

Original Article

Genetic variations in dipeptidyl peptidase 4 gene have a synergetic effect with body mass index on the risk of coronary artery disease in a Chinese Han population with type 2 diabetes

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Received March 1, 2017; Accepted August 12, 2017; Epub October 15, 2017; Published October 30, 2017

Abstract: Objective: Dipeptidyl peptidase 4 (DPP4) not only plays an important role in pancreatic beta cell regulation, but also shows possible protective functions in cardiovascular system. The study aimed to determine whether genetic variations in DPP4 were related to the susceptibility of coronary artery disease (CAD) in Chinese patients with type 2 diabetes (T2D). Methods: In total, 745 patients with T2D of Chinese Han population were enrolled in the case-control study, and 501 of them were diagnosed as CAD. Six haplotype-tagging SNPs in DPP4 gene were selected and genotyped using polymerase chain reaction and restriction fragment length polymorphism. The association between gene polymorphisms and the risk of CAD was analyzed using logistic regression analyses. Results: Among all six genotyped SNPs, the variation of the SNP rs3788979 was significantly related to the risk of CAD in dominant inheritance mode after adjusting for confounders (OR'=1.663, 95% CI'=1.051-2.630, p' =0.030). In subgroup analysis, the carriers of genotype GG or GA had a significantly higher risk of CAD, compared with genotype AA carriers in overweight and obesity subgroup (OR'=2.070, 95% CI'=1.256-3.416, p' =0.004). The SNP rs3788979 showed an interactive effect with BMI in terms of CAD risk (β =0.191, p' for interaction =0.048). In non-smoking subgroup, the carriers of genotype GG or GA had a raised risk of CAD than carriers of AA (OR'=2.041, 95% CI'=1.196-3.484, p' =0.009). The smokers with GG or GA genotype had an increased CAD risk compared to non-smokers with AA genotype (OR'=3.351, 95% CI'=1.589-7.064, p' =0.001). Conclusions: The SNP rs3788979 in the DPP4 gene is associated with the risk of CAD, and has a synergetic effect with BMI on the risk of CAD in Chinese Han patients with T2D.

Keywords: Dipeptidyl peptidase 4, single nucleotide polymorphisms, coronary artery disease

Introduction

Coronary artery disease (CAD) is the most life-threatening complication of type 2 diabetes mellitus (T2DM) and the leading cause of death in diabetic patients. Accumulating evidence proves that diabetes is classified as a coronary artery disease equivalent [1]. It is reported that diabetes adds 1-3 times the possibility of CAD [2]. Alarmingly, the number of diabetic patients is expected to rise to 552 million by the year 2030 according to IDF diabetes atlas [3]. Low- and middle-income countries will largely contribute to the boost of the incident rate of T2DM during the next decade, especially in China, and the complications of diabetes will subsequently increase. Screening underlying risk fac-

tors of these complications, including both genetic and environmental ones, is of great clinical importance in preventing CAD at an early stage, thus it could further reduce the morbidity in diabetic patients.

Dipeptidyl peptidase 4 (DPP4) is a serine protease, which is widely found both in cell membrane and plasma. As a peptidase, DPP4 cleaves dipeptides from diverse substrates [4], including glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), neuropeptide Y (NPY), brain natriuretic peptide (BNP), stromal cell-derived factor-1 α (SDF-1 α), etc [5]. Due to its multiple enzymatic activity, DPP4 is not only involved in the pathogenesis of diabetes mellitus and glucose metabolism [6],

but also participates in modulating cardiovascular system [7]. As a widely known substrate of DPP4, GLP-1 mediates the activation of PKA-cAMP pathway and triggers the secretion of insulin [8]. In this way, GLP-1 agonists and DPP4 inhibitors are widely applied pharmaceutically in the management of diabetes. In recent years, intensive studies were focusing on cardiovascular function and safety of these medications, yet the cardiovascular benefits of DPP4 inhibitors were only proved in molecular and cytological levels, as well as in rodent models [9]. The cardiovascular protection effect of DPP4 inhibitors may conduct directly in cardiovascular system or indirectly through their other physiological effects such as glucose lowering function [10]. Previous genetics studies revealed that GLP-1 receptor gene polymorphisms were associated with cardiovascular risk factors [11, 12]. Researchers found that variants in DPP4 gene were related to the risk of myocardial infarction in patients with atherosclerosis [13]. However, there is still limited data to confirm or explain the connection of DPP4 gene variants and CAD in Asian populations. In this study, we hypothesized that the polymorphisms of DPP4 gene might be associated with the risk of CAD in patients with T2DM via testing the genotypes of DPP4 gene in T2DM patients with or without CAD in a Chinese Han population.

Materials and methods

Patient selection

A total of 745 unrelated Chinese Han individuals with type 2 diabetes were enrolled in the study. 501 of them were CAD-positive and 244 were negative controls. The diagnosis of T2DM was based on the World Health Organization criteria, including fasting plasma glucose (FPG) ≥ 7.0 mmol/L, and/or 2-hour plasma glucose ≥ 11.1 mmol/L, or random plasma glucose ≥ 11.1 mmol/L. All CAD-positive subjects had coronary angiography in Peking University First Hospital, and the results met the criteria of a $\geq 50\%$ stenosis in at least one of the major coronary arteries (defined as follows: left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery and right coronary artery). Negative controls had a less than 50% coronary artery stenosis, which was confirmed using a coronary angiography or coronary computer tomography (CT) scan. Demographic information and cardiovascular risk

factor data of each subject was collected from their medical records during hospitalization or follow-up through phone calls for all individuals. Demographic data consisted of age, gender, body mass index (BMI), FPG, current serum triglycerides (mmol/L), total cholesterol (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), history of hypertension (blood pressure $\geq 140/90$ mmHg or under any antihypertensive medications) and smoking status ('ever' or 'never', 'ever' defined as having been smoking more than 1 cigarette per day for more than 1 year). Written informed consents were taken before inclusion. The study protocol was designed on the basis of Helsinki Declaration, and ethical approval was granted from the Research Ethics Committee of Peking University First Hospital.

DPP4 gene genotyping

Whole blood of each individual was collected in EDTA-containing tubes, and genomic DNA was extracted utilizing a Whole Blood DNA Isolation Kit (Bio Teke).

The DPP4 gene on chromosome 2q24.3 includes 26 exons. A total of 11 haplotype-tagging single nucleotide polymorphisms (SNPs) at DPP4 gene locus in the CHB (Chinese Han Beijing) data from HapMap Phase II database (<http://www.hapmap.org>) (R#27, $r^2 < 0.8$, MAF ≥ 0.05) were identified. Six of them were selected including rs3788979 (G>A), rs12617656 (C>T), rs12469968 (G>A), rs2300753 (G>T), rs12617336 (G>C) and rs1861975 (C>A), and further polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were performed. Target genes were amplified utilizing PCR, and then genotyped using PCR-RFLP, with the genotyping success rate of 95%. 5% of the samples of each SNP were chosen to undergo a direct DNA sequencing (ABI 3730 XL sequencer) to further confirm the genotyping results from RFLP, and the concordance rate between RFLP and DNA sequencing is 98%.

Statistical analysis

Data were analyzed using the Statistical package for the Social Sciences for Windows (SPSS version 16.0, USA). Quantitative variates were expressed as mean \pm standard deviation (SD), and categorical variates were expressed as percentage. Independent sample t-test was

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Table 1. Anthropometric, epidemiological and metabolic characteristics of CAD and controls

	CAD (n=501)	Control (n=244)	<i>p</i> -value
Gender (male, %)	322 (64.3%) (64.3%)	102 (41.8%) (41.8%)	<0.0001
Age (y)	63.55±9.393	62.37±9.651	0.109
Positive history of hypertension (%)	79.0	72.2	0.075
BMI (kg/m ²)	26.2±3.5	25.9±3.8	0.171
HbA1c (%)	7.28±1.48	7.07±1.62	0.183
Fasting glucose (mmol/l)	7.24±2.51	6.91±2.14	0.138
Triglycerides (mmol/l)	1.65±1.00	1.71±1.18	0.203
Total Cholesterol (mmol/l)	4.05±1.06	4.38±1.00	0.231
LDL-C (mmol/l)	2.44±0.90	2.60±0.88	0.316
HDL-C (mmol/l)	0.98±0.28	1.15±0.53	0.001
Dyslipidemia (%)	74.4	73.2	0.830
Smoking history (+) (%)	49.3	18.8	<0.0001

Data was presented as mean ± standard deviation or n (%); CAD: subjects with coronary artery disease; control: individuals free from CAD; TG: triglycerides; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol.

Table 2. Distribution of genotypes in dominant inheritance mode of SNPs in DPP4 gene in CAD and non-CAD patients with type 2 diabetes

SNPs	Genotype	CAD n=501 (%)	Control n=244 (%)	OR	95% CI	<i>p</i>	OR'	95% CI	<i>p</i> '
rs3788979	GG+AG	386 (77.0)	176 (72.1)	1.297	0.915-1.838	0.144	1.663	1.051-2.630	0.030
	AA	115 (23.0)	68 (27.9)	1			1		
rs12617656	TC+TT	277 (55.3)	142 (58.2)	0.888	0.652-1.210	0.453	0.834	0.419-1.661	0.606
	CC	224 (44.7)	102 (41.8)	1			1		
rs12469968	GA+AA	240 (47.9)	125 (51.2)	0.875	0.645-1.289	0.394	0.876	0.581-1.321	0.527
	GG	261 (52.1)	119 (48.8)	1			1		
rs2300753	GT+TT	43 (8.6)	17 (7.0)	1.254	0.699-2.247	0.447	1.172	0.552-2.486	0.680
	GG	458 (91.4)	227 (93.0)	1			1		
rs12617336	GC+CC	87 (17.4)	36 (14.8)	1.214	0.796-1.853	0.368	1.176	0.679-2.038	0.563
	GG	414 (82.6)	208 (85.2)	1			1		
rs1861975	AC+CC	50 (10.0)	25 (10.2)	0.971	0.585-1.612	0.910	0.873	0.457-1.669	0.681
	AA	451 (90.0)	219 (89.8)	1			1		

p', OR': After adjusting for gender, age, history of hypertension, dyslipidemia history, fasting glucose, BMI and smoking status.

used to compare quantitative variates, and categorical variates were compared using Mann-Whitney U test. A chi-square test was used to analyze the allele and genotype frequencies in CAD and control groups. Genetic effects were investigated under dominant, recessive and additive modes of inheritance, respectively. Odds ratios (ORs) and 95% confidence intervals were calculated using multiple logistic regression analysis after adjustment for covariates including age, gender, history of hypertension and smoking status to explore the association between SNPs and CAD. Linkage disequilibrium (LD) and haplotype analysis were performed using Haploview software (version 4.2, USA).

Statistical significance was considered when $p < 0.05$.

Results

Demographics

The baseline anthropometric, epidemiological and metabolic data of all subjects is shown in **Table 1**. Since the values of lipid profile, HbA1c and fasting glucose were acquired after medical intervention, a significant difference in gender, HDL-c level and smoking status between CAD and non-CAD groups was found ($p < 0.05$). Genotype distributions at all six loci were in

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Table 3. Distribution of genotypes in additive inheritance mode of SNPs at DPP4 gene in CAD and non-CAD patients of type 2 diabetes

SNPs	Genotype	CAD n=501 (%)	Control n=244 (%)	OR	95% CI	<i>p</i>	OR'	95% CI	<i>p</i> '
rs3788979	GG	128 (25.5)	66 (27.0)	1.209	0.834-1.754	0.316	1.192	0.696-2.042	0.522 ¹
	GA	258 (51.5)	110 (45.1)	1.387	0.954-2.015	0.086	1.614	0.989-2.634	0.055 ²
	AA	115 (23.0)	68 (27.9)	1.147	0.752-1.749	0.525	1.745	0.957-3.183	0.069 ³
rs12617656	TT	65 (13.0)	35 (14.3)	1.067	0.665-1.711	0.788	1.218	0.623-2.635	0.501
	TC	212 (42.3)	107 (43.9)	0.902	0.649-1.255	0.541	0.879	0.570-1.356	0.560
	CC	224 (44.7)	102 (41.8)	1.183	0.737-1.898	0.487	1.024	0.493-2.123	0.950
rs12469968	AA	48 (9.6)	27 (11.1)	1.102	0.648-1.873	0.720	1.540	0.771-3.077	0.221
	GA	192 (38.3)	98 (40.1)	1.119	0.808-1.551	0.497	1.022	0.657-1.590	0.922
	GG	261 (52.1)	119 (48.8)	1.234	0.734-2.073	0.427	2.193	1.065-4.508	0.033
rs2300753	TT	2 (0.4)	0 (0)	0.953	0.893-1.019	1.000*	#	#	0.999
	GT	41 (8.2)	17 (7.0)	0.837	0.465-1.505	0.551	0.943	0.439-2.022	0.880
	GG	458 (91.4)	227 (93.0)	0.996	0.990-1.002	1.000*	#	#	0.999
rs12617336	CC	3 (0.6)	3 (1.2)	2.545	0.489-13.257	0.494*	1.646	0.131-20.620	0.699
	GC	84 (16.8)	33 (13.5)	0.782	0.506-1.209	0.268	0.833	0.474-1.463	0.525
	GG	414 (82.6)	208 (85.3)	1.990	0.398-9.947	0.674*	1.158	0.109-12.314	0.903
rs1861975	CC	2 (0.4)	2 (0.8)	2.087	0.276-15.764	0.856*	6.280	0.330-119.602	0.222
	AC	48 (9.6)	23 (9.4)	1.013	0.601-1.709	0.960	1.169	0.594-2.300	0.650
	AA	451 (90.0)	219 (89.8)	2.064	0.289-14.749	0.839*	3.675	0.317-42.542	0.298

p', OR': After adjusting for gender, age, history of hypertension, dyslipidemia history, fasting glucose, BMI and smoking status. *indicated that Fisher's exact test was performed since the sample size was less than 5. #indicated that the values could not be calculated by logistic regression analysis due to a low genotype frequency. Taking rs3788979 as example, the values of OR, CI, *p*, OR', CI' and *p*' in ¹ line were in comparison of genotype GG and GA, the values in ² line were of GA and AA, the values in ³ line were of AA and GG.

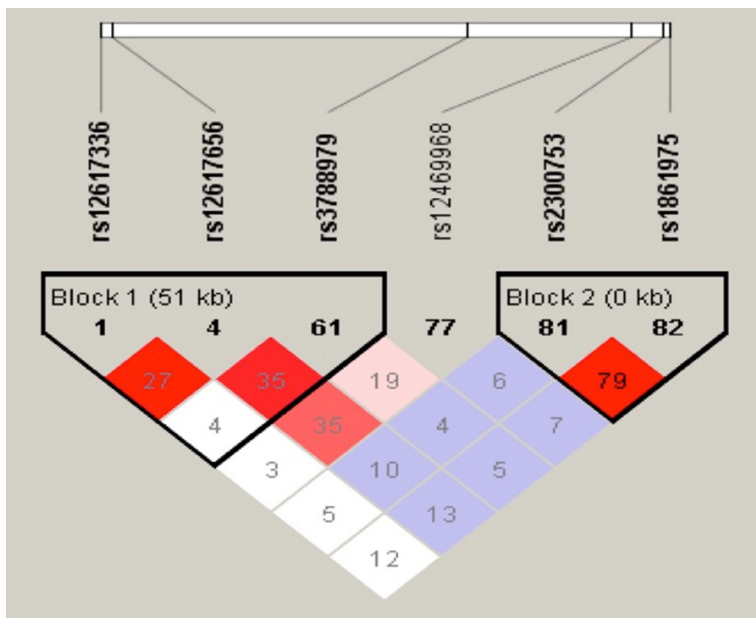


Figure 1. The linkage disequilibrium (LD) plots and the r^2 values between DPP4 SNPs. The colors of the squares indicated the extent of the linkage between SNPs, and the numbers in the squares represented the r^2 values. The LD plots were circled by the triangular blocks.

accordance with Hardy-Weinberg equilibrium ($p > 0.05$).

Genotype analysis

In dominant inheritance mode, the carriers of genotype GG or AG at the SNP rs3788979 had an increased risk of CAD compared with carriers of AA after adjustment for other known CAD risk factors including gender, age, history of hypertension, dyslipidemia, fasting glucose, BMI and smoking status (OR=1.663, 95% CI=1.051-2.630, $p=0.030$) (Table 2). A predisposing effect was observed in the major allele G at the SNP rs12469968, where genotype GG exhibited a higher risk of CAD compared to genotype AA after adjusting for confounders as listed

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Table 4. The association of CAD risk and Haplotypes of DPP4 SNPs

SNPs	Haplotypes	Haplotype frequency		χ^2	p
		CAD n (%)	Control n (%)		
rs12617336	GCA	448.9 (44.8)	225.8 (46.3)	0.281	0.596
rs12617656	GTG	235.9 (23.5)	127.5 (26.1)	1.193	0.275
rs3788979	GCG	195.6 (19.5)	78.8 (16.1)	2.5	0.114
	CTG	72.4 (7.2)	31.2 (6.4)	0.361	0.548
	GTA	31.5 (3.1)	16.9 (3.5)	0.111	0.739
rs2300753	CA	946.0 (94.4)	461.0 (94.5)	0.002	0.964
rs1861975	AC	41.0 (4.1)	17.0 (3.5)	0.324	0.569
	CC	11.0 (1.1)	10.0 (2.0)	2.129	0.145

χ^2 : The distribution of all 8 haplotypes in CAD and non-CAD groups were calculated by Haploview software. p : one haplotype was compared with frequency of all other haplotypes.

Table 5. The interaction effect of SNPs and BMI on CAD in the population

SNPs	p'	β
rs3788979	0.048	0.191
rs12617656	0.500	0.119
rs12469968	0.105	0.027
rs2300753	0.797	0.092
rs12617336	0.926	-0.031
rs1861975	0.415	0.172

p' : After adjusting for gender, age, history of hypertension, dyslipidemia history, fasting glucose and smoking status.

above (OR'=2.191, 95% CI'=1.065-4.508, p' =0.033) (Table 3). No significant association was observed between CAD risk and genotypes in recessive inheritance mode. All six SNPs had similar allele frequencies between the two groups.

Haplotype analysis

The linkage disequilibrium (LD) plots between SNPs and the r^2 values were displayed in Figure 1. Haplotypes were constructed including block 1 (rs12617336, rs12617656 and rs3788979) and block 2 (rs2300753 and rs1861975), based on their physical position and r^2 values. Of all eight haplotypes in DPP4 gene, none of them was associated with CAD risk in the study population (Table 4).

Interactive effect analysis

An interactive effect of SNPs with BMI on CAD risk was further analyzed when subjects were stratified by BMI as a continuous variate. The

cut-point was set as 24 kg/m² according to the definition of over-weight. The interaction was proved significant after adjustment for other known CAD risk factors (p' for interaction =0.048, β =0.091) (Table 5). There was no significant difference between CAD subjects and non-CAD ones in the distribution of alleles or genotypes in normal BMI subgroup. However, overweight and obese carriers of genotype AA at rs3788979 showed a lower risk of CAD after adjustment for other confounders (p' =0.010) (Table 6).

When individuals were categorized by smoking status, the interactive effect of SNPs and smoking on CAD risk was further analyzed. The smokers with GG or GA genotype at rs3788979 had an increased CAD risk compared with non-smokers with AA genotype (OR'=3.351, 95% CI'=1.589-7.064, p' =0.001).

Discussion

Accumulating studies revealed the importance of DPP4 in cardiovascular system, including improvement of cardiac function, promotion of coronary angiogenesis, reduction of myocardial cell apoptosis and regulation of blood pressure both in cytological and rodent experiments [14-17]. Limited data concerned DPP4 gene and its environmental interaction, and the majority of research focused on genetic influence with lipid profile [18], for example the possible association of ApoB level and DPP4 gene in South Asians [19], and DPP4 gene as a genomic marker for periodontitis [20]. To date, genetic variability in DPP4 gene modulating the risk of CAD was not reported in Chinese or other populations.

In the study, 745 Chinese patients with T2D were recruited into CAD or non-CAD group. DPP4 gene SNP rs3788979 was found significantly associated with CAD risk after adjustment for other covariates, which was consistent with a former result, that the very SNP showed a possible effect of predisposing myocardial infarction in non-diabetic patients [13]. As a promoting factor for atherosclerosis and CAD, dyslipidemia was related to another DPP4

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Table 6. Comparisons of genotypes of SNPs at DPP4 loci in CAD and non-CAD subjects with type 2 diabetes in overweight and obesity subgroup

SNPs	CAD (n=376)	Control (n=181)	<i>p</i>	<i>p</i> '
rs3788979				
GG	93 (24.5)	46 (25.4)	0.150	0.010
AG	195 (51.9)	80 (44.2)		
AA	88 (23.4)	55 (30.4)		
rs12617656				
TT	47 (12.5)	22 (12.2)	0.954	0.325
CT	161 (42.8)	80 (44.2)		
CC	168 (44.7)	79 (43.6)		
rs12469968				
GG	199 (52.9)	91 (50.3)	0.781	0.761
GA	138 (36.7)	72 (39.8)		
AA	39 (10.4)	18 (9.9)		
rs2300753				
GG	344 (91.5)	168 (92.8)	0.581	0.981
TG	30 (8.0)	13 (7.2)		
TT	2 (0.5)	0 (0.0)		
rs12617336				
GG	318 (84.6)	158 (87.3)	0.590	0.995
CG	55 (14.6)	21 (11.6)		
CC	3 (0.8)	2 (1.1)		
rs1861975				
AA	340 (90.4)	161 (89.0)	0.707	0.251
AC	34 (9.0)	18 (9.9)		
CC	2 (0.6)	2 (1.1)		

p': After adjustment for age, gender, histories of hypertension and smoking.

gene SNP, rs4664443 [19], but its minor allele frequency in Chinese Han population was too small to be involved in the study. In the study population, the carriers of genotype GG or GA in rs3788979 had a 60% increased risk of CAD comparing with non-carriers. The underlying mechanism to explain that a SNP locating in intronic region could produce clinical effect, was yet beyond our knowledge. Thus we postulated that this intronic SNP exerted strong linkage disequilibrium with other functional genetic polymorphisms that affected the susceptibility of CAD, which might be proved in further study.

Besides genomic and ethnic factors, gene-environment interaction was also explored in the study. Obesity and smoking are definite environmental factors that contribute to the development of CAD. Hence we stratified all subjects

by BMI and smoking status in interaction analysis. Our results indicated a possible synergistic effect between DPP4 gene SNP rs3788979 and BMI on the occurrence of CAD, which might be due to the influence on endothelium function of obesity. Under this conclusion, we consider that a therapeutic lifestyle intervention, especially body weight control, could produce even more benefits to those carriers of risk gene variants.

Poor glycemic control was proved to be another potent promoting factor to CAD in diabetic patients [21]. In demographic data of our study population, random HbA1c between CAD and non-CAD groups showed no significance, and data reflecting glycemic control was unfortunately insufficient for further stratified study.

However, there were inevitably limitations in this study. As a case-control study, we could not completely avoid the recall bias, and a cohort study is expected to confirm our results. Our sample size was relatively small, and larger sample size would enhance the statistical power for conclusions. Our study suggested that some certain SNPs in DPP4 gene could be a possible functional genomic marker for CAD, but extended populations of additional ethnicities with or without diabetes are yet to be studied.

Our modest evidence revealed the association of the DPP4 polymorphisms rs3788979 and rs12469968 with CAD risk in a Chinese Han population with type 2 diabetes. The genetic variants at DPP4 gene SNP rs3788979 have a synergetic effect with obesity to increase the risk of CAD in Chinese Han population with T2DM.

Acknowledgments

The study was granted by National Science and Technology Major Project (2011ZX09307-001-08) in China. Authors appreciate the most supportive work from Dept. of Cardiology and Radiology of Peking University First Hospital for helping collecting samples. We are grateful as well to all the patients contributed to our study.

Disclosure of conflict of interest

None.

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References

- [1] KIM JJ, Hwang BH, Choi IJ, Choo EH, Lim S, Koh YS, Lee JM, Kim PJ, Seung KB, Lee SH, Cho JH, Jung JI, Chang K. A prospective two-center study on the associations between microalbuminuria, coronary atherosclerosis and long-term clinical outcome in asymptomatic patients with type 2 diabetes mellitus: evaluation by coronary CT angiography. *Int J Cardiovasc Imagine* 2015; 31: 193-203.
- [2] Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the framingham study. *Circulation* 1979; 59: 8-13.
- [3] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; 94: 311-21.
- [4] Boonacker E, Van Noorden CJ. The multifunctional or moonlighting protein CD26/DPPIV. *Eur J Cell Biol* 2003; 82: 53-73.
- [5] Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* 2012; 33: 187-215.
- [6] Kazafeos K. Incretin effect: GLP-1, GIP, DPP4. *Diabetes Res Clin Pract* 2011; 93 Suppl 1: 32-6.
- [7] Pala L, Rotella CM. The role of DPP4 activity in cardiovascular districts: in vivo and in vitro evidence. *J Diabetes Res* 2013; 2013: 590456.
- [8] Light PE, Manning Fox JE, Riedel MJ, Wheeler MB. Glucagon-like peptide-1 inhibits pancreatic ATPsensitive potassium channels via a protein kinase A- and ADP-dependent mechanism. *Mol Endocrinol* 2002; 16: 2135-44.
- [9] Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; 368: 1696-705.
- [10] Ban K, Noyan-Ashraf MH, Hoefler J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation* 2008; 117: 2340-50.
- [11] de Luis DA, Pacheco D, Aller R, Izaola O, Bachiller R. Roles of rs 6923761 gene variant in glucagon-like Peptide 1 receptor on weight, cardiovascular risk factor and serum adipokine levels in morbid obese patients. *Nutr Hosp* 2014; 29: 889-93.
- [12] de Luis DA, Aller R, de la Fuente B, Primo D, Conde R, Izaola O, Sagrado MG. Relation of the rs6923761 gene variant in glucagon-like peptide 1 receptor with weight, cardiovascular risk factor, and serum adipokine levels in obese female subjects. *J Clin Lab Anal* 2015; 29: 100-5.
- [13] Aghili N, Devaney JM, Alderman LO, Zukowska Z, Epstein SE, Burnett MS. Polymorphisms in dipeptidyl peptidase IV gene are associated with the risk of myocardial infarction in patients with atherosclerosis. *Neuropeptides* 2012; 46: 367-71.
- [14] Zaruba MM, Theiss HD, Vallaster M, Mehl U, Brunner S, David R, Fischer R, Krieg L, Hirsch E, Nathan P, Israel L, Imhof A, Herbach N, Assmann G, Wanke R, Muller-Hoecher J, Steinbeck G, Franz WM. Synergy between CD26/DPP-IV inhibition and G-CSF improves cardiac function after acute myocardial infarction. *Cell Stem Cell* 2009; 4: 313-23.
- [15] Pleister AP, Baliga RR, Haas GJ. Acute study of clinical effectiveness of nesiritide in decompensated heart failure: nesiritide redux. *Curr Heart Fail Rep* 2011; 8: 226-32.
- [16] Gomez N, Touihri K, Matheussen V, Mendes Da Costa A, Mahmoudabady M, Mathieu M, Baerts L, Peace A, Lybaert P, Scharpe S, De Meester I, Bartunek J, Vanderheyden M, McEntee K. Dipeptidyl peptidase IV inhibition improves cardiorenal function in overpacing-induced heart failure. *Eur J Heart Fail* 2012; 14: 14-21.
- [17] Pacheco BP, Crajoinas RO, Couto GK, Davel AP, Lessa LM, Rossoni LV, Girardi AC. Dipeptidyl peptidase IV inhibition attenuates blood pressure rising in young spontaneously hypertensive rats. *J Hypertens* 2011; 29: 520-8.
- [18] Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemssen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruukonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker

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- AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, KeesHovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllenstein U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010; 466: 707-13.
- [19] Bailey SD, Xie C, Paré G, Montpetit A, Mohan V, Yusuf S, Gerstein H, Engert JC, Anand SS; EpiDREAM and INTERHEART Investigators. Variation at the DPP4 locus influences apolipoprotein B levels in South Asians and exhibits heterogeneity in Europeans related to BMI. *Diabetologia* 2014; 57: 738-45.
- [20] Suzuki A, Ji G, Numabe Y, Ishii K, Muramatsu M, Kamoi K. Large-scale investigation of genomic markers for severe periodontitis. *Odontology* 2004; 92: 43-7.
- [21] Doria A, Wojcik J, Xu R, Gervino EV, Hauser TH, Johnstone MT, Nolan D, Hu FB, Warram JH. Interaction between poor glycemic control and 9p21 locus on risk of coronary artery disease in type 2 diabetes. *JAMA* 2008; 300: 2389-97.