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Abstract:	Maturity onset diabetes of the young (MODY) is a rare form of monogenic diabetes that classically presents as a non-insulin requiring diabetes with evidence of autosomal dominant inheritance in individuals who are typically young and lean. These criteria, however, do not capture all cases and can also overlap with other types of diabetes. The hepatocyte nuclear factor-1 alpha (HNF1A) mutation is a common cause of MODY and is highly sensitive to sulphonylureas which should be first-line therapy. Our case represents the diagnostic challenges of HNF1A MODY and the implications of a delayed diagnosis which can lead to reduced success of sulphonylurea treatment.

Treatment implications of a delayed diagnosis of maturity onset diabetes of the young

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Abstract

Maturity onset diabetes of the young (MODY) is a rare form of monogeneic diabetes that classically presents as ~~a~~ non-insulin requiring diabetes with evidence of autosomal dominant inheritance in individuals who are typically young and lean. These criteria, however, do not capture all cases and can also overlap with other types of diabetes. The hepatocyte nuclear

factor-1 alpha (*HNF1A*) mutation is a common cause of MODY and is highly sensitive to sulphonylureas which should be first-line therapy. Our case represents the diagnostic challenges of *HNF1A* MODY and the implications of a delayed diagnosis which can lead to reduced success of sulphonylurea treatment.

Keywords: maturity onset diabetes of the young; hepatocyte nuclear factor 1-alpha; sulphonylurea

1. Introduction

Maturity onset diabetes of the young (MODY) is characterised by a primary defect in insulin secretion resulting in early onset diabetes (1). It is responsible for 1-5% of all cases of diabetes (2) and demonstrates an autosomal dominant mode of inheritance. The hepatocyte nuclear factor-1 alpha (*HNF1A*) gene mutation accounts for 16-45% of all cases of MODY (3) and confers particular sensitivity to the glucose-lowering effect of sulphonylureas (4), which are the initial pharmacological treatment of choice. Our case represents an example of a missed opportunity to diagnose MODY ~~both the diagnostic challenges of MODY~~ and the implications that a delayed diagnosis as well as decline in beta cell function and insulin resistance may have on the successful implementation of treatment tailored to this condition.

2. Case

A 60-year-old Caucasian male with a body mass index (BMI) of 31 kg/m^2 and a strong family history of diabetes (Figure 1) presented in 2011 for management of presumed type 2 diabetes

mellitus (T2DM). He had been diagnosed with T2DM aged 21 when his BMI was 24kg/m^2. ~~, which was diagnosed aged 31.~~ Antibodies to glutamic acid decarboxylase 65, insulinoma-associated protein-2 and zinc transporter ZnT8 were negative. His diabetes was initially managed with lifestyle measures before metformin was introduced at the age of 22. This was uptitrated with little benefit before a sulphonylurea was added to his medication regimen at the approximate age of 24 years. In 2011, after having gained approximately 22kg of weight since his diagnosis, the patient~~He~~ had a haemoglobin A1c (HbA1c) of 7.6% (60 mmol/mol) and was being treated with metformin, glibenclamide and pioglitazone.

In 2012, his HbA1c increased and pioglitazone and glibenclamide were ceased (Figure 2). He continued on metformin and commenced twice-daily mixed insulin. While on insulin, he reported nocturnal hypoglycaemic episodes and hypoglycaemia with physical activity.

In 2014, the patient's grandson was diagnosed with diabetes and had undergone genetic testing which revealed that he was positive for the previously reported pathogenic *HNF1A p.Asp135fs* gene mutation meaning his diagnosis was therefore MODY. This led to genetic testing of our case patient who was also found to be positive for the same genetic mutation. As a result of this diagnosis, gliclazide was introduced to his diabetes management regimen. With the addition of gliclazide, his HbA1c had improved to 6.1% (43 mmol/mol) in 2016. Insulin was then ceased and at the same time the patient commenced empagliflozin and metformin to help manage hyperglycaemia. The new medication regimen also facilitated 6kg of weight loss (BMI 28 kg/m^2). In 2018, the patient was trialled on glibenclamide as a single agent to see if this would be sufficient to manage his MODY. Repeat HbA1c in March 2019, however, was 9.4% (79 mmol/mol) on glibenclamide alone. His C-peptide level was 0.83 nmol/L with a fasting blood glucose level of 8.0 mmol/L at this time. Metformin was

reintroduced to the patient's medication regimen, which saw his HbA1c improve once again in June 2019.

The patient's first degree relatives were offered genetic counselling to evaluate their risk of MODY.

3. Discussion

3.1 *Pathophysiology*

Monogenic forms of diabetes are due to highly penetrant single gene mutations and present across a clinical spectrum that includes MODY, mitochondrial diabetes and genetic syndromes that include diabetes as part of their clinical presentation (5). Genetic variants of at least 14 known genes cause MODY through pancreatic beta cell dysfunction that leads to hyperglycaemia (Table 1) (2). The three most common forms of MODY are caused by mutations in hepatocyte nuclear factor 1-α, hepatocyte nuclear factor 4-α (*HNF4A*) and glucokinase (6).

Both *HNF1A* and *HNF4A* are genes that encode transcription factors that promote transcription of genes involved in pancreatic beta cell development and insulin production. Patients with *HNF1A*-MODY have a five-fold greater response to sulphonylureas than to metformin and their response to sulphonylurea therapy is nearly four-fold greater than those with T2DM (7). They act by binding to sulphonylurea receptor 1, a subunit of the potassium channel located on pancreatic beta cell membranes, which ultimately stimulates the release of stored insulin (Figure 3) (8).

3.2 *Clinical presentation*

The diagnosis of MODY should be suspected in patients who are lean, have detectable C-peptide levels, are antibody negative and do not have other risk factors for T2DM (e.g. increased BMI, ethnicity) (6). Individuals with MODY who happen to have risk factors for other diabetes types are particularly susceptible to going untested and undiagnosed. It is estimated that approximately 80% of MODY is misdiagnosed as T1DM or T2DM (9) and a delay of more than 10 years from presentation of diabetes to molecular diagnosis is frequently reported (10).

Genetic testing represents the gold standard for diagnosing MODY. The MODY Probability Calculator developed by Shields et al (11) uses models that define an overall probability of MODY using a weighted combination of the most discriminative characteristics. The models are available online at www.diabetesgenes.org and provide clinicians with a positive predictive value that can be used to evaluate the benefits of genetic testing against its cost. Using this model, a positive predictive value of 32.9% was generated for our case patient in 2014 when he was aged 63 years. It is suggested that a value >25% should prompt genetic testing.

3.3 *Treatment implications*

A molecular diagnosis of *HNF1A*-MODY has been shown to alter clinical practice, with one observational study finding that 79% of patients attempted a transition to sulphonylurea therapy (4). This was successful in the majority of patients (71%) without deterioration in glycaemic management. Those patients who later recommenced insulin had a trend toward a longer duration of diabetes compared with those remaining on tablets. Furthermore,

patients who transitioned from insulin to sulphonylureas reported improved lifestyle and self-image as well as feelings of relief associated with discontinuing insulin (12).

Patients with *HNF1A*-MODY are highly sensitive to sulphonylureas and usually require a low starting dose (13) with cautious increments in dosing. Secondary sulphonylurea failure by progressive deterioration in pancreatic beta cell function and development of absolute insulinopaenia can occur over a period of up to 25 years depending on the duration of disease and glycaemic management (4). A study of 49 patients with either *HNF1A* or *HNF4A* MODY showed only 36% of individuals achieved an HbA1c ≤ 7.5% (58 mmol/mol) on sulphonylurea therapy alone at 2 years following a genetic diagnosis (14). As observed in our case patient, higher HbA1c levels, longer duration of diabetes and larger BMI at genetic diagnosis were associated with reduced success on sulphonylurea treatment. In such patients, where both beta cell decline and insulin resistance may co-exist with MODY, it may be more appropriate to add a sulphonylurea to existing therapy rather than ceasing current treatment. However, if individuals are transferred to optimal treatment early on then it may be easier to achieve good ~~control~~ glycaemic management and to maintain it (14), reflecting the importance of early genetic diagnosis.

In pregnancies affected by *HNF1A* MODY, maternal glycaemic control is the major determinant of foetal outcomes (15). There are case reports of congenital hyperinsulinism associated with the *HNF1A* gene mutation, however in the majority of cases, foetal inheritance of the mutation does not in itself result in complications (16, 17). Pregnant women with *HNF1A* MODY may be switched to insulin as there is a risk of macrosomia and

neonatal hypoglycaemia with sulphonylurea use in the third trimester (15). {Dickins, 2018 #30;Dickins, 2018 #30;Dickins, 2018 #30;Dickins, 2018 #30}

A diagnosis of MODY has further implications for genetic counselling and early screening of family members. Patients with a confirmed genetic diagnosis may also avoid unnecessary monitoring for autoimmune conditions associated with a presumed diagnosis of type 1 diabetes.

4. Conclusion

It is important that all clinicians treating patients with diabetes consider MODY as a potential diagnosis. Timely commencement of sSulphonylureas improve glycaemic management and should be first line therapy for patients with *HNF1A* -MODY. Personalised management of MODY results in improved patient care with less burdensome, safer, cheaper and more effective treatment methods.

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Tables

Table 1. Causative genes, clinical features and suggested treatment for the 14 known subtypes of MODY

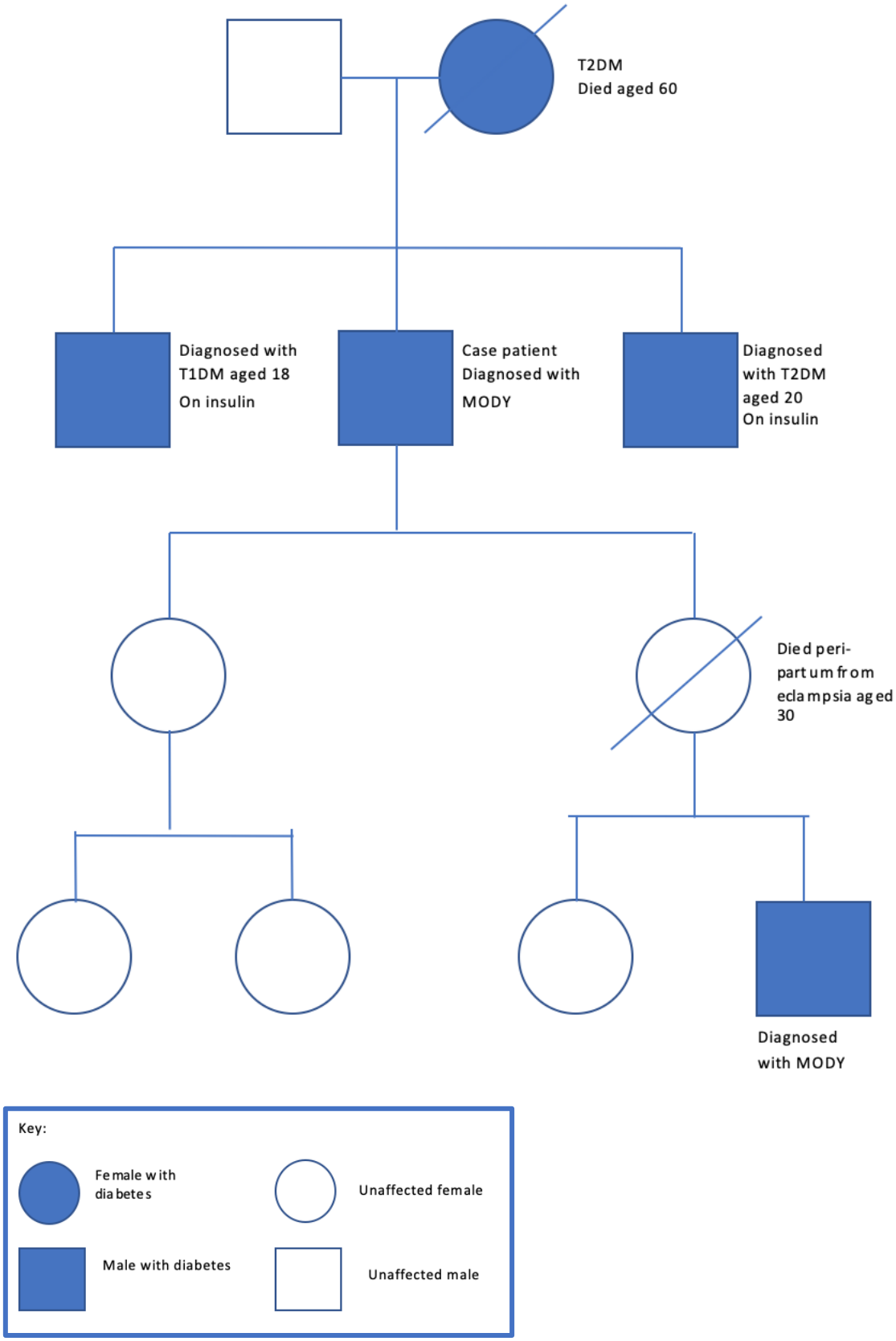
Figures

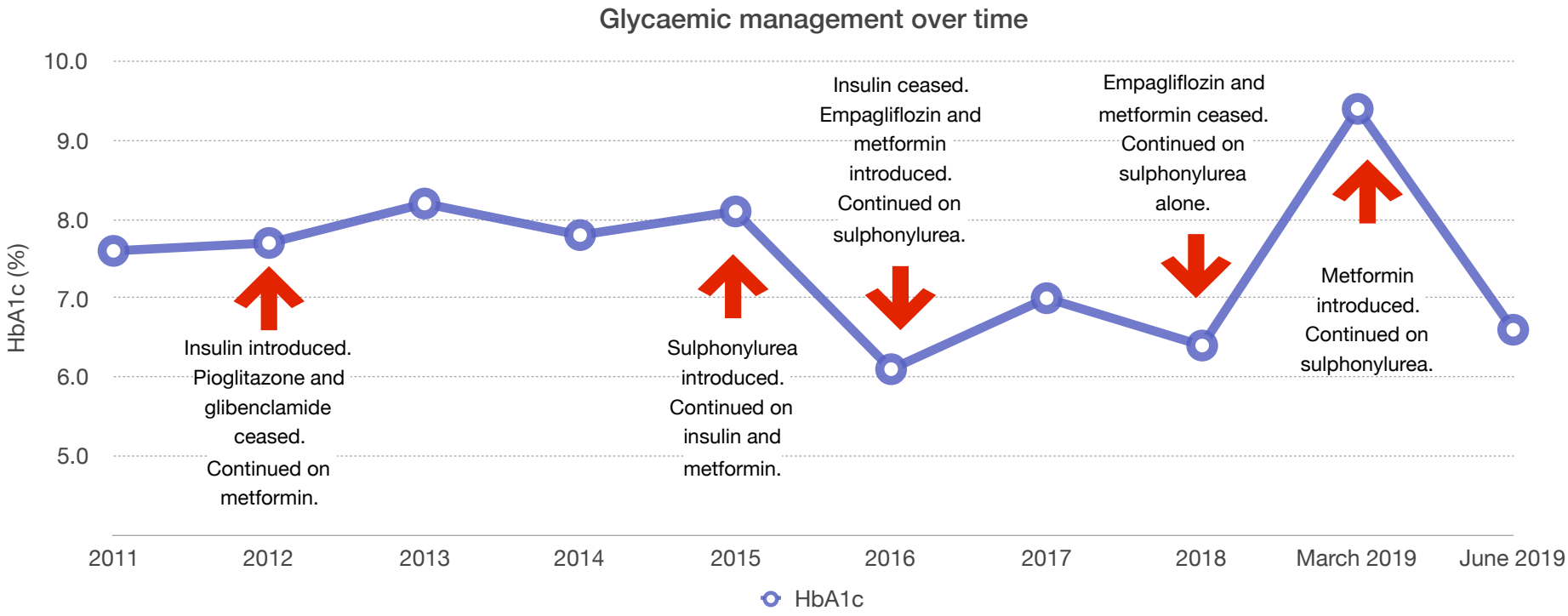
Fig. 1 Pedigree illustrating strong family history of diabetes diagnosed at an early age.

Fig. 2 Graph showing case patient's glycaemic management over time.

Fig. 3 Diagram showing the action of sulphonylureas on beta cells.

Sulphonylurea derivatives bind to sulphonylurea receptor 1 (SUR1) (1). This causes the closure of the ATP-sensitive potassium channel (2) and subsequent rise of membrane potential of the beta cell. This triggers the opening of voltage-gated calcium channel and influx of calcium ions (3), which then stimulates the fusion of vesicles storing insulin with the cell membrane mediating insulin release (4). By this mechanism, sulphonylureas bypass the insulin secretion defect caused by HFN1A and HNF4A mutations.





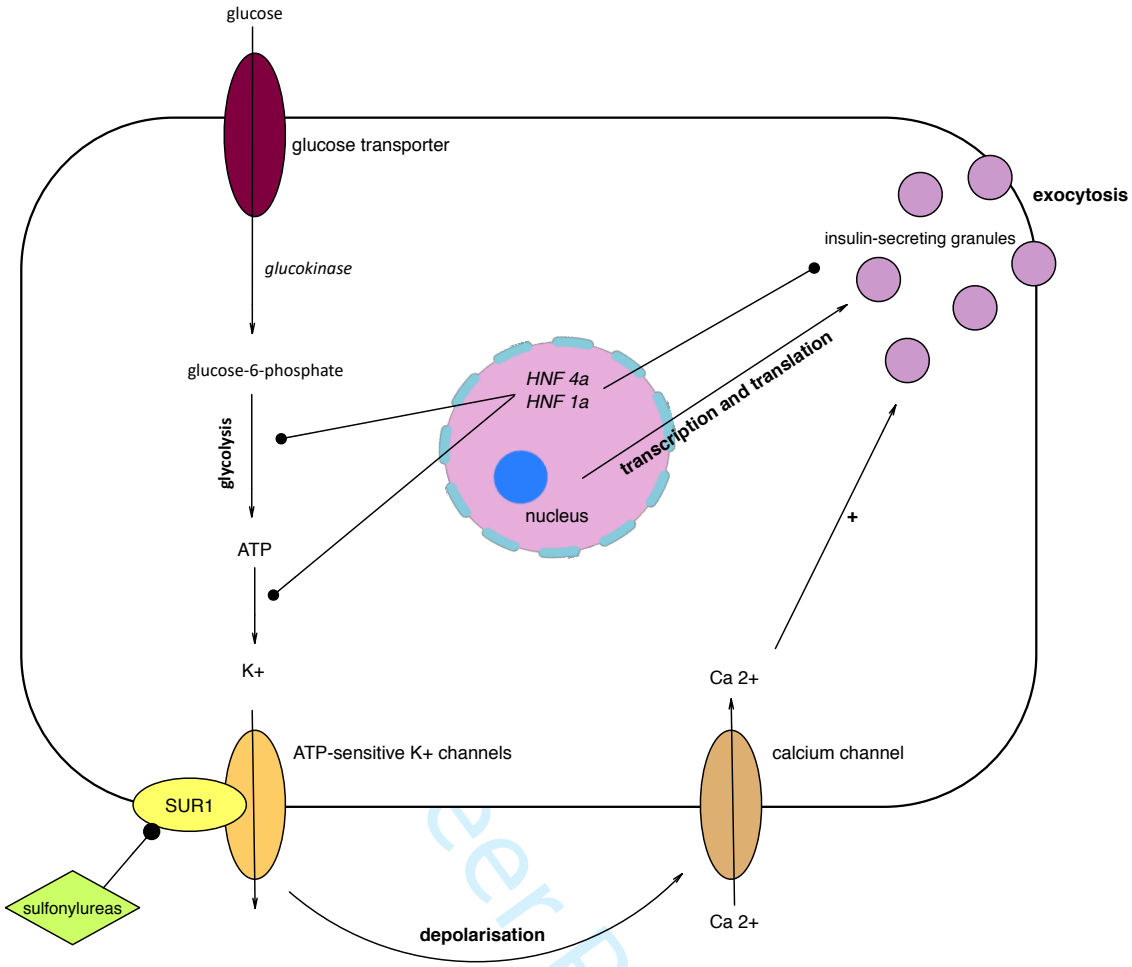


Table 1. Causative genes and clinical features of 14 known subtypes of MODY (2)

MODY gene	Frequency (% in MODYs)	Pathophysiology	Other features	Possible treatment
HNF1α	30–50	β-Cell dysfunction	Glucosuria	Sensitive to sulphonylurea
GCK	15–20	Glucose sensing defect	Stable mild fasting glucose	No medication, or diet
HNF4α	5	β-Cell dysfunction	Neonatal diabetes, hyperinsulinemic hypoglycemia during infancy, low triglycerides	Sensitive to sulphonylurea
HNF1β	5	β-Cell dysfunction	Renal malformations, genito-urinary tract anomalies, pancreatic hypoplasia, low birth weight	Insulin
PDX1	<1	β-Cell dysfunction	Homozygote: permanent neonatal diabetes, pancreas agenesis	Diet or OHGs or insulin
NEUROD1	<1	β-Cell dysfunction	Neonatal diabetes, child or adult-onset diabetes neurological abnormalities.	OHGs or insulin
KLF11	<1	β-Cell dysfunction	Similar to type 2 diabetes	OHGs or insulin
CEL	<1	Pancreas endocrine and exocrine dysfunction	Exocrine dysfunction, lipomatosis	OHGs or insulin
PAX4	<1	β-Cell dysfunction	Ketoacidosis-prone	Diet or OHGs or insulin
INS	<1	Insulin gene mutation	Neonatal diabetes, child or adult-onset diabetes	OHGs or insulin
BLK	<1	Insulin secretion defect	Overweight, relative insulin secretion failure	Diet or OHGs or insulin
ABCC8	<1	ATP-sensitive potassium channel dysfunction	Homozygote: permanent neonatal diabetes, Heterozygote: transient neonatal diabetes	OHGs (sulfonylurea)
KCNJ11	<1	ATP-sensitive potassium channel dysfunction	Homozygote: neonatal diabetes	OHGs or insulin
APPL1	<1	Insulin secretion defect	Child or adult-onset diabetes	Diet or OHGs or insulin