Features of Japanese patients with early-onset, MODY-like diabetes without mutations in the major MODY genes.

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【OBJECTIVES】

To elucidate the molecular basis of MODY-like diabetes in Japan, and gain insight into the etiology of mutation-negative patients

【METHODS】

(Subjects)

263 Japanese patients with suspected MODY who were referred to Osaka City General Hospital seeking molecular diagnosis during 2005 – 2017. diagnoses of suspected MODY were based on

(a) the early-onset of diabetes (<30 years of age),
(b) negative pancreatic autoantibodies,
(c) persistently detectable C-peptide,
(d) non-obesity (BMI <95th percentile),
with or without
(a) dominant inheritance.

(Clinical information)

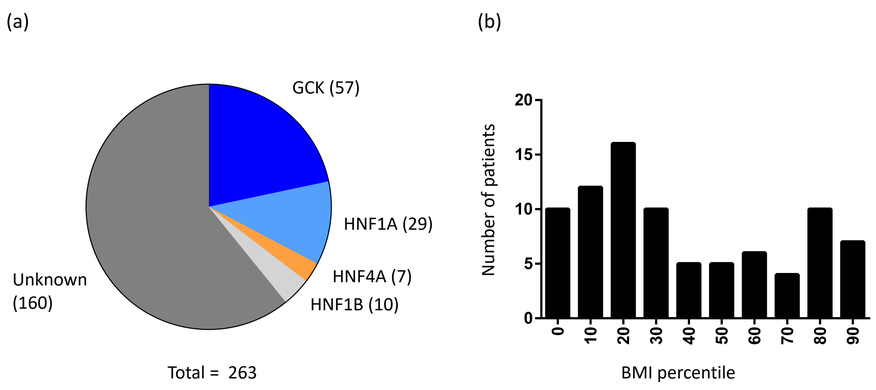
Obtained through questionnaires to the referring physicians: date of birth, sex, age at diagnosis, height and weight at diagnosis, route of ascertainment, laboratory data at diagnosis (blood glucose, insulin, C-peptide, HbA1c, autoantibodies, and ketone bodies), and family history of diabetes including diabetic complications.

(Mutational analyses)

Sanger sequencing and MLPA analyses of the *GCK, HNF1A*, *HNF4A*, and *HNF1B* genes.

【RESULTS】

(1) Mutations were identified in 103 (39.2%) patients (Figure 1a)
Contrary to conventional diagnostic criteria, 8.2% were overweight (BMI >85th percentile).



(2) Table 1. Inheritance patterns of mutation-positive patients.
18.4% of mutation-positive patients did not have affected parents.

Gene	Inheritance known	Mother affected	Father affected	No affected parents (Proven de novo)
GCK	57	24	27	6 (4)
HNF1A	29	15	9	5 (0)
HNF4A	7	3	2	2 (1)
HNF1B	9	1	2	6 (5)

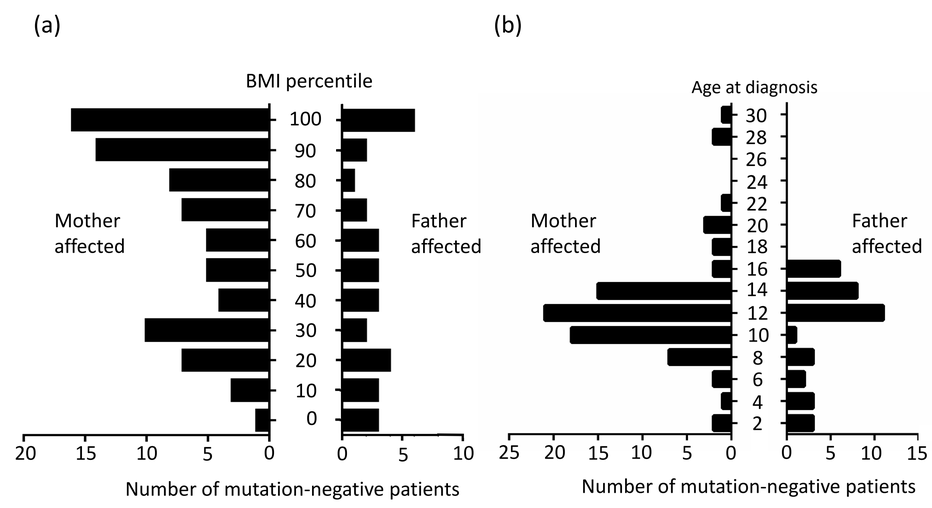
【RESULTS】

(3) Comparison of mutation-negative and mutation-positive patients.
mutation-negative patients were significantly older (p = 0.003), and had higher BMI percentile at diagnosis (p = 0.0006).
Maternal inheritance of diabetes was significantly more common in mutation-negative patients (p = 0.0332, Table 2)
and these patients had significantly higher BMI percentile as compared with mutation-negative patients with paternal inheritance (p = 0.0106, Figure 2).

Table 2

	Mutation negative (N = 160)	Mutation positive (N = 103)	p
Sex (male/female)	57/103	43/60	0.36*
Age (yrs) at diagnosis (95% confidence intervals)	11 (10.5-12.0)	10 (8.9-10.7)	0.003**
BMI percentile at diagnosis	56.5 (0.2-94.9)	30.1 (0.2-94.9)	0.0006**
Incidental/Symptomatic/Unknown	118/36/6	94/9/0	0.0024* (Incidental vs Symptomatic)
Affected parents (Maternal/Paternal/Biparental)	68/32/12	43/40/0	0.0332 *(Maternal vs Paternal)

Figure 2
(a) Distribution of mutation-negative patients with maternal or paternal inheritance at different BMI percentiles.
(b) Distribution of age at diagnosis in mutation-negative patients with maternal or paternal inheritance.



【CONCLUSIONS】

Contrary to the conventional diagnostic criteria, *de novo* diabetes, overweight, and insulin-resistance are common in Japanese patients with mutation-positive MODY.
A significant fraction of mutation-negative patients had features of early-onset type 2 diabetes common in Japanese, and non-Mendelian inheritance needs to be considered for these patients.

【REFERENCES】

Yorifuji T et al. Pediatr Diabetes. 2018 Jun 21. doi: 10.1111/pedi.12714.