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Effect of mutations in HNF-1α and HNF-1β on the transcriptional regulation of human sucrase–isomaltase in Caco-2 cells

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Abstract

Mutations in transcription factors hepatocyte nuclear factors (HNF)-1α and HNF-1β cause maturity-onset diabetes of the young (MODY) types 3 and 5, respectively. HNF-1α and HNF-1β mutations are well studied in some tissues, but the mechanism by which HNF-1α and HNF-1β mutations affect sucrase–isomaltase (SI) transcription in the small intestine is unclear. We studied the effects of 13 HNF-1α mutants and 2 HNF-1β mutants on human SI gene transcription, which were identified in subjects with MODY3 and MODY5, respectively. Transactivation activity of 11 HNF-1α and 2 HNF-1β mutants was significantly lower than that of wild (wt)-HNF-1α and wt-HNF-1β. Furthermore, in co-expression studies with mutant (mu)-HNF-1α/wt-HNF-1β and wt-HNF-1α/mu-HNF-1β, the combination of mu-HNF-1α (P379fsdelCT and T539fsdelC)/wt-HNF-1β impaired SI transcription, but the others were not remarkably different from wt-HNF-1α/wt-HNF-1β. Although wt-HNF-1β inhibited the transactivation activity of wt-HNF-1α on SI transcription, the inhibitory effect was reduced by 2 HNF-1β mutants. These results suggest that SI transcription might tend to be unchanged or lower in MODY3, while occurring more in MODY5.

Keywords: MODY3; MODY5; HNF-1α; HNF-1β; SI gene

Heterozygous mutations in hepatocyte nuclear factor (HNF)-1α and HNF-1β cause maturity-onset diabetes of the young (MODY) types 3 and 5, respectively. HNF-1α and HNF-1β share >90% sequence homology in their DNA-binding domains and recognize the same DNA-binding site [1–3]. It has been reported that these transcriptional factors bind to DNA as heterodimers or homodimers, and are expressed in the liver, kidney, small intestine, pancreas, and genitourinary tissues [4]. Mutations of HNF-1α and HNF-1β genes lead to the synthesis of mutant proteins with simple loss of function or with dominant-negative effect [5–7]. Clinical studies have identified a primary deficiency of insulin secretion in MODY3 patients [8,9]. The molecular mechanism of MODY3 has also been well characterized. In the reports using animals or cell models, HNF-1α has been shown to regulate genes of glycolytic enzyme expressed in pancreatic β-cell, such as glucose transporter 2 (GLUT2) and L-type pyruvate kinase (PKL) [10,11]. In MODY3 patients, the decreased transcription of PKL and GLUT2 genes in β-cells might impair insulin secretion. On the other hand, only a few cases of MODY5 due to HNF-1β mutation have been described. There has been almost no assessment of the molecular mechanism of MODY5. There

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are no useful models of the role of HNF-1β in the β-cell because the HNF-1β (−/−) mice die at an early embryonic stage (E7.5). Despite the ability of mutant HNF-1β to impair insulin reporter gene transcription in MIN6 and HepG2 cells [6], a clinical study has demonstrated that β-cell functions in MODY5 patients do not differ significantly from those in healthy subjects, and that insulin resistance is characteristic [12].

In the small intestine, sucrase–isomaltase (SI) complex is a major component of α-glucosidase. SI transcription is accelerated in diabetic patients [13,14]. We have also found that SI transcription and activity are increased in OLETF and STZ rats [15,16]. The incremental SI activity may cause postprandial hyperglycemia (PPG) and further aggravate the diabetic condition. SI transcription has been reported to be regulated by several transcription factors [17]. HNF-1α and HNF-1β are known as important transcription factors of SI gene. HNF-1α and HNF-1β bind to the promoter site of SI gene and directly regulate its transcription [18]. However, there is little information about the role of mutant (mu)-HNF-1α and mu-HNF-1β in regulation of SI transcription.

To clarify changes in the level of SI transcription in MODY3 and MODY5, we studied the effects of wt- and mu-HNF-1α/HNF-1β on human SI transcription in Caco-2 cells, which are cloned by human colon adenocarcinoma [19–21].

Materials and methods

HNF-1α and HNF-1β mutants. Thirteen mutants (L12H, R131W, K158N, K159Q, R200Q, R203C, R229X, V233L, A239V, R271G, R272H, P379fsdelCT, and T539fsdelC) and wild HNF-1α were used. The mutation L12H-HNF-1α is located in the N-terminal dimerization domain (amino acids 1–32), K158N, K159Q, R200Q, R203C, R229X, V233L, A239V, R271G, and R272H-HNF-1α are located in the DNA-binding domain (amino acids 150–280), and P379fsdelCT, T539fsdelC–HNF-1α are in the C-terminal transactivation domain (amino acids 281–631). R177X and A263fsinsGG-HNF-1β are located in the DNA-binding domain.

Plasmid constructs. Human wild and mutant HNF-1α and HNF-1β cDNA were subcloned into pCMV-6b vector. For luciferase reporter assay, the promoter region (nucleotides −1244 bp to +46 bp relative to the cap site) of human SI gene, including the HNF-1 binding sites (SIF2: −88 to −68 and SIF3: −175 to −158) was subcloned into pGL3-Basic reporter vector (Promega, Madison, WI, USA).

Cell culture and transfection analysis. Caco-2 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) with 20% fetal calf serum, 100 U/ml penicillin, and 100 g/ml streptomycin in 5% CO_2 at 37 °C. Cells were seeded in six-well dishes 24 h before transfection and grown in 50% confluence. Transient transfections were performed using LipofectAmine Reagent (Life Technologies, Grand Island, NY). The cells were transfected with plasmid mixture, which contained 0–2 μg of wild or mutant HNF-1α, 0–2 μg of wild or mutant HNF-1β, 1 μg SI-luciferase reporter vector, and 1 μg p-act-β-gal for internal control. The amounts of HNF-1 plasmid used in each experiment are shown in more detail in Table 1. For 48 h after transfection, the cells were harvested and cell extracts were prepared for luciferase assays and β-galactosidase assays. All transfection experiments were repeated more than three times.

Statistical analysis. Statistical evaluation was performed by ANOVA. All data are shown as means ± SE, and statistical significance is defined as $P < 0.05$.

Results

Transactivation activity of wild- HNF-1α and HNF-1β

SI transcriptional activity was activated 20 times more by transfected wild (wt)-HNF-1α than by the vec-

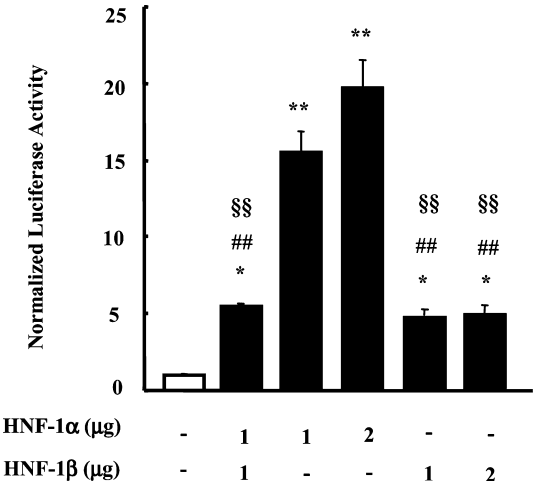

Fig. 1. Transactivation activity of wild HNF-1α and wild HNF-1β. Wild HNF-1α and wild HNF-1β were transfected with luciferase SI reporter gene and p-act-β-gal plasmid in Caco-2 cells. Luciferase activity was normalized by the activity of β-galactosidase. Vector only was defined as 1. The results were from more than three independent experiments. Bars represent mean ± SE. $^{*}P < 0.05$, $^{**}P < 0.0001$ vs. vector only; $^{\#\#}P < 0.0001$ vs. HNF-1α 2 μg; and $^{\S\S}P < 0.0005$ vs. HNF-1α 1 μg.

Table 1
Amount of plasmid for transfection

	Wild HNF-1α (μg)	Wild HNF-1β (μg)	Mutant HNF-1α (μg)	Mutant HNF-1β (μg)
Wild HNF-1α and wild HNF-1β (Fig. 1)	0–2	0–2	—	—
Mutant HNF-1α (Fig. 2A)	—	—	1	—
Mutant HNF-1β (Fig. 2B)	—	—	—	1
Co-expression of wild and mutant HNF-1α (Fig. 3A)	1	—	1	—
Co-expression of wild and mutant HNF-1β (Fig. 3B)	—	1	—	1
Co-expression of mutant HNF-1α and wild HNF-1β (Fig. 5)	—	1	1	—
Co-expression of wild HNF-1α and mutant HNF-1β (Fig. 5)	1	—	—	1

tor only. Wt-HNF-1β also facilitated transcriptional activity, but the effects were significantly lower than those of wt-HNF-1α (Fig. 1). When wt-HNF-1α was co-transfected with wt-HNF-1β, the transactivation activity was decreased compared with wt-HNF-1α alone (Fig. 1).

Transactivation activity of mutant- HNF-1α and HNF-1β

The effects of 13 HNF-1α and 2 HNF-1β mutants on SI transcriptional activity were studied. Eleven HNF-1α mutants (R131W, K158N, R159Q, R200Q, R203C, R229X, V233L, R271G, R272H, P379fsdelCT, and T539fsdelC) showed significantly less activity than wt-HNF-1α (Fig. 2A). Two HNF-1β mutants (R177X, A263fsinsCG) had a repressive effect (Fig. 2B).

Interaction of wild/mutant- HNF-1α and HNF-1β

When each HNF-1α mutant was co-transfected with wt-HNF-1α, 5 HNF-1α mutants (R203C, R271G, R272H, P379fsdelCT, and T539fsdelC) showed significantly less transactivation activity than with either 1 μg wt-HNF-1α or 2 μg wt-HNF-1α (Fig. 3A). This suggests

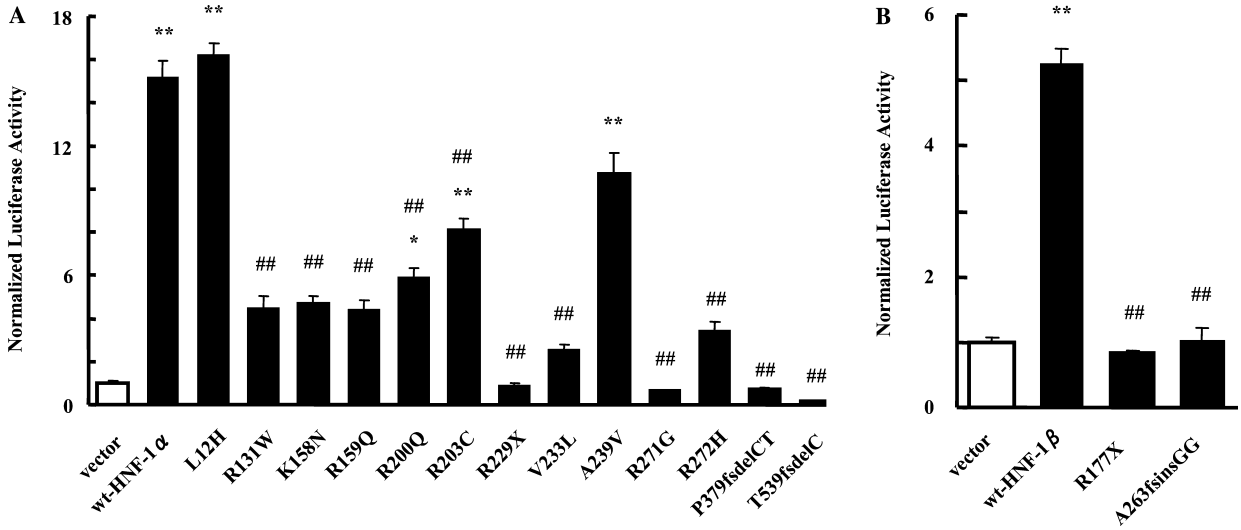

Fig. 2. Transactivation activity of wild and mutant of HNF-1α: HNF-1β. (A) Wild HNF-1α and each mutant HNF-1α were transfected with luciferase SI reporter gene in Caco-2 cells. (B) Wild and mutant HNF-1β were transfected in Caco-2 cells. The results were from more than three independent experiments. Bars represent mean ± SE. $^{*}P < 0.005$, $^{**}P < 0.0001$ vs. vector only; $^{\#\#}P < 0.0001$ vs. wt-HNF-1α (A) or wt-HNF-1β (B).

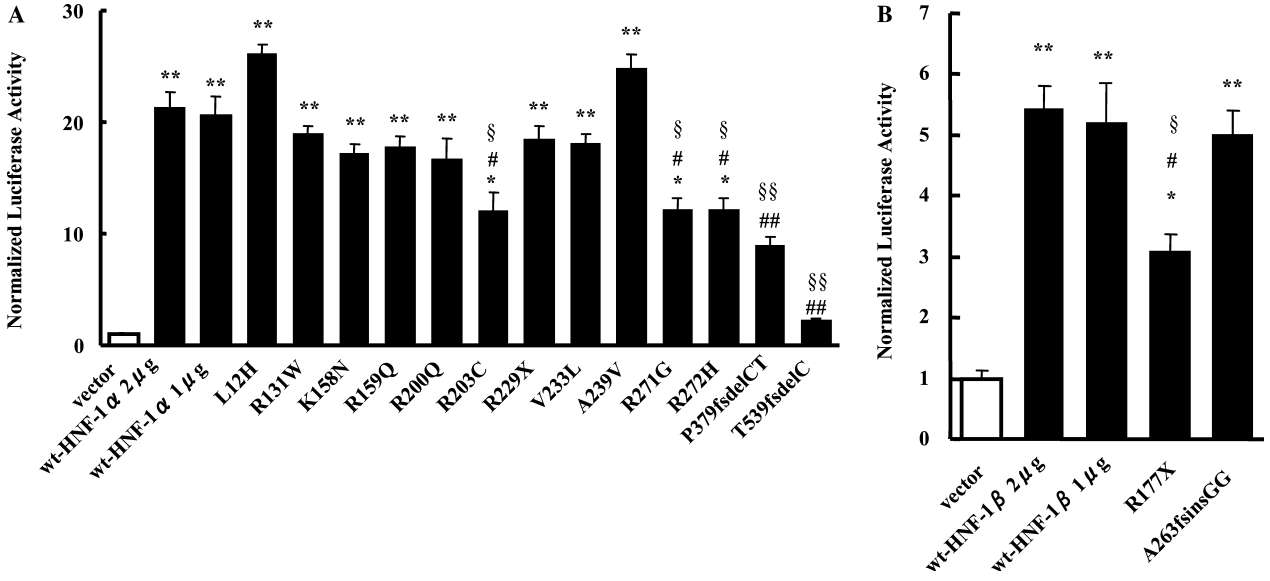

Fig. 3. Co-expression of wild and each mutant HNF-1α: HNF-1β. (A) SI reporter gene, wild HNF-1α, and each mutant HNF-1α were co-transfected in Caco-2 cells. (B) SI reporter gene, wild HNF-1β, and each mutant HNF-1β were co-transfected in Caco-2 cells. The results were from more than three independent experiments. Bars represent mean ± SE. $^{*}P < 0.05$, $^{**}P < 0.0001$ vs. vector only; $^{\#}P < 0.05$, $^{\#\#}P < 0.0001$ vs. HNF-1α 2 μg (A) or wt-HNF-1β 2 μg (B); and $^{\S}P < 0.05$, $^{\S\S}P < 0.0001$ vs. wt-HNF-1α 1 μg (A) or wt-HNF-1β (B).

that these mutants might have dominant-negative effects. We also studied the effect of HNF-1β mutants on wt-HNF-1β. R177X-HNF-1β showed significantly less activity than either 1 μg wt-HNF-1β or 2 μg wt-HNF-1β (Fig. 3B).

Study of the dominant-negative effect

To determine whether these HNF-1α mutants (R203C, R271G, R272H, P379fsdelCT, and T539fsdelC) act as a dominant-negative regulator, varied amounts (0–2 μg) of the mutant constructs were co-transfected with a constant amount of wild (0.5 μg) in Caco-2 cells. Co-transfected mutant dose-dependently reduced transactivation activity of wt-HNF-1α, suggesting that they function as a dominant-negative regulator (Fig. 4A). A239V-HNF-1α was used as a positive control, showing no dominant-negative effect. Transfection of R177X-HNF-β also dose-dependently reduced transactivation activity of wt-HNF-1β, whereas that of A263fsinsGG-HNF-1β led to results that were not significantly different from those for wt-HNF-1β (Fig. 4B).

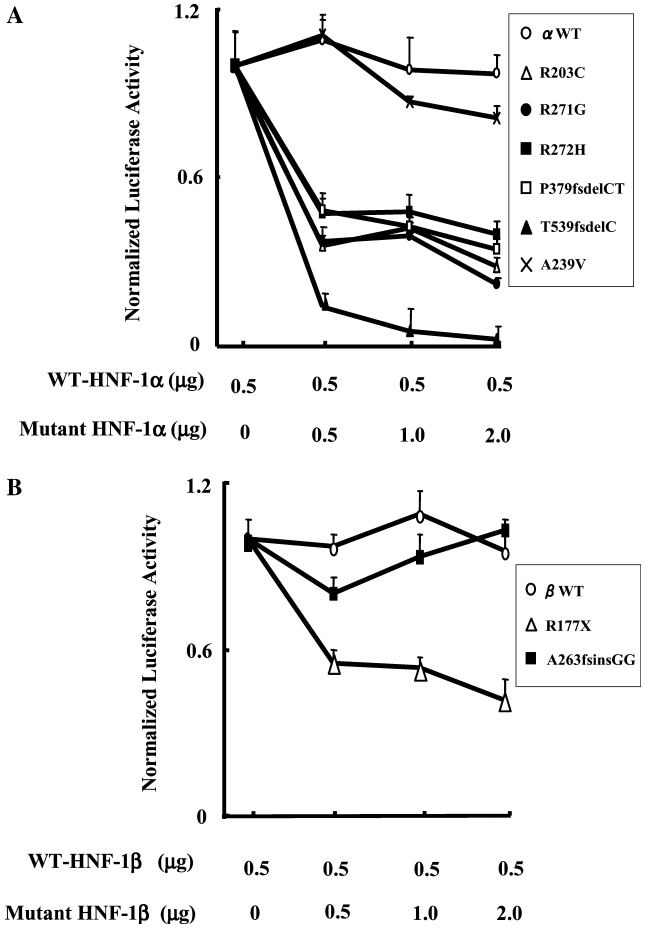

Fig. 4. Study of the dominant-negative effect of HNF-1α and HNF-1β. (A) 0.5 μg of wild HNF-1α was co-transfected with increasing amounts (0, 0.5, 1, and 2 μg) of mutant HNF-1α (R203C, A239V, R271G, R272H, P379fsdelCT, and T539fsdelC) in Caco-2 cells. The total amount of DNA was adjusted to 4.5 μg using empty vector. R203C, R271G, R272H, P379fsdelCT, and T539fsdelC had dose-dependently reduced activity ($P < 0.005$ vs. wt-HNF-1α 0.5 μg). (B) 0.5 μg of wild HNF-1β was co-transfected with increasing amounts (0, 0.5, 1, and 2 μg) of mutant HNF-1β (R177X and A263fsinsGG) in Caco-2 cells. The total amount of DNA was adjusted to 4.5 μg using empty vector. R177X-HNF-1β had dose-dependently reduced activity ($P < 0.05$ vs. wt-HNF-1β 0.5 μg). The results were from more than three independent experiments. Data are shown as means ± SE.

Interaction of wild-HNF-1α/mutant-HNF-1β or mutant-HNF-1α/wild-HNF-1β

When each HNF-1α mutant was co-transfected together with wt-HNF-1β in Caco-2 cells, 11 HNF-1α mutants (L12H, R131W, K158N, R159Q, R200Q, R203C, R229X, V233L, A239V, R271G, and R272H) had no significant changes compared with wt-HNF-1α + wt-HNF-1β. Interestingly, HNF-1α (P379fsdelCT and T539fsdelC) mutants were shown to reduce SI transcription significantly (Fig. 5). SI transcription, in which 2 HNF-1β mutants were co-transfected with wt-HNF-1α, was significantly greater than with wt-HNF-1α + wt-HNF-1β (Fig. 5).

Discussion

Mutations in HNF-1α and HNF-1β cause MODY3 and MODY5, respectively. HNF-1α and HNF-1β mutations have been reported to induce disorders of function, especially in pancreas and kidney [22–24]. HNF-1α and HNF-1β are also expressed in the small intestine and regulate SI transcription [4]. HNF-1α and HNF-1β proteins interact with two elements in the SI gene promoter, SIF2 and SIF3 [18]. HNF-1α transactivates SI transcription whereas HNF-1β has no activation effect [25]. Our results showed that both wt-HNF-1α and wt-HNF-1β transactivated SI gene transcription alone, but that the transactivation activity of wt-HNF-1α was impaired by co-expressed wt-HNF-1β (Fig. 1). Interestingly, in co-expressed mu-HNF-1β and wt-HNF-1α (Fig. 5), HNF-1β mutants lacked inhibitory effect on the transactivation activity of wt-HNF-1α compared with wt-HNF-1β. These results showed that the expression ratio of HNF-1α/HNF-1β might be important in modulating SI transcription.

In studies on the regulatory effect of mu-HNF-1α and mu-HNF-β, HNF-1α and HNF-1β mutants impaired SI transcription, except for L12H- and R239V-HNF-1α (Fig. 2). It has also been reported that L12H-HNF-1α does not reduce transcription activity when GLUT2 promoter is used [6]. R239V-HNF-1α function has not been described. Despite the fact that HNF-1α mutations are in the same gene, diverse effects have also been observed [26].

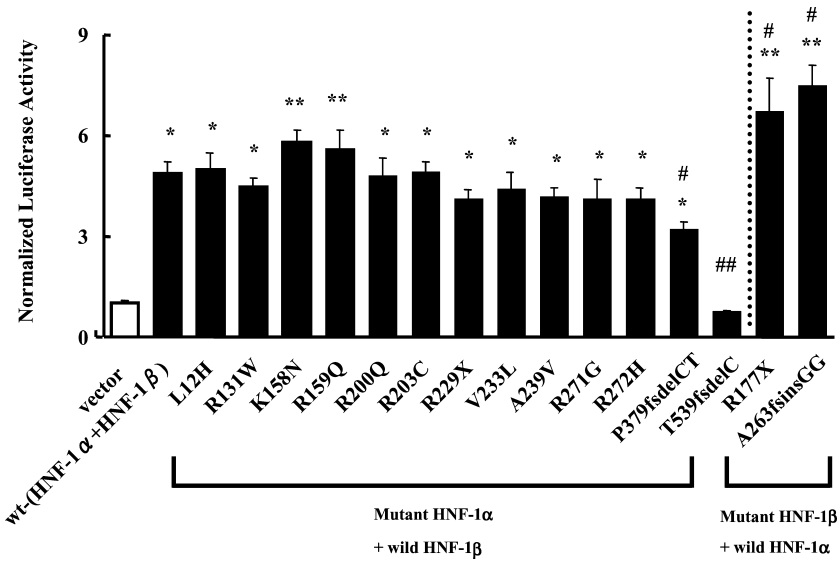

Fig. 5. Co-expression of wild HNF-1α/mutant HNF-1β: mutant HNF-1α/wild HNF-1β. Wild HNF-1β was co-transfected with each mutant HNF-1α, and wild HNF-1α was co-transfected with each mutant HNF-1β in Caco-2 cells. The results were from more than three independent experiments. Bars represent mean ± SE. $^{*}P < 0.05$, $^{**}P < 0.001$ vs. vector only; $^{\#}P < 0.05$, $^{\#\#}P < 0.0001$ vs. wt-HNF-1α + wt-HNF-1β.

MODY3 and MODY5 carry a heterozygous mutation [27]; we therefore estimated the SI transcription by co-expression with wt/mu-HNF-1α and wt/mu-HNF-1β. Five HNF-1α and 1 HNF-1β mutants significantly decreased SI transcription levels and showed dominant-negative effect (Figs. 3, and 4). Although these mutations are located in the DNA-binding or transactivation domain, they may form the homodimers with wt-HNF-1α or wt-HNF-1β and interfere with their normal functions. Although the dominant-negative effects of mutations found in this study are different from those in previous reports [5,6,28], they may have a promoter- and cell-specific transcriptional repressive effect.

Since HNF-1α and HNF-1β are expressed in the small intestine simultaneously, the co-expression studies of wt-HNF-1α/mu-HNF-1β or mu-HNF-1α/wt-HNF-1β were performed (Fig. 5). The results suggested that HNF-1β mutants lacked inhibitory effect on transactivation activity of wt-HNF-1α. However, except for P379fsdelCT and T539fsdelC, HNF-1α mutants failed to affect transactivation activity of wt-HNF-1β compared with wt-HNF-1α + wt-HNF-1β. It seems that HNF-1α mutations in the transactivation domain have significantly less transactivation activity than that in other domains. These data show that SI transcription tends to be unchanged or lower in MODY3, but higher in MODY5.

In general, abnormal increases in SI transcription level are observed in diabetic patients and animals [13–16]. However, there are no reports of SI transcription in MODY3 and MODY5 patients. In this study, though SI transcription might tend to be lower or unchanged in MODY3, it is not clear that SI transcription in MODY3 patients is different from that in other types of diabetic patients. Furthermore, Takenoshita et al. [29] have reported that insulin has a suppressive effect on the synthesis of SI complex. It is surmised that insulin deficiency in MODY3 might stimulate SI transcription. Nearly all MODY3 and MODY5 patients have been diagnosed after adolescence, because of the much greater insulin requirement. Abnormal SI activity may affect absorption of carbohydrate from the small intestine, which would change the quantity of insulin required.

We first investigated changes in SI transcription levels by simulating the small intestine in cases of MODY3 and MODY5. Molecular mechanisms by which mu-HNF-1α and mu-HNF-1β influence SI transcription in MODY3 and MODY5 are rather complex, due to the synergistic effects of insulin [29] and several transcription factors [17]. Further detailed study is currently in progress.

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References

[1] D.B. Mendel, L.P. Hansen, M.K. Graves, P.K. Conley, G.R. Crabtree, HNF-1α and HNF-1β (vHNF-1) share dimerization and homeodomains, but not activation domains, and form heterodimers in vitro, Genes Dev. 5 (1991) 1042–1056.

[2] R. Menzel, P.J. Kaisaki, I. Rjasanowski, P. Heinke, W. Kerner, S. Menzel, A low renal threshold for glucose in diabetic patients

with a mutation in the hepatocyte nuclear factor-1 alpha (HNF-1α) gene, Diabet. Med. 15 (1998) 816–820.
[3] D.B. Mendel, G.R. Crabtree, HNF-1, a member of a novel class of dimerizing homeodomain proteins, J. Biol. Chem. 266 (1991) 677–680.
[4] J. Rey-campos, T. Chouard, M. Yaniv, S. Cereghini, vHNF-1 is a homeoprotein that activates transcription and forms heterodimers with HNF1, EMBO J. 10 (1991) 1445–1457.
[5] Q. Yang, K. Yamagata, K. Yamamoto, J. Miyagawa, J. Taketa, N. Iwasaki, H. Iwasaki, I. Yoshiuchi, M. Namba, L. Miyazaki, T. Hanafusa, Y. Matuzawa, Structure/function studies of hepatocyte nuclear factor-1α, a diabetes-associated transcription factor, Biochem. Biophys. Res. Commun. 266 (1999) 192–202.
[6] S. Yamada, H. Tomura, H. Nishigori, K. Sho, H. Mabe, N. Iwatani, T. Takumi, Y. Kito, N. Moriya, K. Muroya, T. Ogata, K. Onigata, A. Morikawa, I. Inoue, J. Taketa, Identification of mutations in the hepatocyte nuclear factor-1α gene in Japanese subjects with early onset NIDDM and functional analysis of the mutant proteins, Diabetes 48 (1999) 645–648.
[7] S. Kitanaka, Y. Miki, Y. Hayashi, T. Igarashi, Promoter-specific respression of hepatocyte nuclear factor (HNF)-1β and HNF-1α transcriptional activity by an HNF-1β missense mutant associated with type 5 maturity-onset diabetes of the young with hepatic and biliary manifestations, J. Clin. Endo. Metab. 89 (2004) 1369–1378.
[8] E.R. Pearson, B.J. Starkey, R.J. Powell, F.M. Gribble, P.M. Clark, A.T. Hattersley, Genetic cause of hyperglycemia and response to treatment in diabetes, Lancet 362 (2003) 1275–1281.
[9] K. Owen, A.T. Hattersley, Maturity-onset diabetes of the young: from clinical description to molecular genetic characterization, Best Pract. Res. Clin. Endo. Metab. 15 (2001) 309–323.
[10] L.A. Emens, D.W. Landers, L.G. Moss, Hepatocyte nuclear factor 1alpha is expressed in a hamster insulinoma line and transactivates the rat insulin 1 gene, Proc. Natl. Acad. Sci. USA 89 (1992) 7300–7304.
[11] L. Miquerol, S. Lopez, N. Cartier, M. Tulliez, M. Raymondjean, A. Kahn, Expression of the L-type pyruvate kinase gene and the hepatocyte nuclear factor 4 transcription factor in exocrine and endocrine pancreas, J. Biol. Chem. 269 (1994) 8944–8951.
[12] E.R. Pearson, S. Ellard, M.K. Badman, C. Bingham, C.R. Lockwood, A.T. Hattersley, P.M. Clark, Contrasting diabetes phenotypes associated with hepatocyte nuclear factor-1α and -1β mutations, Diabetes Care 5 (2004) 1102–1107.
[13] R.K. Tandon, L.M. Srivastava, S.C. Pandey, Increased disaccharidase activity in human diabetic, Am. J. Clin. Nutr. 28 (1975) 621–625.
[14] J. Dyer, I.S. Wood, A. Palejwala, A. Ellis, S.P. Shirazi-Beechey, Expression of monosaccharide transporters in intestine of diabetic humans, Am. J. Physiol. 282 (2002) G241–G248.
[15] T. Adachi, C. Mori, K. Sakurai, N. Shihara, K. Tsuda, K. Yasuda, Morphological changes and increased sucrase and isomaltase activity in small intestines of insulin-deficient and type 2 diabetic rats, Endocr. J. 50 (2003) 271–279.
[16] T. Adachi, M. Takenoshita, H. Katsura, K. Yasuda, K. Tsuda, Y. Seino, T. Enomoto, R. Yamaji, K. Miyatake, H. Inui, Y. Nakano, Disordered expression of the sucrase–isomaltase complex in the small intestine in Otuka Long–Evans Tokushima Fatty rats, a model of non-insulin-dependent diabetes mellitus with insulin resistance, Biochem. Biophys. Acta 1426 (1999) 126–132.
[17] F. Boudreau, E.H.H.M. Rings, H.M. Wering, R.K. Kim, G.P. Swain, S.D. Krasinski, J. Moffett, R.J. Grand, E.R. Suh, P.G. Traber, Hepatocyte nuclear factor-1α, GATA-4, and caudal related homeodomain protein Cdx2 interact functionally to modulate intestinal gene transcription, J. Biol. Chem. 277 (2002) 31909–31917.
[18] G.D. Wu, L. Chen, K. Forslund, P.G. Traber, Hepatocyte nuclear factor-1α (HNF-1α) and HNF-1β regulate transcription via two elements in an intestine-specific promoter, J. Biol. Chem. 269 (1994) 17080–17085.
[19] M. Pinto, M.D. Appay, P. Simon-Assmann, G. Chevalier, N. Dracopoli, J. Fogh, A. Zweibaum, Enterocytic differentiation of cultured human colon cancer cells by replacement of glucose by galactose in the medium, Biol. Cell 44 (1982) 193–196.
[20] A. Zweibuam, M. Pinto, G. Chevalier, E. Dussaulx, N. Triadou, B. Lacroix, K. Haffen, J.L. Brun, M. Rousset, Enterocytic differentiation of a subpopulation of human tumor cell line HT-29 selected for growth in sugar-free medium and its inhibition by glucose, J. Cell. Physiol. 122 (1985) 21–29.
[21] M. Pinto, L.S. Robine, M.D. Appay, M. Kedinger, N. Triadou, E. Dussaulx, B. Lacroix, P. Simon-Assmann, K. Haffen, J. Fogh, A. Zweibaum, Enterocyte-like differentiation and polarization of the human colon carcinoma cell line Caco2 in culture, Biol. Cell 47 (1983) 323–330.
[22] M. Pontoglio, S. Sreenan, M. Roe, W. Pugh, D. Ostrega, A. Doyen, A.J. Pick, A. Baldwin, G. Velho, P. Froguel, M. Levisetti, S. Bonner-Weir, G.I. Bell, M. Yaniv, K.S. Polonsky, Defective insulin secretion in hepatocyte nuclear factor 1α-deficient mice, J. Clin. Invest. 101 (1998) 2215–2222.
[23] L.D. Dukes, S. Sreenan, M.W. Roe, M. Levisetti, Y.P. Zhou, D. Ostrega, G.I. Bell, M. Pontoglio, M. Yaniv, L. Philipson, K.S. Polonsky, Defective pancreatic β-cell glycolytic signaling in hepatocyte nuclear factor-1α-deficient mice, J. Biol. Chem. 273 (1998) 24457–24464.
[24] L. Gresh, E. Fischer, A. Reimann, M. Tanguy, S. Garbay, X.L. Shao, T. Hiesberger, L. Fiette, P. Lgarashi, M. Yaniv, M. Pontoglio, A transcriptional network in polycystic kidney disease, EMBO J. 23 (2004) 1657–1668.
[25] P.G. Traber, D.G. Silberg, Intestine-specific gene transcription, Annu. Rev. Physiol. 58 (1996) 275–297.
[26] K. Okita, Q. Yang, K. Yamagata, K.A. Hangenfelt, J. Miyagawa, Y. Kajimoto, H. Nakajima, M. Namba, C.B. Wollheim, T. Hanafusa, Y. Matuzawa, Human insulin gene is a target gene of hepatocyte nuclear factor-1α (HNF-1α) and HNF-1β, Biochem. Biophys. Res. Commun. 263 (1999) 566–569.
[27] G.U. Ryffel, Mutations in the human genes encoding the transcription factor of the hepatocyte nuclear factor (HNF)1 and HNF4 families: functional and pathological consequences, J. Mol. Endocrinol. 27 (2001) 11–29.
[28] H. Tomura, H. Nishigori, K. Sho, K. Yamagata, I. Inoue, J. Taketa, Loss-of-function and dominant-negative mechanisms associated with hepatocyte nuclear factor-1β mutations in familial type 2 diabetes mellitus, J. Biol. Chem. 274 (1999) 12975–12978.
[29] M. Takenoshita, R. Yamaji, H. Inui, K. Miyatake, Y. Nakano, Suppressive effect of insulin on the synthesis of sucrase–isomaltase complex in small intestinal epithelial cells, and abnormal increase in the complex under diabetic conditions, Biochem. J. 329 (1998) 597–600.