PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B, Vol. 63 (2009), No. 4/5 (663/664), pp. 174–179.
DOI: 10.2478/v10046-009-0046-1

ANALYSIS OF POLYMORPHISMS AT THE ADIPONECTIN GENE LOCUS IN ASSOCIATION WITH TYPE 2 DIABETES, BODY MASS INDEX AND CARDIOVASCULAR TRAITS IN LATVIAN POPULATION

Ineta Kalniņa*, Gustavs Latkovskis**, Liene Ņikitina-Zaķe*, Vitolds Mackevičs***, Raitis Pečulis*, Ivo Kāpa*, Dāvids Fridmanis*, Andrejs Ērglis***, Valdis Pīrāgs****, and Jānis Kloviņš*

* Latvian Biomedical Research and Study Centre, Rātsupītes iela 1, LV-1067, Rīga, LATVIA;
e-mail: klovins@biomed.lu.lv

** Latvian Centre of Cardiology, Pauls Stradiņš Clinical University Hospital, Pilsoņu iela 13, Rīga,LV-1002, LATVIA

*** Faculty of Medicine, Rīga Stradiņš University, Dzirciema iela 16, Rīga, LV-1009, LATVIA

**** Department of Endocrinology, Pauls Stradiņš Clinical University Hospital,
Pilsoņu iela 13, Rīga, LV-1002, LATVIA

Communicated by Ludmila Vīksna

Despite the number of recently conducted studies seeking to determine the association between genetic variants of adiponectin gene and susceptibility to type 2 diabetes (T2D) and increased body mass index (BMI), the results obtained are often inconsistent. To determine the impact of common polymorphisms in promoter and coding regions of adiponectin gene on these conditions in Latvian population, we selected ten SNPs (rs2241767, rs1501299, rs3777261, rs16861210, rs2241766, rs822396, rs182052, rs17300539, rs16861194, rs266729) based on haploblock structure and previously reported association studies. The selected SNPs were screened in a study group of 835 participants from the Genome Data Base of Latvian Population and mainly consisted of patients with T2D and coronary heart disease. None of the individual polymorphisms were significantly associated with T2D status or BMI when analysed using logistic or linear regression and adjusted for gender, age and other significant covariates. Frequency of rs2241766 T allele homozygotes however was significantly increased in T2D patients compared to controls (uncorrected P *= 0.007). When analysed with other traits, the rs182052 G allele was found to be less frequent in patients suffering from myocardial infarction (*P *= 0.02; OR = 0.76, CI95% [0.61–0.92]) compared to others. Haplotype analysis revealed significant association of one haplotype with atrial fibrillation (uncorrected* P *= 0.01). In summary, we conclude that SNPs in adiponectin gene are unlikely to represent the risk for T2D, but may be involved in pathogenesis of CHD in the Latvian population.*

Key words: ADIPOQ*, tagSNP, BMI, T2D, CHD.*

INTRODUCTION

Adiponectin is an adipose tissue-derived plasma protein that plays an important role in energy homeostasis regulation, glucose and lipid metabolism as well as anti-inflammatory responses in the vascular system (Hu *et al*., 1996; Ouchi *et al*., 2003). Low plasma adiponectin concentrations are linked to type 2 diabetes (T2D) (Weyer *et al*., 2001), obesity (Matsuzawa *et al*., 2003) and coronary heart disease (CHD) related traits (Matsuda *et al*., 2002; Kumada *et al*., 2003). Possible mechanisms of adiponectin action in relation with these inflammatory diseases may include its inhibition of smooth muscle cell proliferation, monocyte adhesion to endothelium, and macrophage uptake of LDL (Chen *et al*., 2005).

Adiponectin is a product of the *ADIPOQ* gene consisting of three exons that occupies 16 kb on chromosome 3q27. During the last five years, a large number of association studies have been performed to search for polymorphisms that may influence metabolic conditions (reviewed in Vasseur *et al*. (2006) and Menzaghi *et al*. (2007)). Even though the number of polymorphisms and haplotypes are repeatedly associated with increased or decreased blood adiponectin levels (Heid *et al*., 2006; Mackevics *et al*., 2006; Li *et al*., 2007; Kyriakou *et al*., 2008), association analysis of these SNPs

with metabolic and cardiovascular phenotypes give inconsistent results across different studies.

The aim of our study was to search for the association between systematically selected adiponectin gene polymorphisms and T2D, body mass index (BMI) as well as CHD phenotypes in the Latvian population.

MATERIALS AND METHODS

Study subjects. The study was based on data and samples from the Genome Data Base of Latvian Population, the disease based biobank. Briefly: participating individuals were over the age of 18; the health status was recorded, the diagnoses were based on approved clinical criteria according to the ICD-10 codes (International Classification of Diseases); andanthropometric measurements (including weight and stature), ethnic, social, environmental information and familial health status was acquired based on a self-reported questionnaire. Written informed consent was obtained from all participants. The study group for the subsequent genotyping of selected markers was selected from all available subjects with validated health records and questionnaires in the biobank. We excluded patients with diseases where outcome or treatment may influence BMI, including all types of cancer and diseases of the thyroid gland, but not excluding patients with cardiovascular diseases. All patients with T2D were included in the study. In total, 835 subjects were selected based on these criteria. The study protocol was approved by the Central Medical Ethics Committee of Latvia.

SNP genotyping. TagSNPs in the adiponectin gene locus were selected using Haploview software (Barrett *et al*., 2005). The SNPs with previously published effect on adiponectin plasma concentration were force included in the tagSNP set. MALDI TOF-based genotyping platform (Bruker Daltonics) was used for genotyping all SNPs (primer sequences and reaction conditions available upon request). Genotype calling and quality control was performed using GenoTools software (Bruker Daltonics).

Statistical analysis. Statistical analyses were performed with the PLINK 1.06 software (http://pngu.mgh.harvard.edu/purcell/plink/) (Purcell *et al*., 2007). In contrast to the natural BMI values, the logarithmically transformed BMI values displayed normal distribution and were further used for all quantitative analyses. Linear regression was applied to examine the association between tagSNPs and log-BMI adjusting for age and gender. The allelic association test (additive model), dominant and recessive model analysis was performed using the exact Fisher's test. Logistic regression analysis adjusting for age and those factors that showed significant association with trait under multivariate logistic regression analysis were used for dichotomous trait analysis. Bonferroni correction was used to adjust for multiple testing. The permutation test was performed using label-swapping between SNP and trait condition or logBMI values but leaving intact correlation with other covariates. 10,000 permutations were performed for each analysis and corrected (EMP2) *P*-values were used. These values are corrected based on calculation of the proportion of permutations in which any of the test statistics exceeds the particular observed statistic and are more stringent then uncorrected *P*-values. Odds ratios (OR) and CI (95%) values were obtained from logistic regression analysis (Exp(B) value), unadjusted mean logBMI values were calculated and back-transformed for each genotype.

RESULTS

Description of the study group is summarised in Table 1. A total of ten SNPs in the adiponectin gene locus were genotyped in all or part of the participants. SNP information, observed minor allele frequency (MAF) and results of deviation from the Hardy–Weinberg equilibrium test are shown in Table 2. None of the SNPs were in disagreement with Hardy-Weinberg equilibrium after correction for multiple testing. The exact number of successfully genotyped samples for each SNP in the study group is displayed in Tables 3 and 4, along with the results of association with T2D and logBMI values, respectively. The SNP rs2241766 was asso-

Table 1

CHARACTERISTICS OF THE STUDY POPULATION

Parameter	Values
Total number of patients	835
Percentage of females (n)	66.7 (557)
Percentage of males (n)	33.3 (278)
Percentage of patients (n) with:	
Type 2 diabetes	20.3 (170)
Hypertension	55.9 (467)
Heart failure	52.2 (435)
Atrial fibrillation	4.6 (39)
Myocardial infarction	46.2 (390)
Age (years) [mean ± SD]	62.82 ±10.12
BMI [mean ± SD]	28.77 ± 4.71

Table 2

CHARACTERISTICS OF TEN SNPs GENOTYPED IN 835 SUBJECTS

SNP No.	rs code	Genome position[a]	Gene position[b]	Common allele	Rare allele	MAF	H-W test *P* value
1	rs16861194	188042119	-11422	A	G	0.12	0.29
2	rs17300539	188042154	-11387	G	A	0.05	0.11
3	rs266729	188042168	-11373	C	G	0.28	0.01
4	rs182052	188043476	-10065	G	A	0.43	0.35
5	rs16861210	188049192	-4349	G	A	0.05	0.27
6	rs822396	188049571	-3970	A	G	0.22	1
7	rs2241766	188053586	45	T	G	0.05	0.66
8	rs1501299	188053817	276	A	C	0.28	1
9	rs2241767	188053890	349	A	G	0.05	1
10	rs3774261	188054253	712	G	A	0.33	0.93

MAF, minor allele frequency; H-W, Hardy-Weinberg equilibrium

[a] - according to the NCBI build 36; [b] - relating to the first position of the starting codon ATG

Table 3

ASSOCIATION OF T2D WITH TEN tagSNPs

SNP	Genetic model	Number of subjects [a]		*P* value (Fisher test)	*P* value [b] (logreg)	OR [95% CI][b]
		T2D	Control			
rs16861194	additive	3/29/110	10/115/439	0.869	0.778	0.93 [0.57–1.51]
	dominant	32/110	125/439	0.924	0.653	0.89 [0.52–1.52]
	recessive	3/139	10/554	0.788	0.646	1.49 [0.28–8.08]
rs17300539	additive	0/18/129	4/48/517	0.407	0.377	1.35 [0.7–2.59]
	dominant	18/129	52/517	0.258	0.302	1.45 [0.72–2.9]
	recessive	0/147	4/565	0.308	-	-
rs266729	additive	13/49/72	50/182/271	0.988	0.959	0.99 [0.7–1.4]
	dominant	62/72	232/271	0.976	0.986	1.01 [0.64–1.6]
	recessive	13/121	50/453	0.934	0.884	0.95 [0.44–2.07]
rs182052	additive	31/57/51	101/270/183	0.95	0.306	0.85 [0.62–1.16]
	dominant	88/51	371/183	0.415	0.114	0.69 [0.43–1.1]
	recessive	31/108	101/453	0.274	0.983	1.01 [0.58–1.76]
rs16861210	additive	0/18/143	4/59/576	0.804	0.793	1.09 [0.58–2.06]
	dominant	18/143	63/576	0.62	0.676	1.16 [0.59–2.26]
	recessive	0/161	4/635	0.314	-	-
rs822396	additive	9/55/98	30/221/395	0.761	0.518	1.12 [0.79–1.6]
	dominant	64/98	251/395	0.879	0.558	1.14 [0.74–1.75]
	recessive	9/153	30/616	0.628	0.666	1.23 [0.49–3.14]
rs2241766	additive	2/13/141	0/50/516	0.443	0.314	1.46 [0.7–3.02]
	dominant	15/141	50/516	0.763	0.562	1.26 [0.59–2.7]
	recessive	2/154	0/566	**0.007**	-	-
rs1501299	additive	13/52/71	47/254/315	0.887	0.545	1.11 [0.78–1.58]
	dominant	65/71	301/315	0.821	0.641	1.12 [0.71–1.76]
	recessive	13/123	47/569	0.452	0.572	1.26 [0.57–2.81]
rs2241767	additive	1/13/133	0/49/508	0.607	0.924	1.04 [0.47–2.32]
	dominant	14/133	49/508	0.784	0.987	1.01 [0.44–2.33]
	recessive	1/146	0/557	0.051	-	-
rs3774261	additive	5/34/32	61/235/249	0.673	0.815	0.95 [0.62–1.46]
	dominant	39/32	296/249	0.922	0.613	1.16 [0.66–2.03]
	recessive	5/66	61/484	0.288	0.177	0.47 [0.16–1.42]

Logreg- logistic regression;

a- Distribution of subjects according to genotypes/models: additive 22/12/11; dominant: 12+22/11; recessive 22/12+11 (1, common allele; 2, rare allele)

b- From logistic regression analysis adjusted for gender, age and logBMI

ciated with T2D under the recessive model (P = 0.007). This association remained significant after applying the permutation test (P = 0.049), but lost its significance after correction for multiple comparisons. Neither of the SNPs showed any association with T2D when tested using logistic regression with adjustment for age, sex and BMI under different genetic models (Table 3). Similarly, no difference in mean values of logBMI was found between genotypes of any SNP included in analysis (Table 4). We also tested for association of SNPs with other traits present in our study group. The results are shown in Figure 1A. Allele A of SNP rs182052 was less frequent in patients with myocardial infarction (39%) compared to controls (45%). This association remained significant using multiple logistic regression analysis adjusting for sex, age, BMI and T2D (P = 0.02; OR = 0.76, CI95%[0.61–0.92]). The permutation test on this SNP gave a corrected P value of 0.028. The association did not retain its significance after Bonferroni correction.

In order to identify possible effects of individual haplotypes on traits analysed in our study we performed haplotype-based association. In total, 14 haplotypes were reconstructed with frequency exceeding 1%. Statistical analysis of the distribution of probabilistically-inferred set of haplotypes for different traits is shown in Figure 1B. Haplotype determined by C and A alleles of rs1501299 and rs3774261, respectively, and common alleles for other SNPs was more frequent (26%) in patients with atrial fibrillation compared to others (14%), P = 0.009.

DISCUSSION

We report in this study the first evaluation of adiponectin gene polymorphisms in relation with T2D, BMI and cardiovascular traits in the Latvian population. First we performed systematic selection of tagSNPs in *ADIPOQ* gene locus in

Table 4

ASSOCIATION OF BMI WITH TEN tagSNPs

SNP	Number of subjects	Mean [± SE] BMI[a]			*P* value[b]		
	11/12/22	11	12	22	Additive	Dominant	Recessive
rs16861194	539/143/13	29.47 [0.23]	29.84 [0.39]	30.23 [1.23]	0.244	0.266	0.536
rs17300539	635/66/4	29.7 [0.22]	29.27 [0.55]	33.22 [2.21]	0.891	0.848	0.175
rs266729	340/227/60	29.79 [0.28]	29.59 [0.32]	29.58 [0.59]	0.427	0.447	0.615
rs182052	232/320/131	29.48 [0.32]	29.57 [0.29]	30.28 [0.41]	0.094	0.358	0.053
rs16861210	706/77/4	29.65 [0.21]	29.71 [0.52]	30.61 [2.24]	0.737	0.757	0.825
rs822396	487/270/38	29.71 [0.24]	29.54 [0.3]	29.45 [0.73]	0.436	0.455	0.670
rs2241766	647/62/2	29.62 [0.21]	29.85 [0.58]	33.15 [3.14]	0.373	0.510	0.137
rs1501299	379/302/60	29.82 [0.26]	29.81 [0.3]	29.47 [0.58]	0.696	0.700	0.836
rs2241767	631/61/1	29.59 [0.22]	30.63 [0.57]	34.78 [4.4]	0.110	0.137	0.256
rs3777261	276/265/66	29.68 [0.34]	29.3 [0.35]	30.09 [0.59]	0.926	0.628	0.328

1, common allele; 2, rare allele

a- BMI values back-transformed from unadjusted mean logBMI values

b- *P* values from linear regression analysis adjusted for gender and age

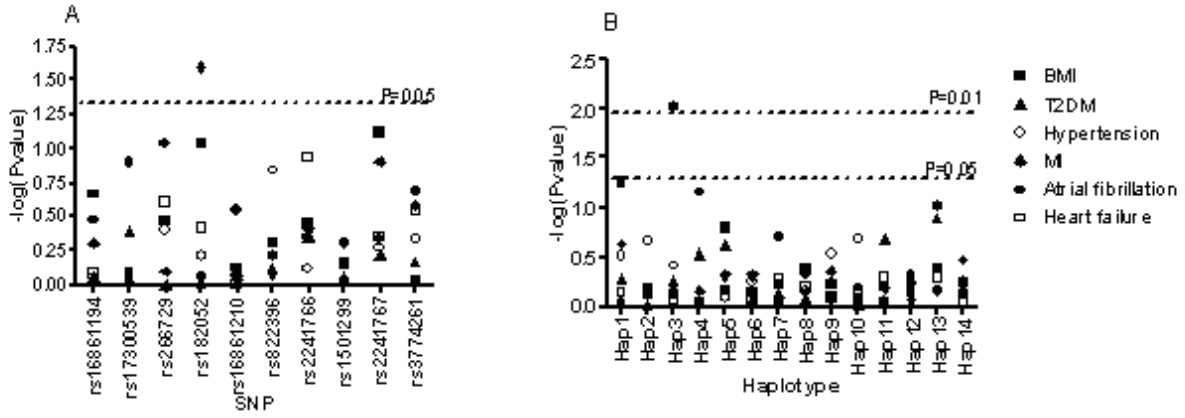

Fig. 1. Significance values depicted as negative logarithm of *P* value from adjusted linear or logistic regression analysis for SNP (A) and haplotype (B) association with all phenotypes.

order to ensure maximal capture of all known alleles. In addition, the forced inclusion of variants shown to influence plasma adiponectin levels was performed. Estimated minor allele frequencies (Table 2) of all ten SNPs were higher than 0.05 in the Latvian population and similar to those reported in the SNP database (www.ncbi.nlm.nih.gov/SNP) or other publications (Heid *et al*., 2006). We believe that altogether this ensures the high informativeness of the selected set of ten markers.

In the present quantitative trait analysis we found no evidence for an association of the tested SNPs with changes in BMI value. Other studies have previously reported that at least three of the SNPs also included in this study (rs266729, rs2241766, rs1501299) might modulate body weight (reviewed in Vasseur *et al*. (2006)). However, recent meta-analysis did not confirm the association of these or other markers with BMI (Menzaghi *et al*., 2007). The failure to identify a stable association between *ADIPOQ* polymorphisms and BMI, despite the repeatedly confirmed relationship between the levels of plasma adiponectin and BMI (Yang *et al*., 2001; Spranger *et al*., 2003), can be explained by the variation in genetic background determining the predisposition to obesity. Stratification of the study group based on common genetic variants influencing body mass regulation could help to estimate the role of adiponectin SNPs more precisely.

The only SNP that was significantly associated with T2D in our study was rs2241766, under the recessive genetic model. The relatively low frequency of this SNP and absence of GG homozygotes in the control group, however, do not allow to precisely determine the relative risk of this variation. G allele of rs2241766 was found to be associated with decreased levels of serum adiponectin (Xita *et al*., 2005; Li *et al*., 2007;) as well as T2D (Li *et al*., 2007). This result is in agreement with finding, that low plasma levels are associated with insulin resistance and T2D. It should be noted, however, that a substantial number of studies failed to replicate these results (Mackevics *et al*., 2006; Potapov *et*

al., 2008; Szopa *et al*., 2009). Since previous studies did not support the recessive model for association of rs2241766 with T2D our result may be as well a false positive finding.

Adiponectin mediates vascular inflammation as an inhibitor of smooth muscle cell proliferation and macrophage uptake and has been associated with decreased risk of hypertension (Iwashima *et al*., 2004), miocardial infarction (Pischon *et al*., 2004) and ischemic stroke (Chen *et al*., 2005). We, therefore, tested the association of all SNPs analysed with presence of different cardiovascular traits. In our study, rs182052 was associated with decreased risk of miocardial infarction. Allele A of rs182052 was previously associated with a decreased adiponectin serum level (Heid *et al*., 2006; Kyriakou *et al*., 2008) and, thus, would be expected to have negative effect on cardiovascular functions which is opposite to our finding. Nevertheless, Hegener *et al.* (2006) reported a decreased risk of ischemic stroke for carriers of this allele. One of the imputed haplotypes was found to be more frequent in another heart disease trait, atrial fibrillation. To our knowledge this is the first report of genetic variants of adiponectin associated with this trait. The two SNPs, rs1501299 and rs3774261, determining this haplotype, have been associated with increased adiponectin level (Heid *et al*., 2006; Kyriakou *et al*., 2008). Interestingly, plasma adiponectin is higher in patients with persistent atrial fibrillation (Shimano *et al*., 2008), which is in opposite to the general tendency of a high adiponectin level being protective to most of the CHD-related pathogeneses. Similarly, high blood adiponectin was found to be a predictor for mortality in heart failure (Chang *et al*., 2009). It has been speculated that this could be explained with lower sensitivity of adiponectin receptors in atrial fibrillation resulting in increased adiponectin secretion (Shimano e*t al*., 2008). In general, however, the situation with CHD and adiponectin polymorphisms is similar to obesity and T2D, where associations found in some studies can not be consistently replicated in other studies (Menzaghi *et al*., 2007; Vasseur *et al*., 2006). It should also be mentioned that none of the genome wide association studies have identified the *ADIPOQ* locus as a candidate for any trait (based on a database search at https://gwas.lifesciencedb.jp and http://www.genome.gov/gwastudies/).

The main drawback of our study is an increased proportion of patients with metabolic and cardiovascular traits in study group. The relatively low number of healthy participants in the study may have increased Type II error, which would mask some existing association or decrease the statistical power. From this respect, additional study with a large control group is needed to fully evaluate the impact of adiponectin polymorphisms on T2D and BMI in the Latvian population. An important problem in all studies on a large number of genetic variations is multiple testing. In our study, none of the discovered associations retained its significance ($P < 0.05$) after applying the Bonferroni test. It has been suggested, however, that study-wide adjustments are not appropriate in the context of genetic association analysis and that permutation based significance testing can be used instead. All associations found in this study remained significant after the permutation test.

In summary, although adiponectin plasma levels are linked with many metabolic traits, our study does not provide strong support for the hypothesis that SNPs in the *ADIPOQ* locus play an important role in development of T2D, obesity and CHD.

ACKNOWLEDGEMENTS

The work was supported by the National Research Programme in Medicine 2006–2009 project No. 14, "Creation of the unified and generally accessible data base on the main life expectancy and life quality threatening pathologies and epidemiology of their risk factors in Latvian population", Latvian Council of Science Grant 01.0023.01. We acknowledge Genome Database of Latvian Population, Latvian Biomedical Research and Study Centre for providing data and DNA samples.

REFERENCES

Barrett, J.C., Fry, B., Maller, J., Daly, M.J. (2005). Haploview: Analysis and visualization of LD and haplotype maps. *Bioinformatics*, **21**, 263–265.

Chang, L.C., Huang, K.C., Wu, Y.W., Kao, H.L., Chen, C.L., Lai, L.P., Hwang, J.J., Yang, W.S. (2009). The clinical implications of blood adiponectin in cardiometabolic disorders. *J. Formos. Med. Assoc*., **108**, 353–366.

Chen, M.P., Tsai, J.C., Chung, F.M., Yang, S.S., Hsing, L.L., Shin, S.J., Lee, Y.J. (2005). Hypoadiponectinemia is associated with ischemic cerebrovascular disease. *Arterioscler. Thromb. Vasc. Biol*., **25**, 821–826.

Hegener, H.H., Lee, I.M., Cook, N.R., Ridker, P.M., Zee, R.Y. (2006). Association of adiponectin gene variations with risk of incident myocardial infarction and ischemic stroke: A nested case-control study. *Clin. Chem*., **52**, 2021–2027.

Heid, I.M., Wagner, S.A., Gohlke, H., Iglseder, B., Mueller, J.C., Cip, P., Ladurner, G., Reiter, R., Stadlmayr, A., Mackevics, V., Illig, T., Kronenberg, F., Paulweber, B. (2006). Genetic architecture of the *APM1* gene and its influence on adiponectin plasma levels and parameters of the metabolic syndrome in 1,727 healthy Caucasians. *Diabetes*, **55**, 375–384.

Hu, E., Liang, P., Spiegelman, B.M. (1996). *AdipoQ* is a novel adipose- specific gene dysregulated in obesity. *J. Biol. Chem*., **271**, 10697–10703.

Iwashima, Y., Katsuya, T., Ishikawa, K., Ouchi, N., Ohishi, M., Sugimoto, K., Fu, Y., Motone, M., Yamamoto, K., Matsuo, A., Ohashi, K., Kihara, S., Funahashi, T., Rakugi, H., Matsuzawa, Y., Ogihara, T. (2004). Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension*, **43**, 1318–1323.

Kumada, M., Kihara, S., Sumitsuji, S., Kawamoto, T., Matsumoto, S., Ouchi, N., Arita, Y., Okamoto, Y., Shimomura, I., Hiraoka, H., Nakamura, T., Funahashi, T., Matsuzawa, Y. (2003). Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler. Thromb. Vasc. Biol*., **23**, 85–89.

Kyriakou, T., Collins, L.J., Spencer-Jones, N.J., Malcolm, C., Wang, X., Snieder, H., Swaminathan, R., Burling, K.A., Hart, D.J., Spector, T.D., O'Dell, S.D. (2008). Adiponectin gene *ADIPOQ* SNP associations with serum adiponectin in two female populations and effects of SNPs on promoter activity. *J. Hum. Genet*., **53**, 718–727.

Li, L.L., Kang, X.L., Ran, X.J., Wang, Y., Wang, C.H., Huang, L., Ren, J., Luo, X., Mao, X.M. (2007). Associations between 45T/G polymorphism of the adiponectin gene and plasma adiponectin levels with type 2 diabetes. *Clin. Exp. Pharmacol. Physiol*., **34**, 1287–1290.

Mackevics, V., Heid, I.M., Wagner, S.A., Cip, P., Doppelmayr, H., Lejnieks, A., Gohlke, H., Ladurner, G., Illig, T., Iglseder, B., Kronenberg, F., Paulweber, B. (2006). The adiponectin gene is associated with adiponectin levels but not with characteristics of the insulin resistance syndrome in healthy Caucasians. *Eur. J. Hum. Genet*., **14**, 349–356.

Matsuda, M., Shimomura, I., Sata, M., Arita, Y., Nishida, M., Maeda, N., Kumada, M., Okamoto, Y., Nagaretani, H., Nishizawa, H., Kishida, K., Komuro, R., Ouchi, N., Kihara, S., Nagai, R., Funahashi, T., Matsuzawa, Y. (2002). Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. *J. Biol. Chem*., **277**, 37487–37491.

Matsuzawa, Y., Shimomura, I., Kihara, S., Funahashi, T. (2003). Importance of adipocytokines in obesity-related diseases. *Horm. Res*., **60** (Suppl 3), 56–59.

Menzaghi, C., Trischitta, V., Doria, A. (2007). Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. *Diabetes*, **56**, 1198–1209.

Ouchi, N., Kihara, S., Funahashi, T., Matsuzawa, Y., Walsh, K. (2003). Obesity, adiponectin and vascular inflammatory disease. *Curr. Opin. Lipidol*., **14**, 561–566.

Pischon, T., Girman, C.J., Hotamisligil, G.S., Rifai, N., Hu, F.B., Rimm, E.B. (2004). Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA*, **291**, 1730–1737.

Potapov, V.A., Chistiakov, D.A., Dubinina, A., Shamkhalova, M.S., Shestakova, M.V., Nosikov, V.V. (2008). Adiponectin and adiponectin receptor gene variants in relation to type 2 diabetes and insulin resistance-related phenotypes. *Rev. Diabet. Stud*., **5**, 28–37.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J., Sham, P.C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *Amer. J. Hum. Genet*., **81**, 559–575.

Shimano, M., Shibata, R., Tsuji, Y., Kamiya, H., Uchikawa, T., Harata, S., Muto, M., Ouchi, N., Inden, Y., Murohara, T. (200). Circulating adiponectin levels in patients with atrial fibrillation. *Circ. J*., **72**, 1120–1124.

Spranger, J., Kroke, A., Mohlig, M., Bergmann, M.M., Ristow, M., Boeing, H., Pfeiffer, A.F. (2003). Adiponectin and protection against type 2 diabetes mellitus. *Lancet*, **361**, 226–228.

Szopa, M., Malczewska-Malec, M., Wilk, B., Skupien, J., Wolkow, P., Malecki, M.T., Sieradzki, J. (2009). Variants of the adiponectin gene and type 2 diabetes in a Polish population. *Acta Diabetol.*, January.

Vasseur, F., Meyre, D., Froguel, P. (2006). Adiponectin, type 2 diabetes and the metabolic syndrome: Lessons from human genetic studies. *Expert Rev. Mol. Med*., **8**, 1–12.

Weyer, C., Funahashi, T., Tanaka, S., Hotta, K., Matsuzawa, Y., Pratley, R.E., Tataranni, P.A. (2001). Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. *J. Clin. Endocrinol. Metab*., **86**, 1930–1935.

Xita, N., Georgiou, I., Chatzikyriakidou, A., Vounatsou, M., Papassotiriou, G.P., Papassotiriou, I., Tsatsoulis, A. (2005). Effect of adiponectin gene polymorphisms on circulating adiponectin and insulin resistance indexes in women with polycystic ovary syndrome. *Clin. Chem*., **51**, 416–423.

Yang, W.S., Lee, W.J., Funahashi, T., Tanaka, S., Matsuzawa, Y., Chao, C.L., Chen, C.L., Tai, T.Y., Chuang, L.M. (2001). Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J. Clin. Endocrinol. Metab*., **86**, 3815–3819.

Received 11 July 2009

ADIPONEKTĪNA GĒNA LOKUSA ASOCIĀCIJAS ANALĪZE SAISTĪBĀ AR OTRĀ TIPA DIABĒTU, ĶERMEŅA MASAS INDEKSU UN KARDIOVASKULĀRĀM PAZĪMĒM LATVIJAS POPULĀCIJĀ

Neraugoties uz daudzajiem adiponektīna gēna variantu asociācijas pētījumiem saistībā ar otrā tipa diabētu (T2D) un paaugstinātu ķermeņa masas indeksu (ĶMI), līdz šim iegūtie rezultāti bieži ir pretrunīgi. Lai noskaidrotu adiponektīna gēna promotera un kodējošā rajona bieži sastopamo polimorfismu ietekmi uz šīm pazīmēm Latvijas populācijā, balstoties uz haplobloku struktūru un iepriekš zināmiem asociācijas pētījumiem, tika izvēlēti desmit SNP (rs2241767, rs1501299, rs3777261, rs16861210, rs2241766, rs822396, rs182052, rs17300539, rs16861194, rs266729). Izvēlētie SNP tika genotipēti pētījuma grupā, kas sastāvēja no 835 Valsts iedzīvotāju genoma datu bāzes gēnu donoriem. Šajā grupā bija pārsvarā no T2D un koronārās sirds slimības (KSS) pacienti. Neviens no individuāliem polimorfismiem nebija būtiski asociēts ar T2D vai ĶMI, lietojot daudzfaktoru loģistiskās vai lineārās regresijas analīzes un koriģējot rezultātus pēc dzimuma, vecuma un citiem būtiskiem līdzfaktoriem. Tomēr tika atrasts, ka rs2241766 T alēles homozigotu frekvence T2D pacientu vidū bija būtiski lielāka nekā kontroles grupā (nekoriģēta $P = 0.007$). Analizējot saistībā ar citām pazīmēm, rs182052 G alēle tika biežāk atrasta pacientiem ar miokarda infarktu ($P = 0.02$; OR = 0.76; CI95%[0.61–0.92]), salīdzinot ar pārējo pētījuma grupu. Haplotipu analīze atklāja viena haplotipa būtisku asociāciju ar mirdzaritmiju (nekoriģēta $P = 0.01$). Kopumā var secināt, ka adiponektīna gēna polimorfismi nav uzskatāmi par būtiskiem T2D riska faktoriem, bet varētu būt iesaistīti koronārās sirds slimības patoģenēzē Latvijas populācijā.