[J Tokyo Wom Med Univ
74 (3) 157～166 (2004)]

Mutations in the HNF-1α Gene Are Not Associated with Glucose Intolerance in Offspring of Diabetic Mothers in Japan

Kaori SASAKI[1], Mayumi SANAKA[2], Naoko IWASAKI[2], Yasue OMORI[2], Yasuhiko IWAMOTO[2] and Makiko OSAWA[1]

[1]Department of Pediatrics and [2]Diabetes Center,
Tokyo Women's Medical University, School of Medicine

(Accepted Jan. 5, 2004)

A study on genetic and environmental factors has been carried out in the 134 offspring of diabetic mothers (50 from type 1 and 84 from type 2), who had been followed up for 1 to 10 years. Offspring were judged to be normal (N), diabetic (D), and borderline (B) by results of glucose torelance test. A search for mutations in the hepatocyte nuclear factor (HNF)-1α gene was conducted using the PCR direct sequencing method. ①Diabetes and abnormal glucose tolerance was found 3.0% and 32.1% in offspring, respectively. ②The mean age abnormal glucose tolerance discovered in the offspring was 11.4 to 14.4 years. ③The rank of mean plasma glucose values during pregnancy in both mothers with type 1 and type 2 diabetes, in descending order, by offspring group was D>B>N. ④There was a significant positive correlation between maternal body mass index in the pre-pregnant state and the maximum degree of obesity of the offspring. ⑤Among the obese offspring, development of abnormal glucose tolerance was significantly more common in the offspring of non-obese mothers than in those of obese mothers. ⑥No HNF-1α gene abnormalities were observed in any of the patients.

Key words: diabetes mellitus, infant of diabetes mother, HNF-1α, MODY

Introduction

Diabetes mellitus (DM) is a multifactorial inherited disease, and the influence of genetic and environmental factors on its onset is widely recognized. It is reported that the offspring of diabetic mothers are under the influence of DM in the mother during pregnancy; that is, the intrauterine environment participates in the onset of DM in addition to the external environment after birth[1].

Maturity onset diabetes of the young (MODY) is a form of diabetes that is caused by a single gene mutation, clinically characterized by diabetes that develops in youth, a family history of diabetes, and decreased insulin secretion[2)~10)]. Hepatocyte nuclear factor (HNF)-1α gene mutations have been reported in patients who exhibit insulin-dependent diabetes mellitus (IDDM) clinically, and they reportedly exhibit a broader clinical spectrums[4)5)10)]. To date five causative genes have been identified[3], but even in cases that do not satisfy the classic criteria, genetic mutations have been reported, and it has become clear that there are phenotypic variations[4)5)]. Among known MODY genes, HNF-1α gene mutation, which is the cause of MODY3, is the most frequent in Japan[6]. DM in the offspring of mothers with early-onset DM, with a family history of DM may be due to a MODY gene mutation.

We examined HNF-1α gene mutation as a genetic factor, as well as the influence of environmental factors, in abnormal glucose tolerance in the offspring of diabetic mothers.

Methods

Patients

Starting in 1989, we performed a follow-up study involving physical measurements and oral glucose tolerance testing (OGTT) in offspring above 10

years of age whose mothers were treated for diabetes during pregnancy at the Diabetes Center of Tokyo Women's Medical University (TWMU)[11]. One hundred and sixty (56 type 1 DM mothers, 104 type 2 DM mothers) had been examined by 1999. Among those 134 subjects were selected as the subject for gene research as they had given informed consent (50 from type 1 and, 84 from type 2 DM mothers' offspring). Because autoimmune islet antibody in mothers could not been examined, we judged their diabetic type by their onset style, insulin secretion and clinical course. Four children were excluded because their diabetes was attributed to a mitochondrial gene mutation.

Follow-up study

We measured heights and weights, and OGTT was conducted with 1.75 g/kg body weight glucose (maximum 75 g). We assessed the results using the 1998 WHO criteria[12], but we also classified some cases of both impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG) as borderline type. Among offspring who underwent GTT more than once, we classified those who responded repeatedly with a DM pattern as the DM group (D), those who showed only a normal pattern into the normal group (N), and others into the borderline group (B). The insulinogenic index (II) was calculated from plasma glucose values at 0 and 30 minutes, and immune reactive insulin (IRI) values at 0 and 30 minutes in the OGTT. A value below II of less than 0.5 was taken to indicate a poor insulin reaction state, because the age of patients ware over ten years. Plasma glucose was measured by the glucose oxidase (GOD) method. IRI was measured by radioimmunoassay (RIA) until 1990, and by enzyme immunoassay (EIA) from 1991 onward.

Survey of family history of DM

The presence of diabetes in the family inquired among third degree relatives by questionnaires and review of medical records.

Maternal and infantile background factors

We examined mean plasma glucose including fasting condition during pregnancy as parameters of the intrauterine environment. We defined maternal obesity as a BMI (body mass index) greater than 25 in the pre-pregnant state. The body weight at birth and gestational weeks were also evaluated.

Obesity in offspring

We evaluated the obesity index based on standard weight which was calculated using the recurrence method of Yamazaki for up to 17 years of age[13]. We determined standard weight as (22 kg) × (height m)^2 for patients more than 18 years old, because a BMI value of 22 kg/m^2 is the standard for Japanese adults. We judged our patients with an obesity index of less than −15% to be underweight, and those whose index exceeded +20% to be obese[14)~16].

We classified offspring into four groups by the presence of obesity in the mother and offspring: ① both mother and offspring were non-obese, ②the mother was obese but not the offspring, ③the offspring was obese but not the mother, and ④both the mother and the offspring were obese.

HNF-α gene mutation

We extracted DNA from peripheral blood leukocytes. The ten exons, flanking introns, and minimum promoter of the HNF-1α (the 336 bp upper exon reaches the initiation codon) gene were screened for mutations by direct sequencing of polymerase chain reaction (PCR) products using specific primers and a Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, CA, USA)[7)17]. The sequencing reactions were analyzed with an ABI Prism 377 Sequencer (Applied Biosystems).

Statistical analysis

The significance of differences was examined using the χ^2 test, Kruskal-Wallis, and Mann-Whitney tests, and correlations were examined using Spearman's correlation coefficient.

Results

Follow-up state

There were 332 offspring of DM mothers, treated during pregnancy at the DM Center of TWMU from 1964 to 1989 (96 offspring of type 1 and 236 of type 2 diabetic mothers). The follow-up rate until 1999 was 48.2% (160/332) overall; 58.3% (56/96) for offspring of type 1 and 44.1% (104/236) for those of type 2 diabetic mothers' offspring.

Table 1 State of offspring at follow-up study

	Diabetes mothers' offspring					
	Type 1			Type 2		
	D	B	N	D	B	N
n	1	12	37	3	31	50
male/ female	1/0	5/7	19/18	2/1	16/15	28/22
mean GTT frequency	4	5.7 ± 4.0	3.3 ± 3.1	4.7 ± 4.6	5.6 ± 2.5	2.8 ± 2.5 *
GTT one time (%)	0 (0)	3 (25)	18 (48.6)	0 (0)	6 (18.9)	23 (42.6) *
mean age of GTT	13.2 ± 2.6	16.0 ± 5.0	13.7 ± 3.9	19.3 ± 5.6	17.4 ± 6.0	14.6 ± 5.6
mean age of abnormal glucose tolerance	14	11.4 ± 3.0		13.0 ± 3.0	14.4 ± 5.2	
2nd degree relation of DM family history (Type 1 DM)	0 (0%)	5 (41.7%)	16(4) (43.2%)	3 (100%)	16 (51.6%)	25 (50.0%)
the three generation of DM family history	0 (0%)	4 (33.3%)	7 (18.9%)	2 (75.0%)	14 (45.2%)	22 (44.0%)
DM onset age of mothers	7	19.4 ± 8.7	18.9 ± 7.1	24.3 ± 1.2	24.1 ± 6.6	26.4 ± 5.8
duration DM of mothers to pregnancy	20	8.8 ± 5.4	9.8 ± 5.4	5.3 ± 1.5	6.7 ± 5.0	4.8 ± 4.3
HFD infants	0 (0%)	3 (25.0%)	8 (21.6%)	0 (0%)	9 (29.0%)	13 (26.0%)
LFD infants	0 (0%)	0 (0%)	3 (8.1%)	0 (0%)	1 (11.1%)	1 (7.7%)
Preterm infants	0 (0%)	4 (33.3%)	4 (10.8%)	0 (0%)	3 (9.6%)	5 (10.0%)
max obesity index (%)	−1.5	6.0 ± 16.0	2.9 ± 12.9	13.1 ± 24.8	11.6 ± 18.7	12.6 ± 19.3
obese offspring	0 (0%)	2 (16.7%)	3 (8.1%)	1 (33.3%)	9 (29.0%)	14 (28.0%)

D: DM group, B: borderline group, N: normal group, GTT: glucose tolerance test, HFD: heavy-for-dates, LFD: light-for-dates.
* : $p < 0.05$ (N vs B + D).

There were 50 offspring from type 1 DM mothers; one (2%) in D, 12 (24%) in B, 37 (74%) in N, and 84 from type 2 DM mothers; three (3.8%) in D, 31 (36.9%) in B, and 50 (59.5%) in N. The frequency of abnormal glucose tolerance was higher in the offspring of type 2 DM mothers than in those of type 1. But the difference did not reach statistical significance in groups D, B, and N of type 1 or in type 2.

The number of times GTT was performed in the children of type 1 DM mothers was 4 in D, 5.7 ± 4.0 (mean ± SD) in B, and 3.3 ± 3.1 in N, with no significant differences between any two groups, whereas the corresponding values for type 2 DM mothers were 4.7 ± 4.6, 5.6 ± 3.5, and 2.8 ± 2.5. The difference was significant between B and N, and also between D and N ($p = 0.048$) (Table 1).

The proportion of patients from type 1 DM mothers, in whom GTT was performed only once, was 0% in D, 25% in B, and 48.6% in N. There were no significant differences between any two groups. On the other hand in the offspring of type 2 DM mothers, the respected proportions were 0, 18.9, and 42.6%. The proportion of patients who underwent GTT only once is significantly ($p = 0.005$) higher in N than both B and D (Table 1).

There were no significant differences among groups D, B,and N in mean age at the time of GTT: Type 1 group D, 13.2 years; group B, 16.0 years; group N, 13.7 years; and type 2 group D, 19.3 years; group B, 17.4 years; group N, 14.6 years. The mean ages at detection of abnormal glucose tolerance were, respectively, 14, 11.4, 13.0 and 14.4 years (Table 1). Four children were diagnosed as having DM, and the type of diabetes in these children was consistent with that of their mothers.

Insulinogenic index (II) in GTT

Age at each GTT and II determination are shown in Figs. 1 and 2. The more abnormal the glucose tolerance, the lower the II of the offspring. There were significant differences in the mean II (for offspring of type 1 DM mothers $p = 0.04$, type 2 $p = 0.014$) among the three groups for each type of diabetes. The frequency of an II less than 0.5 was 100% in D, 50% in B, and 10.8% in N in the offspring of type 1 DM mothers and the difference was significant ($p = 0.028$). For those of type 2 DM mothers, the frequency of an II less than 0.5 was 100% in D, 48.2% in B, and 18% in N, the difference again being significant ($p = 0.04$).

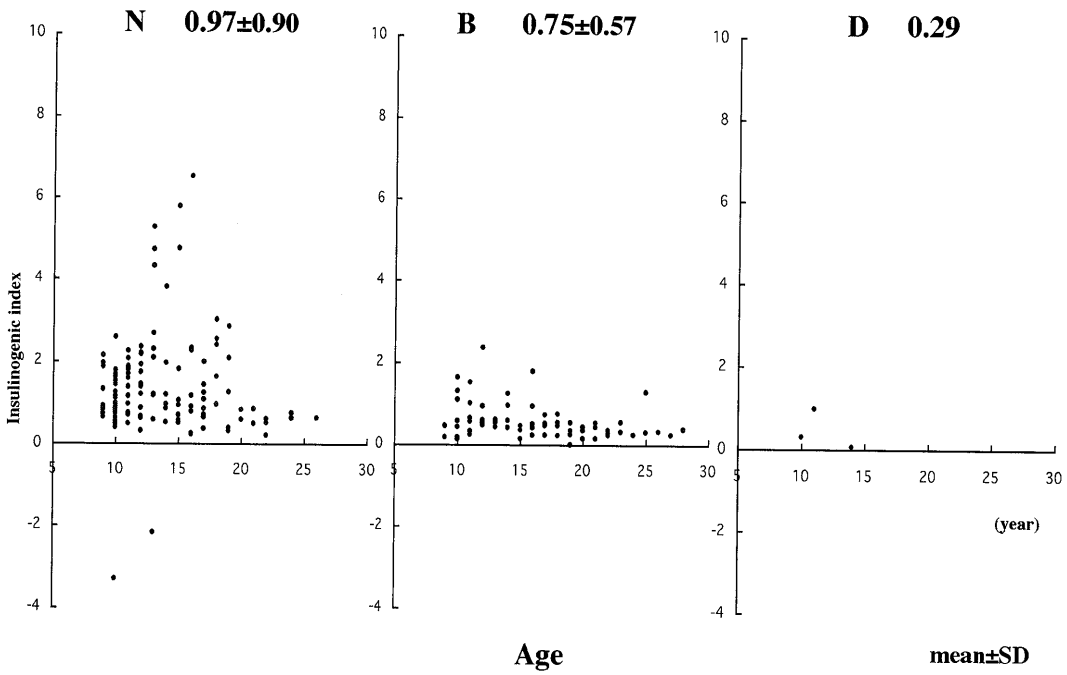

Fig. 1 Insulinogenic indices of offspring of type 1 DM mothers at follo-up study
N: normal group, B: borderline group, D: DM group.

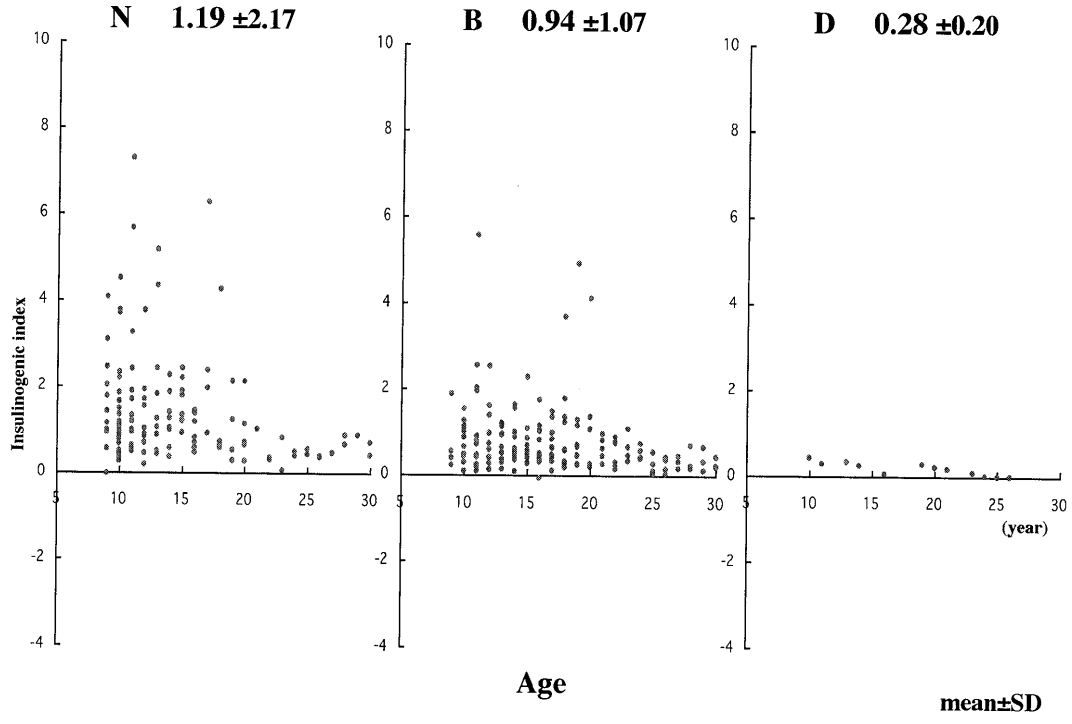

Fig. 2 Insulinogenic indices of offspring of type 2 DM mothers at follow-up study
N: normal group, B: borderline group, D: DM group.

Family history of diabetes

The numbers of subjects with a positive family history of diabetes are shown in Table 1. There was a family history of diabetes in second degree relatives besides the mother in 0% of D, 41.7% of B, and 43.2% of N among the offspring of type 1 DM mothers, and the corresponding values for those whose mothers had type 2 DM mellitus were 100, 51.6, and

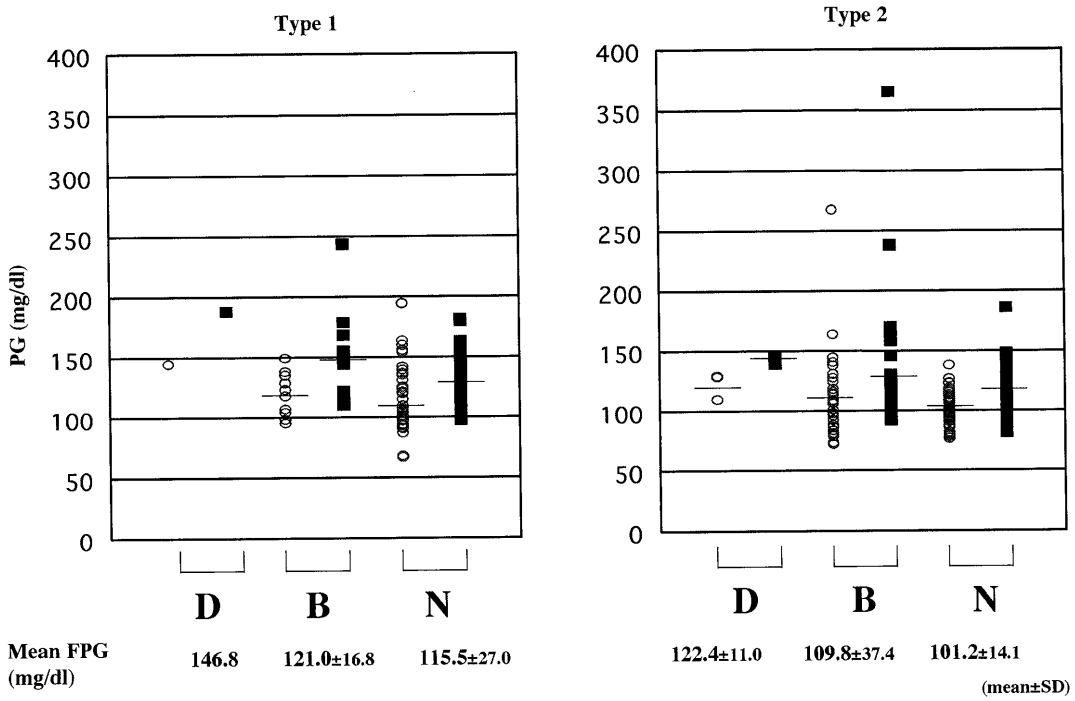

Fig. 3 Mean plasma glucose during pregnancy
D: DM group, B: borderline group, N: normal group.
○: FPG, ■: PG (all).

50%. There was a family history in the grand parents in 0% of D, 33.3% of B, and 18.9% of N among the offspring of type 1 DM mothers. The respective values for those of type 2 DM mothers were 75, 45.2, and 44%. In the group with abnormal glucose tolerance, the offspring of type 2 DM mothers tended to have more diabetic family members. In addition, the type of diabetes in the family was consistently type 2 in the offspring of type 2 DM mothers, but among those whose mothers were type 1 DM only four siblings of the mother had type 1 DM, and the other 17 had family members with type 2 DM.

Backgrounds of mothers

Neither the mothers' age at diabetes onset nor the duration of diabetes before pregnancy differed significantly among the groups (Table 1). Mean maternal plasma glucose values during pregnancy are shown in Fig. 3. FPG (fasting plasma glucose) was 146.8 mg/dl in D, 121.0 ± 16.8 mg/dl in B, and 115.5 ± 27.0 mg/dl in N of type 1 DM mothers, and 122.4 ± 11.0 mg/dl in D, 109.8 ± 37.4 mg/dl in B, and 101.2 ± 14.1 mg/dl in N of type 2 DM mothers. There were no significant differences in FPG among the groups, but there was a tendency for higher glucose levels in pregnancy to be associated with worse glucose tolerance in the offspring. A similar tendency was seen in average plasma glucose levels, including postprandial plasma glucose.

State of offspring at birth

The frequencies of heavy-for-dates (HFD) infants were as follows; 0% in D, 25% in B, and 21.6% in N for the offspring of type 1 DM mothers, and 0% in D, 29% in B, and 26% in N for those of type 2. No significant differences in HFD rates were recognized between any two groups. The respective frequencies of light-for-dates (LFD) infants were 0, 0, and 8.1%, and 0, 11.1, and 7.7%. No significant differences in LFD rates were recognized among the groups (Table 1). The frequency of preterm infants was 0% in D, 33.3% in B, and 10.8% in N for type 1 diabetic mothers, and 0% in D, 9.6% in B, and 10% in N for type 2. There were no significant differences in the frequencies of preterm infants among groups (Table 1). There were no post-term infants.

Obesity of offspring

The mean maximum obesity indices in the follow-

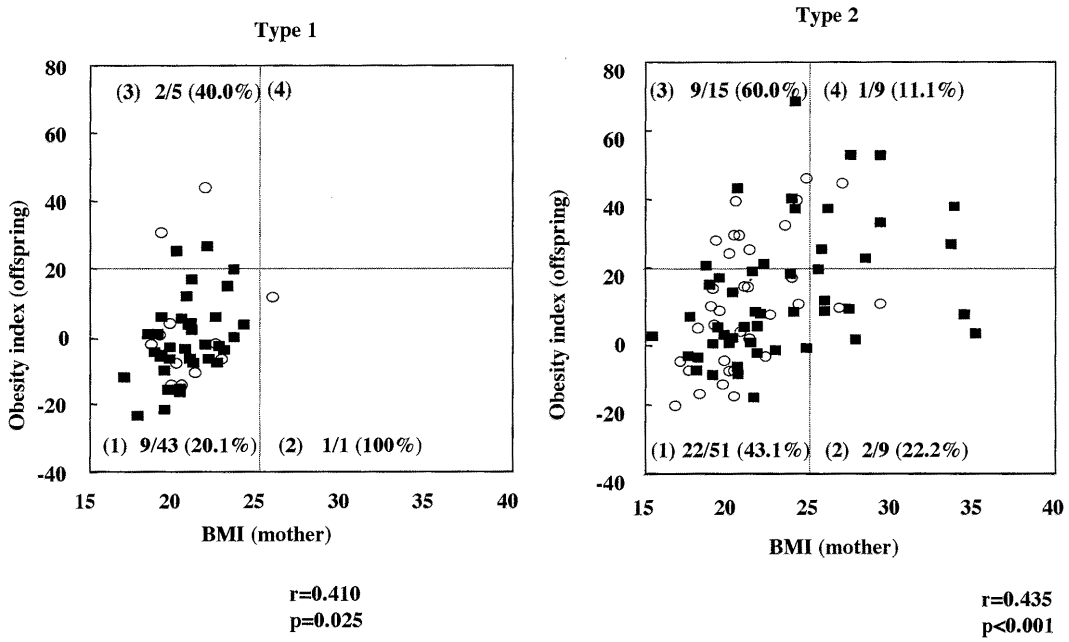

Fig. 4 Relation of maternal BMI before pregnancy and maximum obesity index of offspring at follow-up study
■: N, ○: BD.

up study were −1.5% in D, 6.0% in B, and 2.9% in N of the offspring of type 1 DM mothers, and the corresponding values for those of type 2 DM mothers were 12.6, 11.6, and 13.1%. The obesity index was significantly higher in the offspring of type 2 DM mothers than in those whose mothers had type 1. However, there were no significant differences among groups D, B, and N for either DM type (Table 1).

The proportions of obese children, i.e. with an obesity index≥20%, were 0% in group D, 16.7% in B, and 8.1% in N for type 1 DM, and 33.3% in D, 29.0% in B, and 28.0% in N for type 2 DM, mothers. There were no significant differences among groups (Table 1).

There was a positive correlation between obesity in the mother and the offspring (for the offspring of type 1 DM mothers: $r = 0.410$, $p = 0.025$; for those of type 2 DM mothers: $r = 0.435$, $p < 0.001$) (Fig. 4).

The patients were classified into four groups according to the presence of obesity in the mother and offspring, as shown in Fig. 4. The frequency of abnormal glucose tolerance in obese offspring of type 2 DM mothers was 60% (9 out of 15) in group 3 (obese offspring with non-obese mothers), which was significantly higher ($p = 0.018$) than the 11.1% (one out of 9) in group 4 (obese offspring with obese mothers). In group 4, insulin resistance indicated by HOMA-R was high in 10 among 15 and insulinogenic index was not low among 10 out of 15.

HNF-1α gene mutation

No HNF-1α gene mutations were recognized in any of the offspring. Two reported gene polymorphisms, Ile-27-Leu, a mutation of exon 1, codon 27 from ATC (Ile) to CTC (Leu), and Ser-487-Asn, a mutation of exon 7, codon 487 from AAC (Asn) to AGC (Ser), were found. For Ile-27-Leu, the allele frequency of wild type Ile, A was 0.83 in the offspring of type 1 DM mothers and 0.68 in those of type 2 DM mothers. The allele frequency of wild type Asn, A was 0.85 in the offspring of type 1 DM mothers and 0.82 in those of type 2 DM mothers for Ser-487-Asn (Table 2).

Ile-27-Leu was also found in both groups (Table 3). As to the allele frequency of wild type Ile, A was 1.0 in D, 0.83 in B, and 0.82 in N of the offspring of type 1 DM mothers, and 0.83 in D, 0.58 in B, and 0.74 in N of those of type 2 DM mothers. Asn-487-Ser frequencies in D, B and N are shown in Table 3 As to the allele frequency of wild type Asn, A was 1.0 in

Table 2 Polymorphism rates

	polymorphism of exon 1 (Ile-27-Leu)			polymorphism of exon 7 (Ser-487-Asn)		
	non-DM	Type 1 diabetes mothers' offspring	Type 2 diabetes mothers' offspring	non-DM	Type 1 diabetes mothers' offspring	Type 2 diabetes mothers' offspring
wild type	0.51	0.83 *	0.68 **	0.51	0.85 *	0.82 *
mutant type	0.49	0.17 *	0.32 **	0.49	0.15 *	0.18 *

* $p < 0.01$ (vs non-DM), ** $p = 0.01$ (vs non-DM).

Table 3 Allele frequency of Ile-27-Leu and Ser-487-Asn polymorphism

	non-DM	Type 1 diabetes mothers' offspring			Type 2 diabetes mothers' offspring		
		D	B	N	D	B	N
ATC (Ile)→CTC (Leu)							
A (wild type)	0.51	1.0	0.83	0.82 *	0.83	0.58	0.74 *
C (mutant type)	0.49	0	0.17	0.18 *	0.17	0.42	0.26 *
AAC (Asn)→AGC (Ser)							
A (wild type)	0.51	1.0	0.96 *	0.81 *	0.5	0.81 *	0.81 *
G (mutant type)	0.49	0	0.04 *	0.19 *	0.5	0.19 *	0.19 *

D: DM group, B: borderline group, N: normal group. * $p<0.01$ (vs non-DM).

D, 0.96 in B, and 0.81 in N of the offspring of type 1 DM mothers, and 0.5 in D, 0.81 in B, and 0.81 in N of those of type 2 DM mothers. In addition, there was no linkage disequilibrium between these two gene loci.

Discussion

There have been many reports on the high prevalence of obesity and abnormal glucose tolerance in the offspring of DM mothers, after they grow up [1)18)~23)]. In Japan, Omori et al reported abnormal glucose tolerance to be present in a high percentage of offspring[11)]. In this study, we detected DM in 3.0% and abnormal glucose tolerance detected by OGTT in 32.1% of offspring.

Environmental factors (intrauterine and postnatal environments) and genetic factors may contribute to the development of abnormal glucose tolerance in the offspring of diabetic mothers[11)]. Pedersen and Freinkel have hypothesized that elevated glucose resulting from insufficient insulin activity in the mother leads to nutritional excess and even hyperinsulinemia in the fetus, and that this not only result in the birth of large babies and hypoglycemia in neonates, but also obesity and abnormal glucose tolerance after they grow up[24)]. Pettitt et al showed maternal plasma glucose levels during pregnancy to correlate with plasma glucose levels of their offspring after they grew up, and that HFD infants whose weight is excessive for their gestational age, and those whose birth weight was 4.5 kg or more were at high risk for developing diabetes in their study on Pima Indians[1)19)20)].

We assessed the association of abnormal glucose tolerance in offspring with mean maternal plasma glucose values during pregnancy, to elucidate the contribution of the intrauterine environment to the development of abnormal glucose tolerance in the offspring of diabetic mothers. The results showed that the more severe the abnormal glucose tolerance detected by OGTT in the offspring of both type 1 and type 2 DM mothers, in the condition that maternal plasma glucose value during pregnancy in the fasting state and total mean plasma glucose level were higher, suggesting that maternal plasma glucose during pregnancy may contribute to abnormal glucose tolerance in their offspring.

Our results demonstrate obesity to be significantly more prevalent among the offspring of type 2 diabetics than among those of type 1 diabetics. However, the obese offspring did not always exhibit abnormal glucose tolerance.

It has been said that both postnatal environmental factors and genetic factors contribute to obesity[14)~16)]. This study revealed a significant corre-

lation between maternal BMI in the pre-pregnant state and the degree of obesity of their offspring. Among the obese offspring of mothers with type 2 DM, however from the aspect of glucose tolerance, there was a significantly higher rate of abnormal result in those whose mothers were non-obese than among those whose mothers were obese. It had been clarified that type 2 DM partially induced by obesity. Thus obese person have much more liable for DM. In multifactorial inheritance, the recurrence risk of the disease in offspring is higher in those of parents with less liable factors because those person suffered from disease without inducing factor means they have much more genetic predisposition. Our data that obese offspring of non-obese mother showed abnormal glucose tolerance more frequently than those of obese mother is compatible with this feature of multifactorial inheritance even though further research is necessary with information of father.

In the assessment of family history of diabetes in 2nd degree relatives and spanning three generations, the greater the degree of abnormal glucose tolerance in the offspring of mothers with type 2 DM, the stronger their family history of DM, suggesting a possible genetic contribution besides of multifactorial inheritance. Thus HNF-1α gene have been examined. However, no mutations in the HNF-1α gene, the causative gene for MODY3, were found in either the four offspring of this study in whom DM developed or any of the other offspring.

Gene abnormalities have been detected in 20% of Japanese cases clinically diagnosed as MODY. Among these abnormalities, mutations of the HNF-1α gene, the cause of MODY3, are the most numerous and account for 15% of MODY cases[6]. In addition, Iwasaki reported finding HNF-1α gene mutations in 7 (8%) of 83 NIDDM patients in whom the onset occurred before 30 years of age[17].

The results suggest that HNF-1α gene mutations are not a major cause of abnormal glucose tolerance in the offspring of DM mothers in this study. However, known gene mutations were detected in no more than 20% of the cases clinically diagnosed as MODY, and no mutations were identified in the other 80%[6]. It is also suggested that genetic factors, relating to family history, contribute etiologically in the offspring of mothers with type 2 DM in particular, and this issue is expected to be elucidated in future searches for other genes.

Two types of HNF-1α gene polymorphisms have already been detected. No linkage disequilibrium was found in the second gene polymorphism identified. The frequencies of the wild and mutant types of both polymorphisms have been reported to be almost equal in non-diabetic Japanese[7)17)]. The allele frequency of the wild-type Ile, A in the Ile-27-Leu of exon 1, was significantly higher in both the offspring of mothers with type 1 diabetes ($p<0.01$) and in those of mothers with type 2 DM ($p=0.01$) than the $A=0.51$[17] reported in non-DM Japanese. In addition, the allele frequency of the wild-type Asn, A at the Ser-487-Asn of exon 7, was significantly higher in both the offspring of mothers with type 1 diabetes ($p<0.01$) and in those of mothers with type 2 DM ($p<0.01$) than the $A=0.51$[17] reported in non-DM Japanese. Since the parents were not tested, it is unknown whether this mutation was inherited from the DM mother or the father, and while its significance is unclear, this findings clearly merits future investigation.

The mean age at the time of OGTT in group N was 13.7 years in the offspring of mothers with type 1 DM and 14.6 years in the offspring of mothers with type 2 DM. Furthermore, an insulinogenic index of 0.5 or less, indicating a poor insulin response, was found in 10% of the offspring of type 1 DM mothers and 18% of those of the type 2 DM. Thus, abnormal glucose tolerance may develop in the future in some group N subjects, such that regular follow-up studies are essential.

While GTT was performed more frequently in B, this appears to have been attributable to interventional guidance that encouraged testing the following year whenever an abnormal GTT or obesity was observed. It has also been suggested that follow-up studies are important as a means of secondary prevention of the onset of diabetes.

Dabelea et al[1] hypothesized that a vicious cycle exists in which the offspring of diabetic mothers de-

velop diabetes when they reach reproductive age, that the intrauterine environment is poor, and that these children go on to develop diabetes. This hypothesis has been supported by findings in Pima Indians. Methods of breaking the vicious cycle would seem to be, first, preventing glucose metabolism disorders from developing after the child grows up by improving the intrauterine environment, in other words, by controlling the mother's plasma glucose during pregnancy, and early discovery and treatment of abnormal glucose tolerance by means of follow-up studies might prevent the onset of diabetes from generation to generation.

Conclusions

No HNF-1α mutations were found in the 134 offspring of DM mothers in this study. The further study on genetic analysis in more patients with information of father might be necessary.

References

1) **Dabelea D, Knowler WC, Pettitt DJ**: Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. J Matern Fetal Med **9**: 83–88, 2000
2) **Yasuda K, Kadowaki T**: MODY. Nippon Rinsho **56** (Suppl): 566–572, 1998 (in Japanese)
3) **Yamagake K, Matsuzawa Y**: Gene analysis and pathology of MODY. *In* Advances in Diabetology '99 No. 33, (Japan Diabetes Society eds), pp130–136, Shindan to Chiryosha, Tokyo (1999) (in Japanese)
4) **Kawasaki E, Sera Y, Yamakawa K et al**: Identification and functional analysis of mutations in the hepatocyte nuclear factor-1 α gene in anti-islet autoantibody-negative Japanese patients with type 1 diabetes. J Clin Endocrinol Metab **85**: 331–335, 1999
5) **Yoshiuchi I, Yamagata K, Yang Q et al**: Three new mutations in the hepatocyte nuclear factor-1α gene in Japanese subjects with diabetes mellitus: clinical features and functional characterization. Diabetologia **42**: 621–626, 1999
6) **Iwasaki N**: Causative gene of diabetes—Type 1 and Type 2 MODY. *In* Practical Internal Medicine Series. 6. Diabetes (Iwamoto Y ed) pp216–219, Nankodo, Tokyo (1999) (in Japanese)
7) **Lehto M, Tuomi T, Mahtani MM et al**: Characterization of the MODY3 phenotype—early-onset diabetes caused by an insulin secretion defect. J Clin Invest **99**: 582–591, 1997
8) **Kaisaki PJ, Menzel S, Lindner T et al**: Mutations in the hepatocyte nuclear factor-1α gene in MODY and early-onset NIDDM. Diabetes **46**: 528–535, 1997
9) **Nishigori H, Yamada S, Kohama T et al**: Mutations in the hepatocyte nuclear factor-1 α gene (MODY3) are not a major cause of early-onset non-insulin-dependent (type 2) diabetes mellitus in Japanese. J Hum Genet **43**: 107–110, 1997
10) **Takeda J**: Maturity onset diabetes of the young (MODY)/diabetes mellitus as a "transcription factor" disease. Nippon Rinsho **56**: 2419–2426, 1998 (in Japanese)
11) **Omori Y**: Treatment of special subjects—Diabetes in pregnancy. *In* 1989 Diabetes Investigative Research Report. pp391–395, Ministry of Health and Welfare (1989) (in Japanese)
12) **Japan Diabetes Society Committee to Assess the Diagnostic Criteria for Diabetes Mellitus**: Committee report on the classification and diagnostic criteria of diabetes mellitus. Diabetes **42**: 385–404, 1999 (in Japanese)
13) **Yamazaki K, Matsuoka N, Kawanobe S et al**: Body weight assessment according to sex, age, and height. 1990 ed. Nihon Shonika Gakkai Zasshi **98**: 96–102, 1994 (in Japanese)
14) **Ito K, Murata M**: Epidemiology and criteria for evaluating obesity. Shonika Rinsho **52**: 1182–1186, 1999 (in Japanese)
15) **Yamazaki K**: Obesity and health injury. Shonika Rinsho **52**: 1187–1193, 1999 (in Japanese)
16) **Japan Society for the Study of Obesity Clinical Handbook for Pathological Obesity Editorial Committee**: Guidance Manual for Obesity and Pathological Obesity. Ishiyaku Shuppansha, Tokyo (1997) (in Japanese)
17) **Iwasaki N, Oda N, Ogata M et al**: Mutation in the hepatocyte nuclear facter-1 α/MODY 3 gene in Japanese subjects with early- and late-onset NIDDM. Diabetes **46**: 1504–1508, 1997
18) **Silverman BL, Cho NM, Rizzo TA et al**: Long-term effect of the intrauterine environment. Diabetes Care **21** (Suppl 2): B142–B149, 1998
19) **Phillips DIW**: Birth weight and the future development of diabetes. Diabetes Care **21** (Suppl 2): B150–B155, 1998
20) **Pettitt DJ, Knowler WC**: Long term effect of the intrauterine environment, birth weight, and breast-feeding in Pima Indians. Diabetes Care **21** (Suppl 2): B138–B141, 1998
21) **Hoshi J, Nishida H, Takahashi N**: Perinatal morbidity of infants of diabetic mothers. Acta Pediatr Jpn **33**: 159–165, 1991
22) **Yotsukura M, Mitsuishi C**: Long-term outcome of IDM. Shusanki Igaku **26**: 419–423, 1996 (in Japanese)
23) **Matsuura N**: IDM (infants of diabetic mothers). Sanfujinka Chiryo **76**: 1101–1110, 1998 (in Japanese)
24) **Silverman BL, Ogata ES, Metger BE**: The offspring of the mother with diabetes. *In* Elenberg and Rifkin's Diabetes Mellitus, Theory and Practice. 5th ed (Rifkin H, Porte D eds). Elsevier, New York (1995)

日本人糖尿病母体から出生した児の糖代謝異常にHNF-1α遺伝子変異は関与しない

[1]東京女子医科大学　医学部　小児科学（指導：大澤真木子教授）
[2]同　糖尿病センター

佐々木香織[1]・佐中真由実[2]・岩崎　直子[2]
大森　安恵[2]・岩本　安彦[2]・大澤真木子[1]

糖尿病母体から出生した児における糖代謝異常出現へのHNF(hepatocyte nuclear factor)-1α遺伝子，および環境因子の関与を検討した．1989～1999年の追跡発育発達検診を受診し，遺伝子検索の同意が得られた134名（1型糖尿病母体出生児50名，2型糖尿病母体出生児84名)を対象とした．対象を経口糖負荷試験で判定し，正常結果のみを正常群（N)，糖尿病と診断した糖尿病群（D)，その他を境界群（B）とした．HNF-1α遺伝子はPCR直接シークエンス法で変異を検索した．結果は，①1型糖尿病母体出生児ではD1名（2%)，B12名（24%)，N37名（74%）であり，2型糖尿病母体出生児ではD3名（3.8%)，B31名（36.9%)，N50名（59.5%）であり，糖尿病児の病型は全例が母の病型と一致していた．②糖代謝異常は若年で出現していた．③母体妊娠中平均血糖は，D>B>N群の順に高値であった．④母の妊娠前のBMIと児の最大肥満度は正相関を示した．⑤2型糖尿病母体出生児のうちの肥満児では，母が非肥満の群で糖代謝異常出現率が高値であった．⑥HNF-1α遺伝子変異は認めなかったが，既知の遺伝子多型が非糖尿病者における頻度に比し高率の傾向にあった．糖尿病母体出生児の糖代謝異常にHNF-1α遺伝子の関与は示されなかった．今後も対象を増やし，父方の関与についてもさらに検討する必要がある．