

Discovery of DiPeptidyl Peptidase-4 Gene Variants and the Associations with Efficacy of Vildagliptin in Patients with Type 2 Diabetes - A Pilot Study

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Abstract

Background: The dipeptidyl peptidase-4 (DPP4) inhibitors have become widely used antidiabetic medication. They control glycemia by interacting with serum DPP4 to interfere catalyzation of incretins. The aim of this pilot study was to discover the DPP4 polymorphisms that could affect the efficacy of vildagliptin, a DPP-4 inhibitor in diabetic patients.

Methods: Genetic variations in DPP4 were identified in 48 patients with type 2 diabetes who received vildagliptin treatment at least 12 weeks following metformin monotherapy. Luciferase assay was performed to estimate the effect of the regulatory single nucleotide polymorphism (SNP) on expression of DPP4.

Results: Eight tagging SNPs were genotyped in a sample of 24 patients. Additional sample of 24 patients was used to discover further regulatory SNPs and coding SNPs. In all 48 patients, responders (degree of HbA1c and/or fasting glucose level decrease greater than 10% of baseline after 12 weeks of vildagliptin add-on treatment) did not show any significant difference in selected six DPP4 polymorphisms from non-responders. DPP4 expression was not different according to g.-234A/C in luciferase assay.

Conclusion: Our pilot study could not find any significant genetic variant which is associated with vildagliptin response in patients with type 2 diabetes. Further studies in large population are warranted.

Keywords: Dipeptidyl Peptidase-4; Single nucleotide polymorphism; Vildagliptin

Introduction

Diabetes mellitus is growing global pandemic [1], causing micro- and macrovascular complications [2]. Compared with type 1 diabetes due to an absolute deficiency of insulin secretion, type 2 diabetes, a much more prevalent category, is due to combination of resistance to insulin action and an inadequate compensatory insulin secretory response [3]. Metformin is the preferred initial pharmacological agent for type 2 diabetes, and if metformin monotherapy at maximal tolerated dose does not achieve or maintain the hemoglobin A1c (HbA1c) target over 3–6 months, a second agent is needed to control glycemia. Among the option of add-on therapy is dipeptidyl peptidase-4 (DPP4) inhibitor [4,5]. DPP4 inhibitors have few side effects, and their prescriptions have been increasing [6].

Oral glucose intake induces glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which are insulinotropic depending on glucose level. DPP4 deactivates bioactive peptides, including GLP-1 and GIP. DPP4 inhibitors bind to this DPP4 and control glycemic surge after meal by enhancing the action of GLP-1 and GIP, consequently [7]. Therefore, the efficacy of DPP4 inhibitors might be affected if the expression level of DPP4 is changed or if the altered structure of DPP4 affects the affinity with DPP4 inhibitors. However, there has been no study which analyzed the association between DPP4 polymorphism with the efficacy of DPP4 inhibitors discovered so far. Given these points, we discovered DPP4 single nucleotide polymorphisms (SNPs) in Korean population and searched

for polymorphisms that affect the efficacy of vildagliptin, a member of DPP4 inhibitor group.

Materials and Methods

Subjects

A total of 48 patients with type 2 diabetes mellitus were recruited from the outpatient clinics at Yonsei University Severance Hospital Diabetes Center, Seoul, Korea. For this study, type 2 diabetes mellitus was defined according to the American Diabetes Association criteria [3]. Patients who had received metformin monotherapy and whose HbA1c values ranged from 6% to 8% were enrolled. All patients were treated with vildagliptin for at least 12 weeks as add-on therapy following metformin monotherapy. All enrolled patients took 50 mg vildagliptin daily (as a q.d. dose) or 100 mg vildagliptin daily (as equally divided doses). The inclusion criteria were as follows: (1) age 20 to 90

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years, (2) no previous history of DPP4 inhibitor use, (3) no medication change in the last 3 months, and (4) for women, postmenopause or use of appropriate contraceptive methods. Patients with type 1 diabetes, a history of ketoacidosis, ischemic heart disease, or congestive heart failure (New York Heart Association class II-IV), and pregnant or lactating women were excluded from this study. Response to vildagliptin add-on treatment was defined by modification of criteria suggested by Blüher et al. [8]. Responders were defined as a greater than 10% decrease in HbA1c values or fasting plasma glucose (FPG) levels (or both) after 12 weeks of vildagliptin treatment. Non-responders were defined as those patients who did not meet these criteria. This pilot study protocol was approved by the Institutional Review Board of Yonsei University College of Medicine, Seoul, Korea (4-2011-0912), and all subjects provided written informed consent.

Study assessments

FPG, 2-hour postprandial plasma glucose (PPG), and HbA1c were assessed initially and during two additional visits, at weeks 12 and 24 of treatment. Body mass index (BMI), standard biochemistry laboratory profile and fasting plasma insulin level before initial administration of vildagliptin were collected. Initial homeostatic model assessment of insulin resistance (HOMA-IR) and homeostatic model assessment of beta-cell function (HOMA-B) were calculated. Genomic DNA was isolated from peripheral blood lymphocytes.

Gene scanning

Gene scanning was performed to discover DPP4 polymorphisms prevalent in the Korean diabetes population. For initial discovery, 24 diabetic patients were recruited. A promoter region -2.6 kb from the translation initiation site, the entire coding exons, and flanking intronic sequences of the DPP4 gene were amplified in 28 polymerase chain reaction (PCR) fragments and sequenced by an automated genetic analyzer (Model 3730xl, Applied Biosystems, Foster City, CA). Haplotype analysis was performed using the Haploview 4.1 program based on a standard expectation-maximization algorithm to construct haplotype blocks. For further discovery of regulatory SNPs (rSNPs) and coding SNPs (cSNPs), 24 additional diabetic patients were recruited. DPP4 gene was amplified in 9 PCR fragments and sequenced targeting rSNPs and 17 non-synonymous SNPs (nsSNPs) that were predicted as possible impact on the structure and function of DPP4 protein by Polyphen-2 [9] and/or SIFT [10].

Measurements of DPP4 promoter activity *in vitro*

To construct the reporter plasmids containing human DPP4 promoter region, a 477-bp fragment of human DPP4 (-507 to -31 relative to the translation initiation site) was amplified with DNA samples from homozygotes with DPP4 g.-234C or g.-234A. Manufacture of this fragment was modified from the construct which had showed the most luciferase activity in previous study by Böhm et al. [11]. The amplified products were inserted into pGL3-bas luciferase reporter vectors (Promega Corporation, Madison, WI) using restriction enzyme sites and DNA sequences were confirmed by dideoxynucleotide-based sequencing.

Caco-2 cells originated from human colorectal adenocarcinoma were cultured in Dulbecco's modified Eagle's medium formulated with 4500 mg/L glucose, supplemented with 20% fetal bovine serum, 100 U/mL penicillin G, and 100 mg/mL streptomycin. The pGL3-bas luciferase plasmids containing DPP4 promoters and control *Renilla* luciferase vectors were co-transfected into Caco-2 cells using jetPRIME (Polyplus transfection, Illkirch, France). Luciferase assays were performed using

Dual-Luciferase Reporter Assay System (Promega) according to the manufacturer's instructions. Light emission was measured using a microplate luminometer (Berthold Technologies, Wildbad, Germany).

In silico identification of putative transcription factor binding sites in DPP4 promoter sequences

To identify putative transcription factor binding site in DPP4 promoter sequences, the DPP4 sequences around g.-234 site were analyzed using two different transcription factor binding site prediction programs, PROMO 3.0.2 [12] and MatInspector from Genomatix Software Suite [13].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20 (IBM Corp. Armonk, NY) and Graphpad Prism 5.0 (Graphpad Software, Inc., San Diego, CA) software packages. Differences between responder and non-responder groups were tested by use of chi-square tests or *t*-tests for categorical and continuous variables, respectively. Genotype/allele frequency comparisons between responder and non-responder groups were performed by chi-square tests. Fisher's exact test was used if expected cell frequencies were lower than 5. Multivariate logistic regression was performed to evaluate the major determinants of vildagliptin response. Genotype frequencies at each SNP were tested for Hardy-Weinberg equilibrium. All *P* values were based on two-sided comparisons and *P* values less than 0.05 were considered statistically significant.

Results

The baseline characteristics of the 35 responder and 13 non-responder subjects are presented in Table 1. There were no statistical differences in baseline characteristics between the two groups, including FPG, 2-hour PPG, and HbA1c. After 3 months of add-on therapy, the degree of HbA1c and/or FPG level decrease was significantly greater in the responder group than in the non-responder group (*P*<0.001, respectively). After 6 months of add-on therapy, HbA1c was still maintained significantly lower in responder group (*P*<0.001).

To discover DPP4 polymorphisms, dideoxynucleotide-based DNA sequencing was performed using samples derived from twenty-four type 2 diabetic patients. A total of 14 genetic variations were discovered after comprehensive gene scanning, covering all exons, exon-intron junctions and a promoter region up to 2.6 kb from the translation initiation site. No nsSNP was discovered in enrolled patients. The linkage-disequilibrium (LD) structure of the DPP4 gene is shown in Figure 1. Of the 14 variations, two with an allele frequency less than 5% were excluded from further analyses. Finally, eight tagging SNPs were selected for DPP4 genotyping as detailed in Materials and Methods.

To discover SNPs affecting the efficacy of vildagliptin, 24 additional diabetic patients were recruited. Targeted SNPs were rSNPs within 500 base pairs from starting codon and 17 nsSNPs predicted as possible impact on the structure and function of DPP4 protein. Synonymous SNP (sSNP) G645G (rs17848910), rSNP g.-234A/C (rs13015258) and other intervening sequences (IVSs) were discovered in this step. No nsSNP was discovered. To evaluate whether DPP4 genetic variations are associated with glucose-lowering effect of vildagliptin, a case-control association analysis was performed using genotype data on the 6 SNPs, including G645G and g.-234A/C. (Table 2). The genotype distributions of all SNPs were in accordance with Hardy-Weinberg equilibrium (*P*>0.05) in each set of samples. Of the six SNPs tested, there was no SNP strongly associated with efficacy of vildagliptin.

Multivariate logistic regression analyses were performed to define the major determinants for vildagliptin treatment response and to reveal other parameters influencing the response rate. No SNPs were found to be a major determinant of response rate (Table 3). Multiple logistic regression analyses revealed that baseline HbA1c was the major confounding factor of therapeutic response to vildagliptin.

To measure the promoter activity of DPP4 according to rSNP g.-234A/C, reporter constructs containing the rSNP were constructed and their transcriptional activities were measured in Caco-2 cells. The transcriptional activities of major allele and minor C allele showed no significant difference (Figure 2).

Discussion

In this study, we examined the effects of the polymorphisms of the DPP4 gene on the response to vildagliptin in Korean patients with type 2 diabetes mellitus. The results of this pilot study do not support the notion that DPP4 polymorphisms modulate the efficacy of DPP4

inhibitors among diabetic patients. In the first screening of DPP4 polymorphisms from 24 diabetic patients, we failed to discover nsSNPs that may possibly impact the structure and function of DPP4 protein in Korean population. There was no nsSNP found in the second set of samples from other 24 diabetic patients, either. Only sSNP G645G showed a modest P value of 0.175 in multivariate logistic regression of response to vildagliptin add-on therapy, which leaves room for possibility of association with increased number of subjects enrolled. Instead, the multiple logistic regression tests revealed that baseline HbA1c was the major confounding factor of therapeutic response to vildagliptin add-on: in other words, the efficacy of vildagliptin add-on is less to relatively well-controlled diabetic patients.

Regulatory SNP g.-234A/C discovered in this study did not influence the efficacy of vildagliptin in clinical data and *in vitro* study. To identify potential transcriptional elements that might be involved in regulating the transcriptional activity of DPP4 *in silico*, sequences around g.-234A/C were analyzed using two different transcription

Characteristic	Responder		Non-responder		P value
No. of subjects	35	(72.9)	13	(27.1)	
Male	15	(42.9)	6	(46.2)	0.838
Age (year)	60.4	(12.4)	57.4	(10.1)	0.441
Body mass index (kg/m ²)	25.01	(3.72)	26.24	(3.56)	0.344
Duration of diabetes (year)	7.54	(5.17)	8.85	(4.96)	0.437
Baseline					
FPG (mmol/L)	6.79	(1.05)	6.80	(0.79)	0.980
2-hour PPG (mmol/L)	10.73	(2.84)	11.03	(2.04)	0.737
HbA1c (%)	7.25	(0.40)	7.00	(0.42)	0.059
Fasting plasma insulin (pmol/L)	90.42	(79.03)	48.27	(17.15)	0.214
Blood urea nitrogen (mmol/L)	5.22	(1.25)	4.97	(1.66)	0.568
Creatinine (μmol/L)	72.49	(13.26)	81.33	(15.91)	0.065
eGFR (mL/min/1.73m ²)	89.94	(15.27)	82.50	(15.93)	0.156
Aspartate aminotransferase (IU/L)	20.34	(10.87)	22.62	(7.47)	0.492
Alanine aminotransferase (IU/L)	24.00	(18.69)	24.85	(12.32)	0.881
Total cholesterol (mmol/L)	4.47	(0.76)	4.51	(0.89)	0.902
HDL cholesterol (mmol/L)	1.23	(0.27)	1.21	(0.26)	0.819
LDL cholesterol (mmol/L)	2.59	(0.68)	2.51	(0.82)	0.759
Triglyceride (mmol/L)	1.41	(0.59)	1.78	(0.50)	0.056
HOMA-B	105.52	(141.48)	46.77	(23.61)	0.329
HOMA-IR	3.60	(2.70)	2.06	(0.66)	0.185
Dose of daily metformin (mg)	945.71	(392.65)	976.92	(454.89)	0.816
Dose of daily vildagliptin (mg)	87.14	(22.17)	84.62	(24.02)	0.733
3 month after Vildagliptin administration					
FPG (mmol/L)	6.06	(1.00)	7.42	(1.29)	<0.001
ΔFPG (mmol/L)	-0.73	(0.92)	0.62	(1.13)	<0.001
2-hour PPG (mmol/L)	8.34	(2.28)	10.08	(2.81)	0.035
Δ2-hour PPG (mmol/L)	-2.43	(2.89)	-1.40	(1.40)	0.117
HbA1c (%)	6.26	(0.44)	6.87	(0.59)	<0.001
ΔHbA1c (%)	-0.99	(0.32)	-0.13	(0.51)	<0.001
6 month after Vildagliptin administration					
FPG (mmol/L)	6.24	(1.00)	6.89	(1.29)	0.098
ΔFPG (mmol/L)	-0.59	(0.90)	0.10	(0.81)	0.024
2-hour PPG (mmol/L)	8.66	(2.28)	10.63	(2.81)	0.024
Δ2-hour PPG (mmol/L)	-2.07	(2.65)	-0.39	(2.71)	0.074
HbA1c (%)	6.28	(0.32)	6.80	(0.68)	0.003
ΔHbA1c (%)	-0.97	(0.42)	-0.20	(0.41)	<0.001

Results expressed as n (%) or mean values (SD). Chi-square test or t-test was used for P value where appropriate. Δ means the difference from baseline level. Abbreviations: FPG: Fasting Plasma Glucose; PPG: Postprandial Plasma Glucose; eGFR: Estimated Glomerular Filtration Rate; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; HOMA-B: Homeostatic Model Assessment of Beta Cell Function; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

Table 1: Characteristics of the 48 subjects according to response to vildagliptin add-on therapy.

		Group n (%)					Group n (%)				
SNP	Genotype	Responder		Non-responder		Allele	Responder		Non-responder		P value
g.-234A/C	A/A	16	(45.7)	8	(61.5)	A	50	(71.4)	20	(76.9)	0.590
(rs13015258)	A/C	18	(51.4)	4	(30.8)	C	20	(28.6)	6	(23.1)	
	C/C	1	(2.9)	1	(7.7)						
IVS8-128A/G	G/G	31	(88.6)	11	(84.6)	G	66	(94.3)	24	(92.3)	0.661
(rs17848920)	G/A	4	(11.4)	2	(15.4)	A	4	(5.7)	2	(7.7)	
IVS8+46C/T	C/C	18	(51.4)	5	(38.5)	C	51	(72.9)	17	(65.4)	0.474
(rs10930040)	C/T	15	(42.9)	7	(53.8)	T	19	(27.1)	9	(34.6)	
	T/T	2	(5.7)	1	(7.7)						
IVS11-143A/G*	G/G	20	(57.1)	5	(38.5)	G	51	(72.9)	17	(65.4)	0.474
(rs2302873)	G/A	11	(31.4)	7	(53.8)	A	19	(27.1)	9	(34.6)	
	A/A	4	(11.4)	1	(7.7)						
G645G	C/C	25	(73.5)	12	(92.3)	C	59	(86.8)	25	(96.2)	0.275
(rs17848910)	C/T	9	(26.5)	1	(7.7)	T	9	(13.1)	1	(3.8)	
IVS22+4C/T	T/T	31	(91.2)	10	(76.9)	T	65	(95.6)	23	(88.5)	0.342
(rs2268891)	T/C	3	(8.8)	3	(23.1)	C	3	(4.4)	3	(11.5)	

Nucleotide location number of SNP was assigned according to the DPP4 mRNA sequence (GenBank accession number: NM_001935.3). In comparison between alleles, P values were obtained by using Chi-square test or Fisher's exact test (expected cell value < 5). Abbreviations: IVS: Intervening Sequence; SNP: Single Nucleotide Polymorphism. * Linkage with rs10930040

Table 2: Frequency of DPP4 genetic variations in diabetic patients according to response to vildagliptin add-on therapy.

A. g.-234A/C genotype of DPP4

Variable	OR	(95% CI)	P value
Gender (0=male, 1=female)	0.87	(0.264-2.871)	0.821
Age	0.97	(0.925-1.018)	0.215
Body mass index	1.05	(0.894-1.233)	0.551
Duration of diabetes	1.06	(0.930-1.206)	0.389
HbA1c	0.05	(0.008-0.273)	<0.001
g.-234A/C allele (0=A, 1=C)	0.52	(0.145-1.900)	0.326

B. G645G genotype of DPP4

Variable	OR	(95% CI)	P value
Gender (0=male, 1=female)	0.78	(0.223-2.717)	0.694
Age	0.97	(0.927-1.021)	0.267
Body mass index	1.05	(0.887-1.240)	0.575
Duration of diabetes	1.06	(0.928-1.216)	0.382
HbA1c	0.04	(0.007-0.243)	<0.001
G645G allele (0=C, 1=T)	0.19	(0.017-2.110)	0.175

OR: Odds Ratio; CI: Confidence Interval

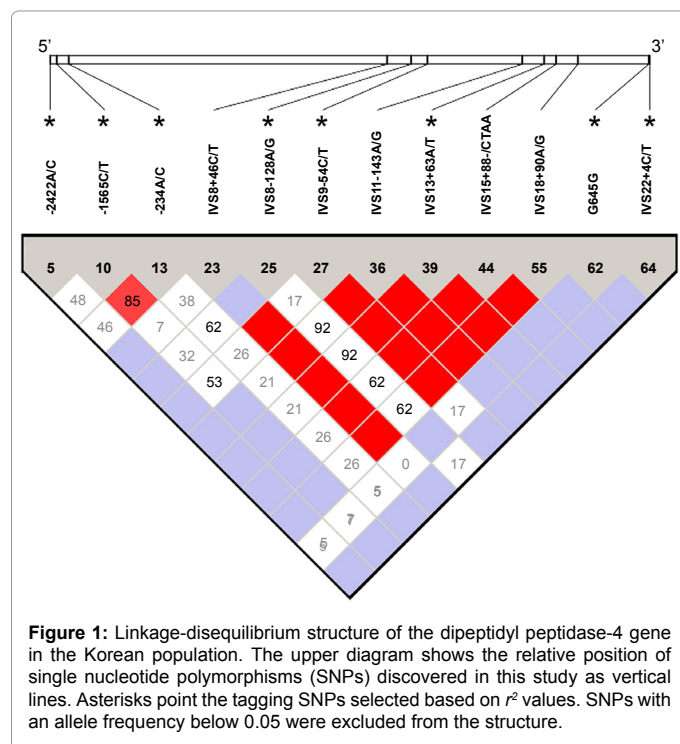
Table 3: Multivariate logistic regression analyses for influence of clinical and biochemical factors on response to vildagliptin treatment.

factor binding site prediction programs (Supplement File). The results showed some different putative transcriptional elements between genotypes for dissimilarity percentage and random expectation (RE; the lower dissimilarity and/or RE value, the more reliable the hit), which might be false positive (Table 1) [14]. Other methods including electrophoretic mobility shift assay (EMSA) and correlation with DPP4 concentration in blood sample can help to discriminate potential binding of transcriptional elements.

DPP4 is the key enzyme responsible for cleaving and inactivating both GLP-1 and GIP at the penultimate alanine residue [15]. To inhibit this inactivation, two drug classes based on their structure have been developed as DPP4 inhibitors: peptidomimetics that mimic the DPP4 molecule (ex. vildagliptin and saxagliptin) and non-peptidomimetics (ex. sitagliptin and linagliptin). When peptidomimetics bind to DPP4, they dissociate slowly resulting in persistent inhibition of DPP4

even after inactivation, although they are cleared from the plasma relatively quickly. In contrast, non-peptidomimetics form non-covalent interactions with residues in the catalytic site, which result in immediate and potent inhibition [16]. In these contexts, DPP4 nsSNPs that have impact on the structure and function of DPP4 protein may exert greater effect on the efficacy of sitagliptin or linagliptin compared to vildagliptin or saxagliptin because of its influence on the binding affinity. Moreover, the effect on the expression level of DPP4 protein according to DPP4 rSNPs might be different between the two classes of DPP4 inhibitors. These points leave room for further pharmacogenetic study of DPP4 inhibitors.

Our group has studied pharmacogenetics of glucose-lowering drugs, including the effect of polymorphism of adiponectin, peroxisome proliferator-activated receptor gamma2 (PPARγ2), and lipin 1 genes on the efficacy of rosiglitazone [17-19], and effect of



methylation rate of DPP4 gene DNA of visceral adipose tissue (VAT) from severe obesity patients to be different between the genotypes for three DPP4 polymorphisms in 2011 [23], including the SNP associated with hyperglycemia/diabetes in the first stage of previous study. DPP4 polymorphisms were also studied for association with diseases other than metabolic disorders including periodontitis and major depressive disorders [24,25]. Rs 6741949 was shown to be associated with reduction in hippocampal volume, which is accelerated by Alzheimer's disease and vascular risk factors [26].

The major limitation of this study is the low number of enrolled subjects due to the nature of this research as a pilot study. The discovery in this study does not include normal healthy control data, which makes impossible to compare DPP4 polymorphisms of diabetic patients with that of healthy control. These points leave room for further pharmacogenetic study of DPP4 polymorphism in Korean population.

Conclusion

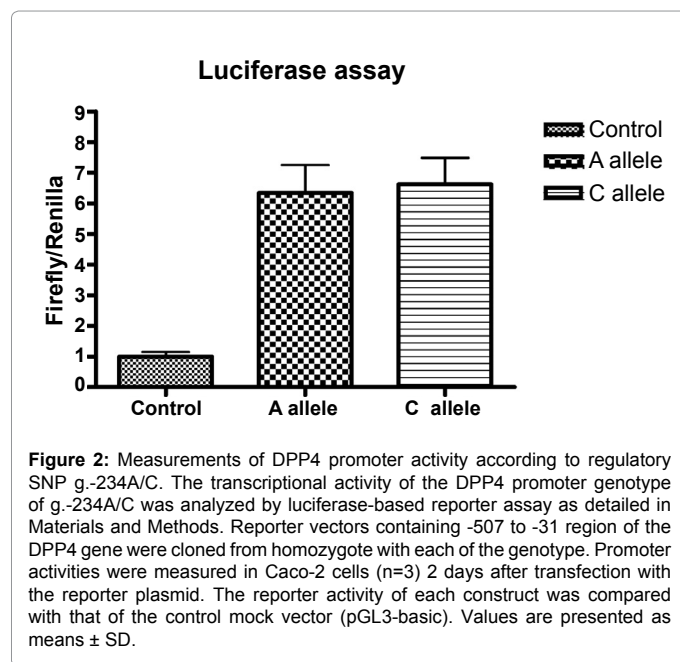
The current study analyzed the genotype of DPP4 gene in Korean diabetic populations. Our results do not support the notion that DPP4 polymorphisms are related with the glucose-lowering effect of vildagliptin. Further investigations with higher number of samples and comprehensive analysis are needed to reveal hidden associations between DPP4 polymorphisms and efficacy of DPP4 inhibitors/GLP-1 analogues in diabetic patients.

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polymorphism of perilipin gene on the side effects of rosiglitazone [20]. For the associations between DPP4 polymorphisms and metabolic diseases, several studies had been published. Aghili et al. [21] revealed that rs3788979 is associated with the risk of myocardial infarction in patients with atherosclerosis. Bouchard et al. [22] analyzed the association between DPP4 polymorphisms and cardiovascular disease risk factors from over a thousand samples in multi-stage study in 2009. Although 3 SNPs were associated with hyperglycemia/diabetes or high plasma triglyceride levels in the first stage, those associations failed to be replicated in stage 2. This study group, however, revealed the

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