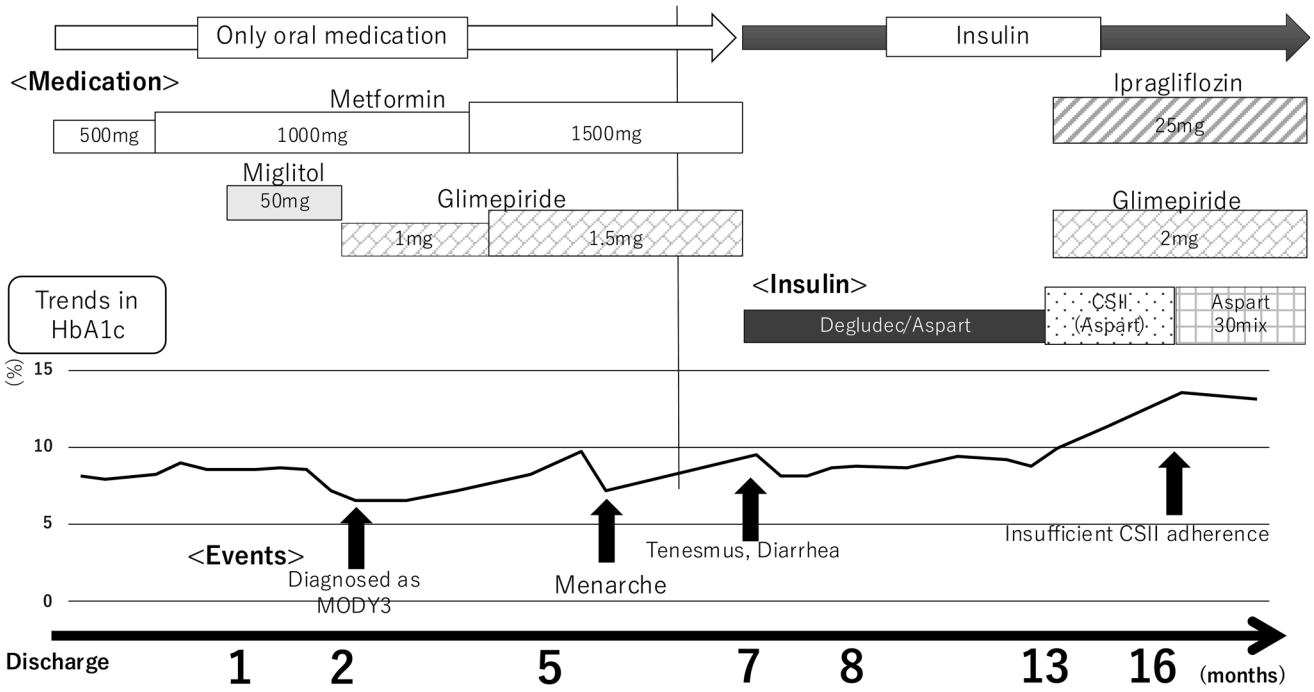

Fig. 1. One to two months after discharge, the patient was diagnosed as MODY3. Then Glimepiride 1mg/d was started. However, blood glucose levels worsened rapidly after menarche. She opted to switch to insulin injections after a thorough discussion with her. Based on her lifestyle, insulin adherence remained poor, and the combination of oral medication and insulin injections was adopted at the latest.

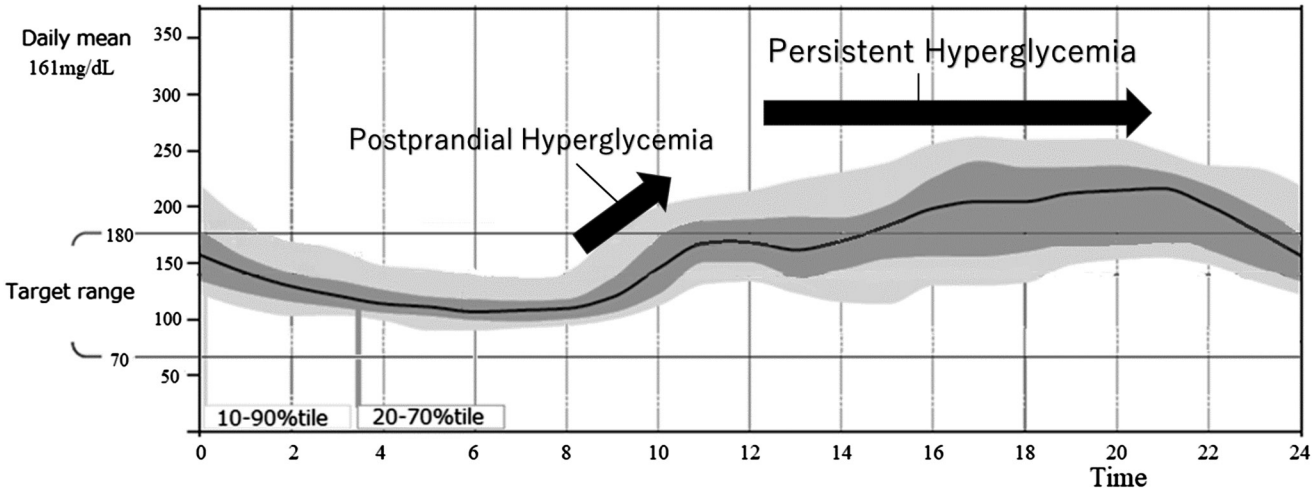

Fig. 2. Hyperglycemia trends after breakfast and subsequent persistent hyperglycemia. The mean glucose level was 161 mg/dL, and the estimated HbA1c 7.2%.

to adhere to the treatment.

The mother (Case 2) was diagnosed with MODY3 at age 34, when the proband was genetically diagnosed with MODY3. During her second pregnancy at 24 yr of age, she had a positive glucose challenge test but did not meet the diagnostic criteria for diabetes mellitus in the 75-g oral glucose tolerance test. At age 34, she was found to have an abnormal blood glucose test result on the annual work-sponsored health check, with a fasting plasma glucose level of 148 mg/dL, HbA1c level of 8.3%, and serum C-peptide 1.08 ng/mL. The fasting IRI levels were not assessed. The patient tested negative for anti-GAD antibodies. Following the diagnosis of diabetes, the patient was started on 500 mg/d of metformin. Due to diarrhea, the patient was switched to 50 mg/d of sitagliptin and 150 mg/d of miglitol. Despite the combination of medications and dietary restrictions, the HbA1c levels remained above 8%. Through close clinical management, she gradually adopted a carbohydrate-strict diet with an insulin/carbohydrate ratio of 1.0 units/

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10 grams and a correction factor of 50 mg/dL/unit, in addition to Degludec at 15 units/d. Finally, she selected intensive insulin therapy, rather than glimepiride, combined with carbohydrate counting due to her busy work schedule and difficulty with continuing dietary therapy. Currently, the mother receives an insulin dose of 1.0 units/kg body weight/d, with HbA1c within the 7% range.

The proband's younger sister (Case 3) was diagnosed with MODY3 at eight years old when the proband was genetically diagnosed with MODY3. She had no significant symptoms before genetic testing, with a fasting plasma glucose level of 90 mg/dL and an HbA1c level of 5.7%. Height was 139.3 cm, body weight 42.2 kg, and BMI 21.75 kg/m^2. No skin pigmentation was observed. Tanner stage was breast 2nd grade and pubic hair 1st grade. She had not attained menarche at the first hospital visit. At 10 yr of age, laboratory tests showed fasting plasma glucose 160 mg/dL, HbA1c 6.7%, IRI 18.1 μU/mL, serum C-peptide 3.47 ng/mL, and anti-GAD antibody negative. She was started on 1 mg/d of glimepiride, which improved tenesmus and HbA1c levels (diminishing to 6.0%). Five months after the start of treatment, the HbA1c levels increased to 6.5%. She underwent continuous glucose monitoring using Libre Pro®, which identified increased glucose levels following a post-lunch snack. Accordingly, she was advised to take 30 mg of nateglinide before consuming a large meal, followed by 25 mg/d of ipragliflozin. At the last clinical examination, her diabetes was under control, with an HbA1c level of 6.5–7%.

Ethical consideration

All procedures performed in this study adhered to the ethical standards of the institutional and national research committees and the 2013-revised Helsinki Declaration. Genetic examinations were approved by the Ethics Committee of Osaka City General Hospital (#742). Written informed consent for the publication of patient data, images, and genetic test results was obtained from the patient's mother.

Discussion

This report describes the diversity of treatments and the need to address individual patients among three family members diagnosed with a single gene mutation in MODY3, who should have similar predisposing factors, such as insulin secretion. MODY3 is classified as a specific type of diabetes with other causes in the Classification and Diagnosis of Diabetes (12). In contrast, patients with type 2 diabetes have various conditions for which the associated genes and predispositions have not been fully identified. This case report indicates that factors other than those defined by genetic predisposition significantly affect diabetes treatment.

MODY3 is caused by HNF1A mutations and is one of the most frequently diagnosed types of MODY. The HNF1A gene controls the expression of the sodium/glucose cotransporter-2 (SGLT2) gene. The glucose reabsorption threshold in the renal tubules is reduced; thus, urinary glucose screening programs in schools are often used for early detection (13). A previous Japanese study employing genetic analysis, including HNF1A, of 83 patients with non-obesity diabetes aged ≤ 30 yr identified 7 (8%) patients with known pathological variants of HNF1A (14). However, not all non-obese diabetics are regularly tested for this mutation, suggesting that some patients with type 1B diabetes or juvenile-onset type 2 diabetes may harbor this mutation.

The two sisters were diagnosed with diabetes mellitus at a younger age than their mother, and the younger sister was diagnosed at a younger age than the older sister (Supplementary Table 1). The MODY3 genotype varied from one report to another. Miedzybrodzka *et al.* (7) reported a family with a mutation in the HNF1A gene; one male with an HNF1A gene mutation was diabetes-free until 87 yr of age, and another male required insulin from 18 yr of age. Furthermore, Awa *et al.* (9) reported that mutations in Exon8-10 in German-Austrian individuals occurred, on average, eight years later than those in Exon1-6. The latter Exon1-6-related acceleration phenomenon may be explained by the transcriptionally less active isoform A by Exon8-10 compared to isoforms AB (Exon7) and ABC (Exon1-6). Regarding intergenerational effects, exposure to maternal diabetes *in utero* can accelerate the onset of diabetes by approximately 12 yr (15, 16). Conversely, Tatsi *et al.* (6) showed no clear phenotype-genotype correlation in 15 diabetic Greeks aged < 15 yr with HNF1A mutations. These reports suggest that factors other than exon mutations affect the early onset of diabetes. Unfortunately, we could not perform genetic analysis for the entire family because the parents were divorced and the father moved to a different city. Further case accumulation is desirable to identify the factors that promote early onset of the condition.

Typical MODY3 is reported to be markedly responsive to SU agents, from early onset to long-term disease (1, 4, 5). Other oral medications, such as meglitinide analogs and SGLT-2 inhibitors, are also considered suitable therapeutic agents (17, 18). However, these early reports were short-term, and, to our knowledge, there are currently no published long-term studies or treatment guidelines. Insulin secretion usually decreases over time in MODY3, and insulin therapy is often required in the long term. (16). Similar to type 1 diabetes, glycemic control aimed at an HbA1c level < 6.5% appears to prevent the development of various microvascular and macrovascular complications in MODY3 (19). When blood glucose levels can be appropriately managed while avoiding hypoglycemia, early insulin therapy is a strong candidate for MODY3, like type 1 diabetes. In the family described here, the older sister also showed relatively stable glycemic control in the early stages of the disease. However, the glycemic control of the older sister worsened rapidly after

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menarche. Notably, the older sister initially refused the insulin injections. However, she later changed her mind when she became convinced that adjusting her insulin dose to match her food intake was more manageable than following a strict diet with oral medications. Her mother initially found it easier to eat what they wanted, adjusted their insulin levels with carbohydrate calculations, and never prescribed oral antidiabetic agents. In contrast, the younger sister was resistant to injections and preferred oral treatment with strict dietary therapy. The above treatment choices and changes indicate the importance of avoiding a uniform treatment regimen, such as using only SU and strict dietary therapy, for all cases of MODY3. Instead, they amplify the significance of shared decision-making with the patient/guardian regarding the best treatment choice that can be used over the long term and that is suited for insulin secretion and insulin resistance.

Conclusion

We described three MODY3 cases in one family, including the mother and two sisters, who were diagnosed with diabetes at different ages and presented with treatment challenges; one was successfully treated with SU agents, while the other two required other treatment regimens based on different lifestyles and secondary sexual characteristics. For long-term adherence to therapy, flexible treatment options (including oral medications, insulin injections, insulin pumps, or their combinations) and shared decision-making with patients is desirable to suit environmental changes and to be in line with the psychosocial status of the individual patient, without limiting the use of SU or insulin therapy because of MODY3.

Conflicts of interests: All authors declare no conflict of interest.

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References

1. Hattersley AT, Greeley SAW, Polak M, Rubio-Cabezas O, Njølstad PR, Mlynarski W, *et al*. ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2018;19(Suppl 27): 47–63. [Medline] [CrossRef]
2. Kavvoura FK, Owen KR. Maturity onset diabetes of the young: clinical characteristics, diagnosis and management. Pediatr Endocrinol Rev 2012;10: 234–42. [Medline]
3. Yorifuji T, Fujimaru R, Hosokawa Y, Tamagawa N, Shiozaki M, Aizu K, *et al*. Comprehensive molecular analysis of Japanese patients with pediatric-onset MODY-type diabetes mellitus. Pediatr Diabetes 2012;13: 26–32. [Medline] [CrossRef]
4. Horikawa Y. Maturity-onset diabetes of the young. Japan Diab Soc. 2019;62: 461–3.
5. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. Lancet 2003;362: 1275–81. [Medline] [CrossRef]
6. Tatsi C, Kanaka-Gantenbein C, Vazeou-Gerassimidi A, Chrysis D, Delis D, Tentolouris N, *et al*. The spectrum of HNF1A gene mutations in Greek patients with MODY3: relative frequency and identification of seven novel germline mutations. Pediatr Diabetes 2013;14: 526–34. [Medline] [CrossRef]
7. Miedzybrodzka Z, Hattersley AT, Ellard S, Pearson D, de Silva D, Harvey R, *et al*. Non-penetrance in a MODY 3 family with a mutation in the hepatic nuclear factor 1α gene: implications for predictive testing. Eur J Hum Genet 1999;7: 729–32. [Medline] [CrossRef]
8. Lehto M, Tuomi T, Mahtani MM, Widén E, Forsblom C, Sarelin L, *et al*. Characterization of the MODY3 phenotype. Early-onset diabetes caused by an insulin secretion defect. J Clin Invest 1997;99: 582–91. [Medline] [CrossRef]
9. Awa WL, Thon A, Raile K, Grulich-Henn J, Meissner T, Schober E, *et al*. DPV-Wiss. Study Group. Genetic and clinical characteristics of patients with HNF1A gene variations from the German-Austrian DPV database. Eur J Endocrinol 2011;164: 513–20. [Medline] [CrossRef]
10. Naoko K, Daisuke F, Yoshio A, Takahiro S, Kenji T, *et al*. Cases of a mother and her daughter with MODY3 diagnosed at daughter's onset of diabetes. Japan Diab Soc. 2018;61: 544–9.
11. National Center for Biotechnology Information. ClinVar; [VCV000014927.16], https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000014927.16 (accessed Oct. 1, 2022).
12. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, *et al*. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig 2010;1: 212–28. [Medline] [CrossRef]
13. Miyachi Y, Miyazawa T, Ogawa Y. HNF1A Mutations and beta cell dysfunction in diabetes. Int J Mol Sci 2022;23: 3222. [Medline] [CrossRef]
14. Iwasaki N, Oda N, Ogata M, Hara M, Hinokio Y, Oda Y, *et al*. Mutations in the hepatocyte nuclear factor-1alpha/MODY3 gene in Japanese subjects with early- and late-onset NIDDM. Diabetes 1997;46: 1504–8. [Medline] [CrossRef]

15. Pihoker C, Gilliam LK, Ellard S, Dabelea D, Davis C, Dolan LM, *et al*. SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013;98: 4055–62. [Medline] [CrossRef]
16. Stride A, Vaxillaire M, Tuomi T, Barbetti F, Njølstad PR, Hansen T, *et al*. The genetic abnormality in the beta cell determines the response to an oral glucose load. Diabetologia 2002;45: 427–35. [Medline] [CrossRef]
17. Becker M, Galler A, Raile K. Meglitinide analogues in adolescent patients with HNF1A-MODY (MODY 3). Pediatrics 2014;133: e775–9. [Medline] [CrossRef]
18. Sriravindrarajah A, Fernandes A, Wu T, Hocking S. The use of SGLT2 inhibitors in achieving glycaemic control in maturity-onset diabetes of the young type 3. Endocrinol Diabetes Metab Case Rep 2021;2021: 21–102. [Medline]
19. Isomaa B, Henricsson M, Lehto M, Forsblom C, Karanko S, Sarelin L, *et al*. Chronic diabetic complications in patients with MODY3 diabetes. Diabetologia 1998;41: 467–73. [Medline] [CrossRef]