Maturity-onset diabetes of the young as a model for elucidating the multifactorial origin of type 2 diabetes mellitus

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Keywords
Maturity-onset diabetes of the young, Penetration, Type 2 diabetes mellitus

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J Diabetes Investig 2018; 9: 704–712
doi: 10.1111/jdi.12812

ABSTRACT
Maturity-onset diabetes of the young (MODY) is a form of diabetes classically characterized as having autosomal dominant inheritance, onset before the age of 25 years in at least one family member and partly preserved pancreatic β-cell function. The 14 responsible genes are reported to be MODY type 1–14, of which MODY 2 and 3 might be the most common forms. Although MODY is currently classified as diabetes of a single gene defect, it has become clear that mutations in rare MODYs, such as MODY 5 and MODY 6, have small mutagenic effects and low penetrance. In addition, as there are differences in the clinical phenotypes caused by the same mutation even in the same family, other phenotypic modifying factors are thought to exist; MODY could well have characteristics of type 2 diabetes mellitus, which is of multifactorial origin. Here, we outline the effects of genetic and environmental factors on the known phenotypes of MODY, focusing mainly on the examples of MODY 5 and 6, which have low penetrance, as suggestive models for elucidating the multifactorial origin of type 2 diabetes mellitus.

INTRODUCTION
Maturity-onset diabetes of the young (MODY) is a form of diabetes with partly preserved pancreatic β-cell function, and is caused by a single gene defect; it develops with an autosomal dominant mode of inheritance and onset age usually of <25 years.1 After a rapid advancement in molecular genetics, the first GCK gene (MODY2) was identified in 1992, followed by a series of genes for MODY 1 and 3–6. The MODY gene was identified using a family-based genetic method called parametric linkage analysis to calculate the matching or discrepancy between deoxyribonucleic acid markers scattered across the genome and the transmission of diabetes in large MODY families. The MODY gene has since been reported to the 14th MODY, but in general, MODY 1–6 has been established as MODY from the viewpoint of reproducibility by multiple families worldwide. There is as yet no report of MODY 4 in Japanese. The causal genes of monogenic diabetes, including MODY, are often involved in the glucose-responsive insulin secretory pathway of pancreatic β-cells. Thus, MODY shows low glucose-responsive insulin secretion and, generally, a lean phenotype, which is common to type 2 diabetes in Japanese patients. Although MODY has been classified as a single gene defective diabetes, it has been clarified that the development of MODY is influenced by other modifying factors including ethnicity, specific genetic background and/or intrauterine environment, leading to the concept that MODY, especially low penetrant MODYs, such as MODY 5 and MODY 6, has characteristics of common type 2 diabetes having a multifactorial origin.

MODY 5
In 1997, the hepatocyte nuclear factor 1 homeobox B (HNF1B, transcription factor 2) gene was identified as the causal gene of MODY 5. The HNF1B gene has high homology with the HNF1A gene, forming heterodimers or homodimers with HNF1A. HNF1A is expressed mainly in the liver, but also in the kidney and islets, whereas HNF1B predominates in the kidney in adulthood. Compared with MODY 3, phenotypes of MODY 5 differ greatly and are often rare. The most frequent mutations of MODY 5 are monoallelic defects in all or some exons, which are seldom inherited beyond the generation and are often sporadic. The HNF1B gene is located at 17q12, which is considered to be a region prone to recombination errors during meiosis as a result of overlapping sequences of very homologous sequences, known as segmental duplication.
In a previous study involving the present author, criteria were selected including onset age of ≤35 years, autoimmune antibody negativity and no obesity (body mass index <30 kg/m² as the international classification of adult obesity according to body mass index). Family history was not included, so as not to miss sporadic or low penetrant cases. Obesity was not included, as compensatory hyperinsulinemia can mask the phenotype of insulin deficiency. Nevertheless, some MODY 5 was not diagnosed until after 25 years-of-age, whereas MODY 3 was likely to be diagnosed before 15 years-of-age (Figure 1). It is considered that this reflects differences in gene expression levels between the HNF1A gene and the HNF1B gene in pancreatic β-cells in adulthood. In Caucasian MODY 5 patients, hyperinsulinemia and/or hypertriglyceridemia are observed in the early stage of the disease, reflecting insulin resistance, but in Japanese MODY 5 patients, insulin secretion is decreased from an early stage of the disease. In addition to the low insulin secretory capacity in Japanese people, a low amount of pancreatic β-cell mass as a result of failure of pancreatic formation during the developmental stage and insulin resistance as a result of suppressor of cytokine signaling 3 activation due to HNF1B inactivation in the liver are often seen, resulting in absolute insulin deficiency at an early stage. Indeed, most of the patients in the previous study involving the present author had insulin treatment from the onset of diabetes and could not be withdrawn from insulin treatment, which could suggest that insulin secretion deficiency is a characteristic feature of the disease in Japanese patients.

The causal gene, HNF1B, is a transcription factor that is highly expressed at undifferentiated periods, and presents various clinical manifestations across many organs. MODY 5 is characterized by a variety of phenotypes that differ from early onset type 2 diabetes, the most common one being renal disease (multiple renal cysts, renal dysplasia, renal dysfunction etc.). The HNF1B mutation is related to malformation of ureteric bud-derived structures presenting as an anomaly of the collecting duct and hypoplastic glomerulocystic disease. Renal structure anomalies and diabetes mellitus were detected in 96.6 and 21.6% of patients under the age of 25 years, respectively, indicating that formation of renal structure anomalies usually precedes the onset of diabetes. Thus, MODY 5 is also called renal cysts and diabetes. However, in a recent study, renal cysts were not found by repeated abdominal magnetic resonance imaging or echography in two Japanese children having whole gene deletion. Interaction with other modifying genetic or environmental factors could therefore play a role in the determination of some of the phenotypic features.

Pancreatic malformations are found in approximately 10% of patients, and include atrophy, calcification and cysts. Approximately half of these patients show diffuse pancreatic atrophy; the others show body and tail atrophy or head atrophy. Interestingly, the same mutation, p.Q477Ter, in the family we examined showed a different clinical phenotype regarding morphological abnormality of the pancreas (Figure 2), suggesting interactions with other disease-modifying factors. Recently, using human induced pluripotent stem cells (HNF1B<sup>51–48L</sup>), PAX6 pancreatic gene expression was found to be decreased without compensation. The lack of downregulation of HNF1B, PDX-1, GATA4, GATA6, PTFT1A, ISL1 and RFX6 implies that the mechanism underlying dorsal pancreatic agenesis in MODY 5 is independent of these genes, which are also known to result in pancreatic agenesis/hypoplasia when mutated. PAX6-deficient pancreatic progenitors that are unable to mature and reach terminal differentiation later in life cannot be rescued by postnatal neogenesis, contributing to a pancreatic hypoplasia phenotype in MODY 5 patients. Future study must be carried out to elucidate all genetic factors, including modifying factors, for pancreas formation. In addition, gonadal dysplasia, hepatic dysfunction, hyperuricemia, bile duct dilatation and so on are sometimes found together.

An average of approximately 12 years of follow-up study of patients with MODY 5 has been reported; those patients with microdeletion of a monoallele are leaner, whereas those with missense mutations show lower capacity of renal function. There are 17 genes other than HNF1B gene in the monoallelic defect site, and the possibility that the phenotype has been affected by them cannot be ruled out; the details including gene interactions are still unknown.

**MODY 6**

The MODY 6 (NEUROD1) gene mutation was first reported in two families in 1999. The NEUROD1 gene is a basic helix-loop-helix type transcription factor that is specifically expressed in pancreatic secretory cells, gastrointestinal secretory cells and neuronal cells. It forms heterodimers with the

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**Figure 1** Distribution of onset-age of maturity-onset diabetes of the young type 1 (MODY 1), MODY 2, MODY 3, MODY 5 and MODY 6. Onset age of MODY 1–3, 5 and 6 is dotted with black circles. *P*-values < 0.01 and **P*-values < 0.05 by the Kruskal–Wallis test followed by the Steel–Dwass test, respectively.
basic helix-loop-helix transcription factor E47, which is expressed ubiquitously, and binds to the E-box of the insulin promoter. In addition, it has been reported that NEUROD1 is involved in sulfonylurea factor 1 gene activation and the expression of the GCK gene (MODY2), contributing to diverse roles from insulin synthesis to secretion.

MODY 6 is very rare, and just seven families have been reported since the discovery of the disease 18 years ago by family-based studies; the characteristic phenotype has not been clarified. In cases of homozygous NEUROD1 gene mutation, neurological abnormalities, such as cerebellar hypoplasia and permanent neonatal diabetes mellitus, have been reported; in cases of heterozygous mutation of MODY 6, abnormality in the nervous system was not found (Table 1).

So as to not miss sporadic or low penetrant cases, we used criteria of genetic testing not including family history, such as three consecutive generations of diabetes; we have recently identified four cases of the NEUROD1 mutation in Japanese people. In the previous reports, 21 of 35 patients with the NEUROD1 heterozygous mutation developed overt diabetes after the age of 35 years with obesity, whereas seven of eight Japanese patients with the NEUROD1 heterozygous mutation developed overt diabetes before the age of 35 years without obesity. This difference was considered to be due to the genetic predisposition of Japanese people to lower insulin secretion.

In addition, three of the four parents with heterozygous mutation of probands with neonatal diabetes by homozygous mutation had a normal glucose tolerant type by oral glucose tolerance test, and one of them had late-onset diabetes, suggesting low penetrance of the mutation in Caucasians. Although 15 of 20 patients inheriting the mutations from their mothers had diabetes, two of five patients inheriting

Table 1  Clinical features of seven pedigrees of maturity-onset diabetes of the young type 6 identified in more obese populations

| Pedigree | Mutation | Age of onset (years) | BMI | Microangiopathy (retino/nephro/neuro) | Therapy Ins/OHA/diet (n) |
|----------|----------|---------------------|-----|--------------------------------------|-------------------------|
| 1        | R111L    | 40 (30–59)          | %IBW138 | NA                                   | 2/1/2 (5)               |
| 2        | H206FfsTer38 | 31 (17–56)     | %IBW115 | 3/2/5                                | 4/1/1 (6)               |
| 3        | E110K    | 33 (12–68)          | 24.1 (17.5–30.3) | 2/1/0                               | 4/1/2 (7)               |
| 4        | S159P    | 60 (27–63)          | 22 (19.2–23.7) | 1/2/1                                | 1/1/0 (2, homo 1)       |
| 5        | R103P    | 35.6 (23–50)        | 26.4 (22.9–31.1) | 3/4/5                                | 1/1/0 (2, homo 1)       |
| 6        | D122GfsTer12 | 8 weeks (homo) | 34 weeks of pregnancy | Cerebellar hypoplasia deafness | 1/1/0 (2, homo 1)       |
| 7        | L143AfsTer55 | 4 weeks (homo) | 34 weeks of pregnancy | Learning difficulties (homo) | 1/1/0 (2, homo 1)       |

%IBW, percentage excess or deficit in the ideal bodyweight (assuming 100% is the ideal); BMI, body mass index; homo, homozygote of the mutation; NA, not available; OHA, oral hypoglycemic agent.

Figure 2  Abdominal computed tomography scan at the pancreas head levels of patients, (a) the daughter and (b) the mother, with maturity-onset diabetes of the young type 5. (a) The uncinate process and the posteroinferior part of the pancreas head are shown by arrows in the computed tomography. (b) Overall atrophy of the pancreas is shown by arrows. Although both patients have the same nonsense mutation (p.Q477X), (a) body and tail loss are observed in the daughter’s pancreas and (b) overall atrophy in the mother’s. A renal cyst was found in the left kidney of the mother.
the mutations from their fathers developed overt diabetes. In the case of patients with mutations inherited from their mothers, overt diabetes mellitus was found often, and this seemed to be affected by conditions of the intrauterine environment, such as hyperglycemia, indicating the presence of a parent-of-origin effect in the inheritance pattern of MODY 6\textsuperscript{29–32}. In a previous study involving the present author\textsuperscript{33}, four Japanese probands inheriting the mutations from their mothers developed overt diabetes at an earlier age (Table 2).

Furthermore, it is noteworthy that the four probands had episodes of diabetic ketosis. MODY seldom presents with ketosis, suggesting that Japanese patients with MODY 6 are prone to becoming ketotic as a result of intrinsically lower insulin secretion in concert with contributions of other NEUROD1-related phenotypes or unknown modifying factors. Again, there is a considerable difference in disease severity within the phenotype, even in cases with the same mutation in the same family. Furthermore, abnormality of the central nervous system can occur in Japanese patients even with heterozygous mutation (Table 2).

These results suggest that MODY 6, as is the case with MODY 5, is a low-penetrant MODY, and that the development of diabetes mellitus is affected by other genetic modifying factors, environmental factors, and/or the effects of interactions with genetic and environmental factors. Accordingly, it is considered to be appropriate to designate the disease NEUROD1-deficient diabetes rather than NEUROD1-MODY (MODY 6).

**MODY 3**

The HNF1A gene, a causal gene for MODY 3, was identified in 1996\textsuperscript{3}; it encodes transcription factors with homeodomains, and is widely expressed in the liver, kidneys, pancreas and gastrointestinal tract. MODY 3 is the most common MODY, and comprises 52% of all MODY in the UK\textsuperscript{34}. It also accounts for approximately 40% of the known MODY in Japanese patients. The penetration rate of the HNF1A gene mutation in Europe and America is reported to be 63% by 25 years-of-age\textsuperscript{35}; the average age of diagnosis in Japanese patients is concentrated around 10 years-of-age, and the diagnosis is often triggered by a school urinary test\textsuperscript{11}. One of the reasons for this is that the HNF1A gene controls the expression of the sodium–glucose cotransporter 2 gene\textsuperscript{36}, and a low glucose reabsorption threshold in the tubule is associated with early diagnosis of MODY 3 together with lower insulin secretory capacity in Japanese patients.

In MODY 3, there are also cases in which the insulin secretion failure is severe, due to unknown modifying factors, and the case is mistaken for type 1 diabetes, even in Caucasians\textsuperscript{37,38}. We reported a case of the co-occurrence of mutations of HNF1A and the small heterodimer partner\textsuperscript{39}, which is known as a mild obesity\textsuperscript{40} and a type 2 diabetes gene\textsuperscript{41}, but in that case, there was a period in which the insulin secretion failure was not observed with obesity and it was considered that the interaction of the HNF1A gene with the small heterodimer partner gene modified the clinical phenotype of MODY 3\textsuperscript{39}.

The G319S HNF1A variant is associated with an increased risk of type 2 diabetes in the Canadian Oji-Cree population\textsuperscript{42}. The G319S variant results in the production of two abnormal transcripts and a reduction in the relative balance of normal splicing products. A combination of abnormal splicing and reduced activity of the G319S protein might explain the diabetes susceptibility\textsuperscript{42}. By an association study\textsuperscript{43} of Norwegians

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**Table 2 | Clinical features of the patients and affected parents with maturity-onset diabetes of the young type 6 in Japanese patients**

| Mutation (heterozygote) | H206PfsTer38 | P245RfsTer17 | L157R | H206TfsTer56 |
|-------------------------|-------------|-------------|-------|-------------|
| Age at diagnosis        | 14 years    | 11 years    | 10 years | 12 years    |
| Bodweight at diagnosis  | −1.1 SD     | −1.9 SD     | −0.3 SD | −0.9 SD     |
| Neurological abnormality| None        | Developmental delay, mild cerebellar dysfunction, dysplasia of hippocampus | None | None |
| HOMA-β                  | 60.8%       | NA          | 55.2% | NA          |
| Insulinogenic index     | 0.12        | NA          | 0.091 | NA          |
| Treatment (at initiation)| OHA (14 years) | Ins (11 years) | Ins+OHA (11 years) | Ins+OHA (12 years) |
| Diabetic ketosis or ketoacidosis | DKA (15 years) | DK (11 years) | DKA (20 years) | DK (12 years) |
| Microangiopathy         | None        | None        | Microalbuminuria | NA |
| Mother age at diagnosis | 31 years (GDM) | 34 years (GDM) | NA | 27 years (GDM) |
| Treatment (at present)  | OHA | NA | Ins (at initiation) | Ins |
| Complications and neurological abnormality | None | Nephropathy hemodialysis (52 years) | Proliferative retinopathy | Nephropathy hemodialysis (46 years) |
|                         |             | Intellectual disability |          | Foot ulcers intellectual disability |

DK, diabetic ketosis; DKA, diabetic ketoacidosis; GDM, gestational diabetes mellitus; HOMA-β, homeostatic model assessment of β-cells; Ins, insulin; NA, not available; OHA, oral hypoglycemic agent; SD, standard deviation.
with 11 rare polymorphisms comprising MODY 3 mutations with <60% activity and <60% of the nuclear translocation, it became evident that the 11 rare polymorphisms are associated with the onset of type 2 diabetes mellitus by an odds ratio of approximately 5. Accordingly, each of the rare polymorphisms (frequency 0.22%) is a susceptibility variant of mild effect. Therefore, a mutation of HNF1A develops a MODY 3 form or common type 2 diabetes mellitus due to the extent of the damage by the mutation.

Recently, a wide variety of clinical symptoms, such as the presence of pancreatic autoantibodies and the occurrence of diabetic ketoacidosis, has been reported to be observed in a large family with the mutation of exon 4 of HNF1A, possibly due to unknown modifying factors. Furthermore, in the case of patients with mutations inherited from mothers with overt diabetes, MODY 3 often develops earlier than in those inheriting from fathers or from mothers without diabetes, and it seems to be affected by conditions of intrauterine environment, such as hyperglycemia, suggesting the presence of an interaction between genetic and intrauterine environmental factors in determining the onset age of high penetrant MODY 3 (Figure 3).

**MODY 2**

The phenotype of MODY 2 is observed immediately after birth, but the age of diagnosis is widely distributed from age 0 to the 40s. Some cases are not diagnosed because of the mildness of the disease. In fact, MODY 2 is estimated to occur in a number of patients just less than that in MODY 3; one in 1,000 Caucasians is estimated to have MODY 2, 99% of whom remain undiagnosed. Although MODY 2 has long been considered to be very rare in Japan, it has recently been found that the frequency of MODY 2 is similar to or higher than that of MODY 3.

In our analysis of 48 families diagnosed with MODY 2, the age of diagnosis of MODY 3 (52 families diagnosed with MODY 3) had peaks around 10 years-of-age, whereas the age of onset of MODY 2 was widely distributed from 0 to the 40s (Figure 1). MODY 2 and 3 are similar with regard to obesity. The birthweight of patients with MODY 2 is approximately 400 g lower than that of MODY 3, a significant difference. The birthweights of these patients with MODY 2 and MODY 3 were compared as to whether the genetic mutations were paternally or maternally inherited. In MODY 2, the birthweight of patients paternally inheriting mutations was approximately 600 g lower than that of those with mutations of maternal origin, which is a significant difference (Figure 4). The birthweight of patients with MODY 3 with paternal mutations also tended

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**Figure 3** The age of onset or diagnosis of maturity-onset diabetes of the young type 3 is dependent on the pattern of inheritance of the mutation (paternal or maternal) and also maternal affected status (diabetic or non-diabetic) when the mutation is of maternal inheritance. DM+, diabetes mellitus-positive; DM−, diabetes mellitus-negative.

**Figure 4** Birthweight of maturity-onset diabetes of the young type 2 (MODY2) and MODY3 is dependent on the pattern of inheritance of the mutation (paternal or maternal). *P < 0.05. NS, not significant.
to be lower than that of those having maternal origin, but the difference was not significant. We examined the birthweight of patients with MODY 2 as to whether the mothers with MODY 2 had insulin treatment during pregnancy. The average birthweight of the group of patients whose mothers had not received insulin treatment during pregnancy was approximately 400 g higher compared with that of those treated with insulin, but there was no significant difference, possibly because of the small number of cases (Horikawa Y, unpublished data, 2017).

For pregnancies of patients with MODY 2, insulin therapy is considered to be necessary, because the fetus is at risk for large for gestational age if it does not have the mutation. In Caucasians, if the fetus has the mutation, it is considered not to be necessary to treat the mother\textsuperscript{45,48}.

The long-term prognosis of Japanese MODY 2 remains unclear because of the lack of an accumulation of cases. Further investigation as to whether or not Japanese MODY 2 patients require treatment, as is the case with Caucasian MODY 2

### Table 3 | Clinical features of Japanese maturity-onset diabetes of the young types 1–3, 5 and 6

|                          | MODY 1 | MODY 2 | MODY 3 | MODY 5 | MODY 6 | Total |
|--------------------------|--------|--------|--------|--------|--------|-------|
| Family number            | 10     | 48     | 52     | 18     | 4      | 132   |
| Sex (male/female)        | 5/5    | 25/23  | 17/35  | 11/7   | 0/4    | 58/74 |
| Age at diagnosis (years) | 15.3 ± 7.1 | 10.3 ± 6.8 | 13.2 ± 4.5 | 17.9 ± 8.0 | 12.0 ± 1.4 | 13.0 ± 6.4 |
| Frequency of obesity at diagnosis\textsuperscript{3} | 20% (1/5) | 25.9% (7/27) | 14.8% (4/27) | 15.3% (2/13) | 0% (0/4) | 18.4% (14/76) |
| Therapy                  |        |        |        |        |        |       |
| Diet                     | 2      | 30     | 7      | 1      | 0      |       |
| OHA                      | 2      | 8      | 20     | 4      | 0      |       |
| Ins                      | 5      | 8      | 19     | 13     | 4      |       |
| NA                       | 1      | 2      | 6      | 0      | 0      |       |
| FH ≥3 generations        | 44.4% (4/9) | 55.6% (25/45) | 44.1% (19/43) | 0% (0/15) | 100% (4/4) | 44% (51/116) |
| Age at diagnosis ≤25 years and FH ≥3 generations | 44.4% (4/9) | 53.3% (24/45) | 44.1% (19/43) | 0% (0/15) | 100% (4/4) | 44% (51/116) |

\textsuperscript{3}Age at diagnosis: <18 years, body mass index percentile ≥95% (http://jspe.umin.jp/taikakushisuv3xlsx); if age at diagnosis is ≥18 years, participants with body mass index ≥25 are defined as obese in Japan. FH, family history; Ins, insulin; NA, not available; OHA, oral hypoglycemic agent.

### Table 4 | Summary of frequencies, characteristics and treatment of maturity-onset diabetes of the young types 1–3, 5 and 6

| MODY    | Gene  | Frequency in Japanese, % | Characteristics                                                                 | Treatment                           |
|---------|-------|--------------------------|--------------------------------------------------------------------------------|-------------------------------------|
| MODY 1  | HNF4A | 7.6                      | Hyperinsulinemic hypoglycemia in the neonatal period, Macrosmia (rare in Japanese) | Small dose of SU drugs              |
| MODY 2  | GCK   | 36.3                     | Onset immediately after birth, Mild increased level of fasting glucose           | Not necessary?                      |
| MODY 3  | HNF1A | 39.4                     | Most common in Japanese MODY, Often diagnosed by school urinary test, First hit of hepatocellular tumor, Complications common in patients with type 1 diabetes mellitus and type 2 diabetes mellitus | SU drugs                            |
| MODY 5  | HNF1B | 13.6                     | Monoallelic defects in all or some exons are frequent, Often diagnosed in adulthood, Insulin secretion is decreased from the early stage, Variety of phenotype are seen (kidney, pancreas, uterus, gout) | Insulin from the early stage        |
| MODY 6  | NEUROD1 | 3.0                     | Low penetrance, Risk of diabetic ketosis in Japanese, Abnormality in CNS         | Diet ~ insulin                      |

CNS, central nervous system; MODY, maturity-onset diabetes of the young; SU, sulfonylurea.
patients\textsuperscript{59}, or how many Japanese patients diagnosed with gestational diabetes have MODY 2 is required. At least one clinical phenotype of MODY 2, birthweight, has been found to be determined by the interaction between genetic and intrauterine environmental factors\textsuperscript{50}.

**MODY 1**

MODY 1 (HNF4A) is rare among MODYs, and is reported to account for 10% of cases diagnosed with MODY in the UK\textsuperscript{24}. In Japan, MODY 1 accounts for approximately 7% of the known MODY diagnosed. Because the HNF4A gene forms a feed-forward loop that activates the transcription of the HNF1A gene in the pancreas\textsuperscript{51}, the phenotype of MODY 1 is similar to that of MODY 3. As for the treatment, the sensitivity to sulfonylureas is good, as it is in MODY 3. The clinical features that differ from MODY 3 include hyperinsulinemic hypoglycemia in the neonatal period and macrosomia, a large for gestational age baby\textsuperscript{52}. However, in the study involving the present author study, a giant baby weighing >4,000 g at birth was not recognized in a Japanese woman partly because of the intrinsically lower capacity of insulin secretion (Horikawa Y, unpublished data, 2017). Furthermore, a common polymorphism in the P2 promoter and the mutation of T130I are found to be associated with late-onset type 2 diabetes mellitus in Japanese\textsuperscript{53,54}.

Clinical features of Japanese MODY 1–3, 5 and 6 identified so far by studies involving the present author are summarized in Table 3, and frequencies, characteristics and treatment of MODY 1–3, 5 and 6 are summarized in Table 4.

**CONCLUSIONS**

Of the type 2 diabetes mellitus susceptibility single-nucleotide polymorphisms identified before the use of genome-wide association studies\textsuperscript{55–57}, the pathogenic mechanisms are well understood partly based on the results of studies in monogenic diabetes, such as MODYs. It is therefore strategically effective to apply information pathophysiologically obtained from rare diabetes mellitus, such as MODY, to that from common type 2 diabetes mellitus. However, it has been shown that the complexities of genetic background among races can significantly affect even the occurrence of a single gene defect MODY, especially low penetrant MODYs, such as MODY 5 and 6. Environmental factors, especially intrauterine environment, also can significantly affect the phenotype of MODY, as manifested by age of onset and birthweight. Japanese patients with MODY are relatively hypoinsulinemic because of their intrinsically lower capacity for insulin secretion compared with that of Caucasians, contributing to the easier development of diabetes in low penetrant MODY cases among Japanese people. Therefore, it could be advantageous to closely examine Japanese MODY candidates selected by criteria not including family history of diabetes, so as not to miss sporadic or low penetrant cases for genetic mutations\textsuperscript{11,33}. Just 44% of cases of MODY 1–6 meet the definition of the classical criteria for MODY, even in Japanese patients. As the definition of classical MODY is not applicable to more than half of MODY 1–6 Japanese patients, novel criteria reflecting the genetic background of specific ethnicities should be defined. Furthermore, in the future, we hope to identify novel MODY genes, likely low penetrant genes, as a group of constitutively enriched “islet function network” genes\textsuperscript{28,59}. Functional analyses of identified mutations will then be carried out to elucidate the mechanisms of insulin secretion insufficiency.

**ACKNOWLEDGMENTS**

The author thanks M Enya and J Takeda for critical reading of this manuscript. This work was supported by a Health and Labor Science Research Grant for Research on Rare and Intractable Diseases from the Japanese Ministry of Health, Labor and Welfare; a Grant-in-Aid for Scientific Research from the Japanese Ministry of Science, Education, Sports, Culture and Technology; and a Strategic International Research Cooperative Program Grant from Japan Science and Technology Agency.

**DISCLOSURE**

The author declares no conflict of interest.

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