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PEDIATRIC TYPE 2 AND MONOGENIC DIABETES (O PINHAS-HAMIEL, SECTION EDITOR)

Genetic Dissection and Clinical Features of MODY6 (NEUROD1-MODY)

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Abstract

Purpose of Review MODY6 due to mutations in the gene NEUROD1 is very rare, and details on its clinical manifestation and pathogenesis are scarce. In this review, we have summarized all reported cases of MODY6 diagnosed by genetic testing, and examined their clinical features in detail.

Recent Findings MODY6 is a low penetrant MODY, suggesting that development of the disease is affected by genetic modifying factors, environmental factors, and/or the effects of interactions of genetic and environmental factors, as is the case with MODY5. Furthermore, while patients with MODY6 can usually achieve good glycemic control without insulin, when undiagnosed they are prone to become ketotic with chronic hyperglycemia, and microangiopathy can progress. MODY6 may also cause neurological abnormalities such as intellectual disability.

Summary MODY6 should be diagnosed early and definitively by genetic testing, so that the correct treatment can be started as soon as possible to prevent chronic hyperglycemia.

Keywords MODY · NEUROD1 · β cell dysfunction · Neurological abnormalities · PNDM · Intrauterine environment

Introduction

Maturity onset diabetes of the young (MODY; online Mendelian inheritance in man [OMIM] #606391) is an autosomal dominant form of diabetes with partly preserved pancreatic β cell function, and typically occurs before 25 years of age [1]. MODY is genetically heterogeneous; there are 14 responsible genes (MODY1–14) in the OMIM database. Of them, MODY1, 2, 3, and 5 may be the most common. MODY6 (OMIM #606394) is caused by a heterozygous mutation in the NEUROD1 gene on chromosome 2q32. In 1999, Malecki et al. for the first time described two mutations in NEUROD1 that were associated with the development of type 2 diabetes in the heterozygous state. One is a missense mutation (p.Arg111Leu) that lies in the DNA-binding domain and abolishes the E-box-binding activity of NEUROD1. The other is a frameshift mutation (c.His206Profs*38) that gives rise to a truncated polypeptide lacking the carboxy-terminal transactivation domain, a region that associates with the co-activators CREB binding protein (CBP) and p300. Both mutations were found to be less active on insulin gene expression (Fig. 1) [2].

So far, many case reports and studies of MODY have been reported; the characteristics of each MODY subtype have therefore become clear gradually. However, MODY6 is very rare, and its clinical and pathophysiological details remain to be elucidated. In this review, we have summarized all reported cases of MODY6 diagnosed by genetic testing for mutations in NEUROD1, and examined their clinical features in detail to facilitate diagnoses at the earliest possible stage and determine the most suitable treatment for the disease.

Molecular Mechanisms

NEUROD1 (otherwise known as BETA2) is a type II basic helix loop helix (bHLH) transcription factor with expression confined to pancreatic islet endocrine cells, the intestine, and a subset of neurons in the central and peripheral nervous system. NEUROD1 dimerizes with E47, a class I bHLH transcription

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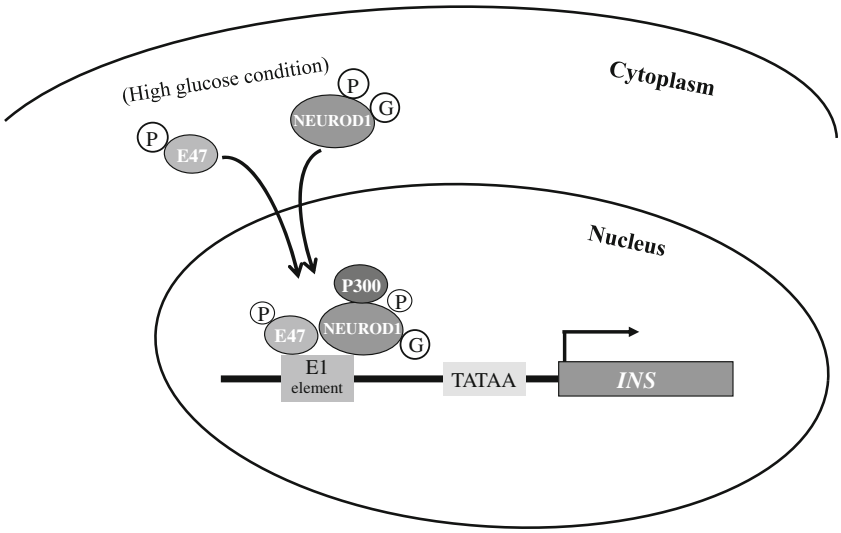

Fig. 1 In response to high glucose (> 10 mM), phosphorylated and O-GlcNAc-modified NEUROD1 heterodimerizes with E47 and activates insulin gene expression by recruiting co-activators such as p300. E47 heterodimerizes with NEUROD1 and binds to the E1 element within the insulin promoter

G, GlcNAc; P, phospho group

factor with ubiquitous expression, to form a heterodimer. It binds to the bHLH consensus E-box-binding site within the insulin promoter and activates transcription [3]. In addition to the insulin gene, NEUROD1 is known to bind and activate the promoter of the sulfonylurea receptor 1 (SUR1) [4], glucokinase (GCK) [5], the glucose-6-phosphatase catalytic subunit-related protein [6], and PAX6 [7]. These all are important molecules in maintaining normal glucose homeostasis. NEUROD1 also affects β cell dysfunction during chronic hyperglycemia, namely glucotoxicity. At least two mechanisms are thought to be involved. One engages small heterodimer partner (SHP; NR0B2), an atypical orphan nuclear receptor that represses other nuclear receptors. We reported that SHP mutations in Japanese increase susceptibility to type 2 diabetes in adults [8]. SHP plays an important role in the development of β cell dysfunction induced by glucotoxicity. It has been reported that high glucose concentrations induce SHP gene expression. Activated SHP then downregulates insulin gene expression and secretion by inhibiting p300-mediated pancreatic duodenal homeobox factor 1 (PDX1) and Neurod1-dependent transcriptional activity from the insulin promoter [9]. The key molecule in the second potential mechanism is the cyclic AMP-responsive element-binding protein (CREB). It has been reported that in chronic hyperglycemia, CREB is constantly activated due to the decreased PP2A level. Upon glucose stimulation or hormonal cues, CREB is further activated for an extended period of time, leading to prolonged inducible cAMP early repressor (ICER) induction. Consequently, excessively produced ICER proteins repress expression of NEUROD1 and NEUROD1's target genes, including insulin, SUR1, and components of the exocytotic machinery [10]. Chronic hyperglycemia is progressively aggravated through this vicious, negative cycle of insulin depletion, and ultimately progresses to β cell failure.

Mice lacking Neurod1 die within 5 days after birth due to severe diabetes mellitus marked by high ketone levels in the urine as a result of a loss of insulin producing pancreatic β cells [11]. Miyata et al. were able to obtain transgenically rescued Neurod1 knock-out mice using myc-tagged Neurod1 under control of the insulin promoter [12]. Schwab et al. generated double knock-out mice by crossing Neurod1-null mice to Nex-null genetic background mice [13]. These mice displayed severe neurological disorders including ataxia, and fell down frequently due to the pronounced reduction in the size of the cerebellum and complete loss of the dentate gyrus of the hippocampus. These results imply that Neurod1 plays a principal role in the development and maintenance of pancreatic islets and neuronal elements.

Clinical Manifestations in the Homozygous Mutations in NEUROD1: Permanent Neonatal Diabetes Mellitus and Neurological Abnormalities

Rubio-Cabezas et al. reported two cases with homozygous frameshift NEUROD1 mutations (c.364dupG; p.Asp122Glyfs*12 and c.427_428del; p.Leu143Alafs*55) identified by sequencing patients with permanent neonatal diabetes mellitus (PNDM) of unknown genetic etiology [14]. These patients had been diagnosed with permanent diabetes at the age of 4 and 8 weeks, and both of them exhibited normal morphological pancreas and normal exocrine function. In addition to diabetes, they had severe neurological abnormalities including developmental delay, cerebellar hypoplasia, sensori-neural deafness, and visual impairment. Recently, Demirbilek et al. reported a novel homozygous missense

NEUROD1 mutation (c.449T>A; p.I150N) in a girl with PNDM and neurological abnormalities [15•]. Wang et al. identified a NEUROD1 homozygous missense mutation (c.724G>A; p.V242I) in a proband and his younger sister in a consanguineous family who had autosomal recessive non-syndromic retinitis pigmentosa [16]. These siblings had no neurological disorders but might have had an abnormality in glucose metabolism, as their glycated hemoglobin (HbA1c) levels were slightly increased (6.5 and 6.2%, respectively). The reason why these siblings with homozygous mutation had no neurological abnormality is unknown. It is possible that their missense mutation caused less damage to NEUROD1 function than the other three mutations mentioned above.

Clinical Manifestations in the Heterozygous State in NEUROD1: MODY6

The remaining 16 families only with heterozygous mutations in NEUROD1 have been reported so far [17–22, 23•]. Most of the reported mutations are present in the bHLH domain or the transactivation domain. The bHLH domain is responsible for DNA binding, and mutations in this domain can cause disruption of DNA recognition of downstream target genes. On the other hand, the transactivation domain interacts with the cellular coactivator p300, and mutations in this domain can be less active in stimulating target gene activation.

Several notable points were observed in the clinical features of MODY6. Among the 20 families with the mutations in NEUROD1 reported worldwide to date (Table 1), there are 86 mutation carriers, of which 68 (79.1%) are glucose intolerant and 18 (20.9%) are glucose tolerant. In the group with glucose tolerance, there are several children who might develop diabetes as they age. However, several subjects remain glucose tolerant. Accordingly, MODY6 shows incomplete penetrance of diabetes, especially in Europeans. Of the Japanese patients we reported previously, all of them developed overt diabetes at less than 15 years of age, reflecting the underlying genetic difference between races [23•].

The overall phenotype of MODY6 is a broad clinical spectrum that ranges from patients with typical MODY features to those who appear to have common type 2 diabetes mellitus. Age at onset of diabetes is distributed widely from teenage years to the 60s, and there are both lean and obese patients. We have screened for MODY3 (*HNF1A*) in Japanese, and found that Japanese patients with MODY3 tend to be non-obese and show impaired insulin secretion, together with an age of onset of less than 15 years [24]. We also reported that Japanese patients with MODY5 (*HNF1B*) are relatively lean and hypoinsulinemic, most likely due to the intrinsically lower capacity of insulin secretion compared to Europeans, and that this difference might underlie the earlier onset of overt disease. We thus showed that complexities of genetic background among races can significantly affect even the pathogenesis of monogenic forms of diabetes [25, 26•].

MODY6 has a tendency to present with diabetic ketoacidosis or ketosis only, with a defect of early phase insulin secretion without insulin dependence in Japanese [23•]. The reason remains to be elucidated, but it may be possibly due to the vicious cycle of insulin depletion induced by SHP and CREB under chronic hyperglycemia mentioned above. Since one allele of NEUROD1 does not function normally in MODY6, it is supposed that even under chronic hyperglycemia, the transcription activity of NEUROD1 would decrease more severely than that of patients with diabetes without mutations in NEUROD1.

Another point is that there is a male-to-female ratio difference in patients with NEUROD1 mutations. The number of female patients is more than twice that of male patients (males, 22; females, 46). In contrast, the number is identical (males, 9; females, 9) in nondiabetic family members with mutations. Furthermore, of 49 patients with diabetes whose parent of origin was known, 42 of them inherited heterozygous mutations from the mother (85.7%). One reason for this may be that the intrauterine environment of an affected mother promotes the onset of diabetes after the children grow up. Another reason could be that the intrauterine environment of an affected mother protects the affected fetus (as in GCK-MODY), whereas an affected fetus in an unaffected mother might have early lethality and subsequent miscarriage. Whether or not this female dominance in sex difference and parent of origin in MODY6 families can be determined by the accumulation of new diagnosed cases.

As for diabetic microangiopathy, its severity ranges from mild to serious (proliferative retinopathy and renal failure). Gonsorcíková et al. reported a patient with MODY6 (p.His241Gln) who died of renal failure at the age of 44 years [19]. In our formerly reported MODY6 families, two affected mothers also had diabetic nephropathy leading to chronic renal failure, and died in their 50s. Both of them had intellectual disability, which might hinder glycemic control indirectly due to impaired communication abilities, difficulties with diabetes education, and other obstacles [23•]. It is suspected that a background related to the neurological problems resulted in the worsening of diabetic microangiopathy.

For treatment, insulin therapy is most commonly used in patients with MODY6. However the number of patients treated with oral glucose-lowering agents or diet only is similar to that of patients treated with insulin. Furthermore, members of the same family who carry the same mutation display considerable differences in disease severity. In one of the four MODY6 families we reported recently, a proband girl with a frameshift mutation (c.616_617insC; p.His206ProfsTer38) was diagnosed with diabetic ketoacidosis at 15 years of age, and began insulin therapy at 53 units/day. After improvement

Table 1 Summary of genotype and clinical features of NEUROD1-MODY

Family	Ethnic group	Homo/ Hetero	DM/ NGT	Gender (DM/ NGT)	Parent of origin (DM)	Parent of origin (NGT)	Age at onset	AAO (Mo)	AAO (Fa)	BMI	FPG (mmol/L)
1	Japanese	Hetero	3/0	Ml F2/.	Mol Fal Unl	.	40.3 (14–76)	14	31	18.6 (17.4–19.7)	7.2 (6–8.7)
2	Japanese	Hetero	2/0	M0 F2/.	Mol Fa0 Un0	.	22.5 (11–34)	11	.	16.1	6.7 (6.2–7.2)
3	Japanese	Hetero	1/0	M0 F1/.	Mol Fa0 Un0	.	10	10	.	23.9	6.9
4	Japanese	Hetero	2/0	M0F2/.	Mol Fa0 Unl	.	19.5 (12–27)	12	.	16.3 (16.2–16.4)	5.6
5	Thai	Hetero	3/1	M0 F3/MO Fl	Mo2 Fa0 Unl	Mo0 Fa0 Unl	14	14	.	22.2	17.8
6	Czech	Hetero	4/2	M1F3/M1F1	Mo4 Fa0 Un0	Mo0 Fa2 Un0 (4–30 years, ave. l7 years)	21(19–25)	21(19–25)	.	30.9 (16.5–36.9)	6.1
7	Czech	Hetero	3/2	M2 Fl/M1 Fl	Mo2 Fal Un0	Mo0 Fa2 Un0 (11–13y, avel2y)	33.3 (19–51)	40.5 (30–51)	19	31.4 (20.5–42.2)	5
8	Asian Indian	Hetero	1/0	M1 F0/.	Unnown	.	28	NA	NA	22.8	NA
9	Asian Indian	Hetero	1/0	M0 Fl/ .	Unnown	.	24	NA	NA	39.7	NA
10	Asian Indian	Hetero	1/0	M1 F0/.	Unnown	.	30	NA	NA	19.3	NA
11	Asian Indian	Hetero	1/0	M1 F0/.	Mo0 Fal Un0	.	30	.	30	27.5	NA
12	European	Hetero	6/0	M3 F3/.	Mo5 Fal Un0	.	40.3 (33–59)	42.4	30	29.9 (28.5–32.5)	8.5 (5.7–14.7)
13	European	Hetero	7/2	M3 F4/M1 Fl	Mo4 Fa0 Un3	Mol Fal Un0 (38-51y, ave. 44.5 years)	31.4 (17–56)	23 (17–38)	.	25.2 (21.4–30.5)	7.8 (4.1–10.5)
14	Icelander	Hetero	14/0	M2 F12/.	Mol0 Fa2 Un2	.	33 (12–68)	28.4 (12–64)	37	24.1 (17.5–30.3)	8.6 (4.0–19.3)
15	Polish	Hetero	7/4	M1 F6/M1 F3	Mo7 Fa0 Un0	Mo3 Fal Un0 (3–46 years, ave. 20)	35.6 (23–50)	35.6 (23–50)	.	25.1 (20.4–31.1)	5.7 (4.3–8.5)
16	Chinese	Hetero	4/1	M3 Fl /M0 Fl	Mo3 Fal Un0	Mo0 Fal Un0 (43 years)	50.3 (27–63)	58 (50–63)	27	21.1 (19.2–23.7)	6.9 (5.4–8.5)
17	Pakistani	Homo	1/0	M0 Fl/.	From parents	.	8 weeks			1490 g	NA
		Hetero	1/1	M0 Fl/M1 F0	Mo0 Fa0 Unl	Mo0 Fal Un0 (33 years)	33	NA	NA	NA	NA
18	Hungarian	Homo	1/0	M0 Fl/.	From parents	.	4 weeks	.	.	2230 g	NA
		Hetero	1/3	M1 F0/M2 Fl	Mo0 Fa0 Unl	Mo0 Fa2 Unl(12–37 years, ave. 24 years)	68	NA	NA	NA	NA
19	Chinese	Homo	2?/0	Ml Fl/.	From parents	.	NA	.	.	19.3 (18.4–20.2)	5.3 (5.1–5.4)
20	Turkish	Homo	1/0	M0 Fl/.	From parents	.	9 weeks	.	.	21	NA
		Hetero	1/2	M1 F0/M2 F0	Mol Fa0 Un0	Mo0 Fa2 Un0 (18–20 years, ave. l9 years)	52	52	.	25.7	4.7 (4.5–5)
Sum				M22 F46/M9 F9	Mo42 Fa7 Un10 pare4	Mo4 Fal2 Un2					

Table 1 (continued)

Family	Fasting CPR (pmol/L)	HbA lc (%)	Ketosis	Treatment	Complication	Neurological abnormality	Mutation (protein)	Mutation (DNA)	Mutation (GRCh37/hg19)
1	346 (235–457)	6.0 (5.8–6.1)	Yes	D0 O2 I1	None	.	p.His206fs*38	NM_002500.4:c.616_617insC	chr2:182542971_182542972insG
2	369 (298–440)	15	Yes	D0 O0 I2	R1Nepl	Developmental decay, dysplasia of hoppocampus, multiple deformity	p.Pro245Argfs*17	NM_002500.4:c.734delC	chr2:182542854_182542854delG
3	NA	9.1	Yes	Ins	R0 Nepl	.	p.Lue157Arg	NM_002500.4:c.470T>G	chr2:182543118A>C
4	NA	10.9	Yes	D0 O0 I2	NA	.	p.His206Thrfs*56	NM_002500.4:c.616delC	chr2:182542972_182542972delG
5	NA	7.6	No	NA	NA	.	p.Ala322Asn	NM_002500.4:c.964_965delinsAA	chr2:182542623_182542624delinsTT
6	1540	NA	NA	D0 O0 I4	R4 Nep4 Neu4 44 years death (renal failure)	.	p.His241Gln (family-A)	NM_002500.4:c.723C>G	chr2:182542865G>C
7	1262	NA	No	D1 O1 I1	NA	.	p.His241Gln (family-B)	NM_002500.4:c.723C>G	chr2:182542865G>C
8	NA	NA	No	OHA	NA	.	p.His241Gln	NM_002500.4:c.723C>G	chr2:182542865G>C
9	NA	NA	No	OHA	NA	.	p.His241Gln	NM_002500.4:c.723C>G	chr2:182542865G>C
10	NA	NA	No	OHA	NA	.	p.Glu59Gln	NM_002500.4:c.175G>C	chr2:182543413C>G
11	NA	NA	No	OHA	NA	.	c.-162G>A	NM_002500.4:c.-162G>A	chr2:182545307C>T
12	347.7 (298–397.3)	NA	NA	D2 O1 I3	NA	.	p.Arg111Leu	NM_002500.4:c.332G>T	chr2:182543256C>A
13	182.1 (165.5–198.7)	NA	NA	Dl O1 I5	NA	.	p.His206Profs*38	NM_002500.4:c.616_617insC	chr2:182542971_182542972insG
14	NA	7.6 (5.3–11.4)	NA	D4 O7 I3	R3 Nep2 Neu5	.	p.Glu110Lys	NM_002500.4:c.328G>A	chr2:182543260C>T
15	453.6 (198.7–827.7)	6.1 (3.8–7.6)	NA	D2 O1 I4	R2 Nepl Neu0	.	p.Arg103Pro	NM_002500.4:c.308G>C	chr2:182543280C>G
16	721.8 (198.7–993.3)	NA	NA	Dl O2 I1	NA		p.Ser159Pro	NM_002500.4:c.475T>C	chr2:182543113A>G
17	NA	NA	Yes	Ins		Developmental delay, deafness, myopia, retinal dystrophy, cerebellar hypoplasia	p.Asp122Glyfs*12	NM_002500.4:c.364dupG	chr2:182543223_182543224insC
	NA	NA	NA	OHA	NA	.			
18	0	NA	No	Ins	.	Developmental delay, deafness, myopia, pigmental epithelial atrophy, enlarged fovea, cerebellar hypoplasia	p.Leu143Alafs*55	NM_002500.4:c.427_428del	chr2:182543160_182543161delAG
	NA	6	NA	Diet	NA	.			
19	NA	6.4 (6.2–6.5)	No	NA	NA	Retinitis pigmentosa	p.Val242Ile	NM_002500.4:c.724G>A	chr2:182542864C>T
20	NA	8.9	No	Ins	.	Mental retardation, ataxic gait, seizure,retinitis pigmentosa, deafness, cerebellar hypoplasia	p.Ile150Asn	NM_002500.4:c.449T>A	chr2:182543139A>T
Sum	NA	6.3 (5.2–8.2)	NA	OHA D12 O21 I30	NA	.			

Table 1 (continued)

Family	SIFT	SIFT score	Provean	Provean score	Mutation taster	Mutat ion taster score	PolyPhen-2	PolyPhen-2 score (HumDiv)	In vivo funct ional analysis	ExAC	1000G	Ref.
1	.	.	.	.	Disease causing	.	.	.	NA	0.000657/79	Not found	[23•]
2	.	.	.	.	Disease causing	.	.	.	NA	Not found	Not found	[23•]
3	Damaging	0	Deleterious	− 5.68	Disease causing	102	Probably damaging	1	NA	Not found	Not found	[23•]
4	.	.	.	.	Disease causing	.	.	.	NA	Not found	Not found	[23•]
5	Damaging	0.022	Neutral	− 0.91	Disease causing	111	Benign	0.023	NA	Not found	Not found	[20]
6	Tolerated	0.117	Deleterious	− 3.09	Disease causing	24	Possibly damaging	0.787	NA	0.0010/120	0.0018/9	[19]
7	Tolerated	0.117	Deleterious	− 3.09	Disease causing	24	Possibly damaging	0.787	NA	0.0010/120	0.0018/9	[19]
8	Tolerated	0.117	Deleterious	− 3.09	Disease causing	24	Possibly damaging	0.787	NA	0.0010/120	0.0018/9	[21]
9	Tolerated	0.117	Deleterious	− 3.09	Disease causing	24	Possibly damaging	0.787	NA	0.0010/120	0.0018/9	[21]
10	Tolerated	0.078	Neutral	− 0.88	Disease causing	29	Benign	0.056	NA	0.00005/5	0.0004/2	[21]
11	.	.	.	.	Disease causing	.	.	.	NA	Not found	Not found	[21]
12	Damaging	0	Deleterious	− 6.89	Disease causing	102	Probably damaging	1	Yes	Not found	Not found	[2]
13	.	.	.	.	Disease causing	.	.	.	Yes	0.000657/79	Not found	[2]
14	Damaging	0	Deleterious	− 3.94	Disease causing	56	Probably damaging	0.999	NA	Not found	Not found	[17]
15	Damaging	0	Deleterious	− 6.79	Disease causing	103	Probably damaging	1	NA	Not found	Not found	[22]
16	Damaging	0.013	Deleterious	− 3.47	Disease causing	74	probably damaging	0.988	NA	Not found	Not found	[18]
17	.	.	.	.	Disease causing		.	.	NA	Not found	Not found	[14]
18	.	.	.	.	Disease causing		.	.	NA	Not found	Not found	[14]
19	Tolerated	0.181	Neutral	− 0.1	Disease causing	29	Benign	0.322	NA	Not found	Not found	[16]
20	Damaging	0	Deleterious	− 6.62	Disease causing	194	Probably damaging	1	NA	Not found	Not found	[15•]
Sum												

Gender: M, male; F, female; DM, diabetes mellitus (including IGT); NGT, normal glucose tolerance; parent of origin: Mo, from the mother; Fa, from the father; Un, unknown; pare, from the parents; AAO (Mo), age at diabetes onset, patients inherited heterozygous mutations from the mother; AAO (Fa), age at diabetes onset, patients inherited heterozygous mutations from the father; R, retinopathy; Nep, nephropathy; Neu, neuropathy; D, diet; O or OHA, oral hypoglycemic agent; I or Ins, insulin; NA, not available

SIFT/PROVEAN, http://provean.jcvi.org/index.php; Polyphen-2, http://genetics.bwh.harvard.edu/pph2/; Mutation Taster, http://www.mutationtaster.org/; 1000 Genomes, http://www.internationalgenome.org/; ExAc, http://exac.broadinstitute.org/

of glycemic control, she has continued the multiple insulin injection therapy (17 units/day). Alternatively, her mother who carried the same mutation, had maintained good glucose control without diabetic complications by using only the oral glucose-lowering agents mitiglinide and metformin for a 15-year period [23•].

Although most homozygotes have neurological abnormalities [14, 15•], heterozygotes from only two families presented neurological abnormalities. One of the patients was a girl with multiple deformities (webbed neck, low hairline, slightly high-arched palate, cubitus valgus, bilateral brachydactylia of the fifth digit, bilateral incomplete dactylsymphysis of the third and fourth digits, and joint contracture of left ankle). She manifested intellectual disability at the age of about 1–2 years and her IQ was 70, the lower limit of normal in the Tanaka-Binet test. Brain magnetic resonance imaging revealed dysplasia of the right hippocampus. Also, her affected mother had slight intellectual disability and the same deformities as the daughter. Both of them carried the same frameshift mutation (c.734delC; p.pro245Argfs*17). The other patient with neurological abnormality is a patient with a missense mutation (c.470T>G; p.Leu157Arg). Her intelligence level was low, and she had hearing loss and seizures. At age 56, her brain computed tomography showed diffuse brain atrophy, and she became bed-ridden until death at age 58 [23•].

Conclusion

In conclusion, in light of the cases of MODY6 that we have summarized here, it is likely that patients with genetically low insulin secretory capacity in Japanese may be at increased risk of development of diabetic ketoacidosis and ketosis, and under sustained hyperglycemia without appropriate treatment, raising the risk of microangiopathy progression. On the other hand, MODY6 usually can be maintained in good control without insulin even in Japanese. MODY6 may also cause neurological abnormalities such as intellectual disability. As MODY6 is very rare and its characteristics are not yet well defined, clinical genetic testing of NEUROD1 may not occur when MODY is suspected. Clinicians should diagnose MODY6 positively by genetic testing to start continuous and effective treatment as soon as possible so as to prevent chronic hyperglycemia.

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Compliance with Ethical Standards

Conflict of Interest Yukio Horikawa and Mayumi Enya declare that they have no conflict of interest.

Human Rights and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revision. Informed consent or substitute for it was obtained from all patients for being included in the study.

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