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Association of the peroxisome proliferator–activated receptor γ gene with type 2 diabetes mellitus varies by physical activity among non-Hispanic whites from Colorado

Tracy L. Nelson[a,b,*], Tasha E. Fingerlin[b], Laurie K. Moss[b], M. Michael Barmada[c], Robert E. Ferrell[c], Jill M. Norris[b]

[a]Department of Health and Exercise Science, Colorado State University, Fort Collins, CO 80523, USA
[b]Department of Preventive Medicine and Biometrics, University of Colorado at Denver and Health Sciences Center, Denver, CO 80262, USA
[c]Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, USA

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Abstract

The objective of the study was to test for an association between type 2 diabetes mellitus (T2DM) and the Pro12Ala polymorphism in the peroxisome proliferator–activated receptor γ gene (*PPAR-γ*) in families from Colorado. We were also interested in whether there was any modification by diet or physical activity. We studied 216 Hispanic pedigrees (1850 nuclear families) and 236 non-Hispanic white (NHW) pedigrees (1240 families) from the San Luis Valley and Denver, CO. We genotyped the Pro12Ala polymorphism of the *PPAR-γ* gene. Historical physical activity (average metabolic equivalent task units per week) as well as average dietary intake over the past year was assessed by self-report. Using the family-based association test, we found that in NHWs the Pro12 allele was associated with T2DM only among those with low physical activity ($P = .006$), or with high polyunsaturated fat intake ($P = .034$). A significant interaction between low physical activity and the Pro12 allele in association with T2DM was also detected using generalized estimating equations models ($P = .022$). Furthermore, after stratifying by physical activity similar to the family-based association test, we found the Pro12 allele was significantly associated with T2DM in those with low physical activity (odds ratio, 2.37; 95% confidence interval, 1.14-4.94). There may be a gene-environment interaction between the Pro12 allele of the *PPAR-γ* gene and physical activity that results in increased risk of T2DM in NHWs.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major cause of morbidity and mortality among Americans. From 1980 through 2004, the crude prevalence of diagnosed diabetes increased 104% [1]. Genes play a major role in determining who will develop T2DM, and it is commonly assumed that nongenetic factors interact with genetic variation to increase risk for T2DM [2,3]. The peroxisome proliferator–activated receptor γ (*PPAR-γ*) gene is located on chromosome 3. The *PPAR-γ* gene is a transcription factor that regulates adipocyte differentiation and insulin sensitivity by promoting transcription of numerous target genes [4,5] and has been associated with T2DM [6-8]. It is activated by fatty acids and the insulin-sensitizing thiazolidinediones [5]. Specifically, the Pro12Ala polymorphism has been associated with T2DM in some studies [7,9,10], and in others, this polymorphism has been found to be protective [11-14].

Because diet and physical activity are known factors in the development of T2DM, it is important to consider them when evaluating genetic risk. Diets high in saturated fat, in particular, have been shown to increase the risk of T2DM [15], whereas polyunsaturated fatty acids (PUFAs)[1] have shown to decrease the risk [16]. Furthermore, PUFAs are ligands for *PPAR-γ*, which regulates insulin sensitivity. Physical activity is also important in regulating glucose metabolism, with higher activity being associated with lower risk for T2DM [17]. Because gene-gene and gene-

* Corresponding author. Department of Health and Exercise Science, Colorado State University, Fort Collins, CO 80523, USA. Tel.: +1 970 491 6320; fax: +1 970 491 0445.
E-mail address: tnelson@cahs.colostate.edu (T.L. Nelson).

[1] Fatty acids with 2 or more double bonds between carbon atoms and found in such oils as soybean, corn, sesame, and sunflower or fish and fish oil.

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environment interactions are proving to be important in determining risk for chronic diseases such as T2DM [18-20], we were interested in determining if T2DM was associated with the rare allele (Ala12) of the Pro12Ala polymorphism in the *PPAR-γ* gene among Hispanics and NHWs from Colorado. We were also interested in whether such associations varied by dietary fat intake or physical activity.

2. Subjects, materials and methods

2.1. Sample

Data were collected from families in the San Luis Valley and the Denver metropolitan area in Colorado as part of the Gene ENvironment Interactions (GENI) study. Families were identified through at least 1 individual with T2DM. There were 216 Hispanic pedigrees (1850 nuclear families) and 236 NHW pedigrees (1240 nuclear families) used for analysis in this study. Informed consent was obtained from all subjects and approval was obtained from the institutional review board at the University of Colorado at Denver and Health Sciences Center (Denver, CO).

2.2. Genotyping

The buffy coat for DNA extraction was isolated from EDTA anticoagulated whole-blood samples from each participant. DNA was extracted using the Pure Gene kit (Gentra Systems, Minneapolis, MN). The Pro12Ala polymorphism in the *PPAR-γ* gene was detected through an engineered *Bst*UI restriction enzyme site and the primers used for amplification were 5′-GCCAATTCAAGCCCAGTC-3′ and 5′-GATATGTTTGCAGACAGTGTATCAGTG-AAGGAATCGCTTTCCG-3′. Digestion products were resolved on 2% agarose gels. Fragment sizes were assigned by comparison to known size markers.

Genotypes were checked for deviations from Hardy-Weinberg equilibrium proportions. Mendelian inconsistencies were identified by using Pedcheck [21], and probable genotyping errors were retyped. Genotypes that resulted in mendelian inconsistencies that could not be resolved by retyping were set to missing.

2.3. Diabetes status and anthropometrics

Subjects were defined as having T2DM if they were diagnosed by a physician and were on oral hypoglycemic agents or insulin treatment. For those who reported no T2DM or untreated T2DM, diabetes status was determined by an oral glucose tolerance test (OGTT) using American Diabetes Association criteria (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). Those determined to have T2DM from the OGTT were also included in the analysis. Plasma glucose was measured at the University of Colorado School of Medicine Adult General Clinical Research Center.

Weight was measured in kilograms by using a balance beam scale calibrated weekly with standard weights. Subjects were measured while wearing a hospital scrub suit to standardize clothing weight across seasons. Height was measured with a stadiometer to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. For diabetic subjects, self-reported BMI at the time of diabetes diagnosis was used.

2.4. Physical activity

Both lifetime and current leisure time and occupational physical activity were assessed in each study participant by using the Physical Activity Questionnaire developed by Kriska et al [22]. This questionnaire has been found to be reliable and valid among the Pima Indian population to evaluate the relationship between physical activity and T2DM [22]. Each study participant completed the questionnaire one time during the study (at the clinic visit). The participant was asked to list all the physical leisure-time activities they participated in at least 10 times since the age of 12. The amount of time (hours per week, months per year, and number of years) spent performing each activity was broken into the periods of 12 to 18, 19 to 34, 35 to 49, 50 years and older, past 12 months, and past 7 days. The participant was also asked to list all of the jobs they held, their age at the start of the job, the amount of time they spent on the job (hours per day, days per week, and months per year), and the hours they spent in light, moderate, or hard activity. Energy expenditure was assessed as metabolic equivalent task (MET) units. The MET is the ratio of the metabolic rate during exercise to the metabolic rate at rest [23]. The average METs per week (before the diagnosis of T2DM for affected individuals) was calculated for each study participant.

2.5. Diet

A diet assessment questionnaire that is a modified version of the National Cancer Institute Health History and Habits Questionnaire [24,25] was used in this study. This is a food frequency questionnaire that asks about intake in the past year. This questionnaire was modified to assess regional and ethnic diversity for use in the Insulin Resistance and Atherosclerosis Study (IRAS), which has a site in the San Luis Valley, and found to be valid in this population [26]. Total polyunsaturated and saturated fatty acid (SFA)[2] intake was estimated and the PUFA/SFA ratio was estimated using total PUFA and total SFA intake.

2.6. Statistical analyses

To test for the association between the individual alleles and T2DM, the family-based association test (FBAT) [27] was used. The FBAT is a generalization of the transmission disequilibrium test [28] that is valid in the presence of missing parental data and relatedness among parent-

[2] Fatty acids with no double bond between carbon atoms, found in foods such as whole milk and red meats.

Table 1
Descriptive statistics for Hispanic and non-Hispanic white: GENI study population

	Hispanic		Non-Hispanic white	
	N	Frequency/mean ± SD	N	Frequency/mean ± SD
Sex (% female)	915	58.0%	566	56.0%
Age, mean ± SD, (y)	914	51.5 ± 13.4	566	53.5 ± 13.9
Ala12 allele frequency	914	13.5%	566	10.5%
BMI (kg/m^2)	871	30.0 ± 6.3	519	31.3 ± 7.1
Percent diabetic	914	58%	566	66%
PUFA fat, mean ± SD (g)	903	16.1 ± 10.6	563	13.4 ± 8.1
SFA fat, mean ± SD (g)	903	27.7 ± 17.2	563	25.7 ± 15.5
PUFA/SFA ratio, mean ± SD	903	0.6 ± 0.3	563	0.6 ± 0.2
Mean physical activity (METs)				
Males	384	177.3 ± 124.9	249	147.1 ± 111.1
Females	531	61.0 ± 79.9	317	72.7 ± 77.8

offspring trios. When parental information is missing, the FBAT conditions on the partially observed parental genotypes to obtain the conditional distribution of the offspring genotypes [29]. To test for linkage disequilibrium while accounting for familial correlation, the FBAT statistics were calculated using the empirical variance (−e) option [30]. The primary analyses assumed an additive model because it has been shown to be powerful over a range of true underlying disease models [27], and using only one model reduced the number of tests performed. We conducted overall and stratified analyses by tertiles of PUFA and SFA intake, the PUFA/SFA ratio, and gender-specific physical activity level tertiles. Only the lowest and highest tertiles were used (ie, the individuals in the middle tertile were excluded) to limit misclassification of exposure.

To further explore the FBAT findings, we analyzed our data by using a generalized estimating equations (GEE, SAS Institute, Cary, NC) model, with a sandwich estimator to account for familial correlation. We considered diet and physical activity as categorical variables (categorized by tertiles and using only the upper and lower tertiles). Similar to the FBAT, an additive model was used; however, unlike the FBAT, the interaction terms were included in our models. We then removed the interaction term and stratified these GEE models by diet and physical activity tertiles similar to the analyses in the FBAT. Odds ratios (ORs) and 95% confidence intervals (CIs) were then obtained.

3. Results

Descriptive statistics are provided in Table 1. The subjects used in the GEE analysis are presented. There were 66 fewer subjects among Hispanics in the family-based association analysis and 31 fewer among NHWs because the family-based method does not use the founders in the analyses, whereas GEE uses all family members. The means for this reduced group were nearly identical for the variables listed (data not shown). The *PPAR-γ* Ala12 allele frequency was 13.5% among Hispanics, which is similar to that in a study among Mexican Americans from San Antonio, TX (11.1%) [31]. Among NHWs, the *PPAR-γ* Ala12 allele frequency was 10.5%, which is also similar to that in other studies among NHWs (~9.2%) [32]. The frequency of the Ala12 allele was consistent with Hardy-Weinberg expectations (data not shown). Fifty-eight percent of the Hispanic population and approximately 66% of the NHW population had T2DM and both groups were considered, on average, obese (BMI ≥30 kg/m^2) based on World Health Organization standards [33]. The composition of the fats consumed varied, with mean consumption of SFA almost twice that of PUFA. Table 2 shows the

Table 2
Number of subjects by *PPAR-γ* genotype stratified by diabetes status, and high and low tertiles of dietary factors and physical activity among Hispanic (H) and non-Hispanic whites (NHW) from the GENI study

	Pro12Pro		Pro12Ala		Ala12Ala	
	H	NHW	H	NHW	H	NHW
SFA fat						
High SFA fat tertile	240	155	59	38	3	1
Diabetic	123	105	31	24	0	0
Nondiabetic	117	50	28	14	3	1
Low SFA fat tertile	227	154	66	35	4	0
Diabetic	142	101	34	23	3	0
Nondiabetic	85	53	32	12	1	0
PUFA fat						
High PUFA fat tertile	238	159	61	33	4	1
Diabetic	129	110	31	22	0	0
Nondiabetic	109	49	30	11	4	1
Low PUFA fat tertile	225	148	78	36	6	1
Diabetic	149	97	43	23	4	0
Nondiabetic	76	51	35	13	2	1
PUFA/SFA ratio						
High PUFA/SFA tertile	235	150	64	40	3	1
Diabetic	146	104	32	29	1	0
Nondiabetic	89	46	32	11	2	1
Low PUFA/SFA tertile	227	149	74	37	2	1
Diabetic	125	99	42	22	1	0
Nondiabetic	102	50	32	15	1	1
Physical activity (PA)						
High PA tertile	232	145	64	40	6	0
Diabetic	145	95	31	30	4	0
Nondiabetic	87	50	33	10	2	0
Low PA tertile	235	153	69	35	1	1
Diabetic	135	107	42	18	1	0
Nondiabetic	100	46	27	17	0	1

Table 3
Association between the *PPAR-γ* gene Pro12 allele and T2DM

	N	S	E(S)	*P*
Overall: Pro12 allele	535	132.00	127.82	.315
SFA intake tertile				
High	186	59.00	55.73	.280
Low	173	47.00	44.83	.405
PUFA intake tertile				
High	183	65.00	57.38	.034[a]
Low	171	34.00	33.75	.915[a]
PUFA/SFA ratio intake tertile				
High	178	68.00	63.30	.187
Low	180	38.00	39.40	.563
Physical activity tertile				
High	177	50.00	51.25	.638
Low	174	42.00	35.25	.006[a]

Data are results of the FBAT overall and stratified by tertiles of dietary intake and physical activity among NHWs from the GENI study. *S* indicates test statistic; E(*S*), expected value of *S* under Ho (null hypothesis).

[a] Greater prevalence of T2DM in those with the common allele.

number of Hispanic and NHW participants by genotype categorized by diet, physical activity, and diabetes status. Among both Hispanics and NHWs, the Pro12Pro genotype was more common among diabetic subjects in all diet and physical activity groups. The same was true when the Pro12Ala genotype was considered, although not to the same magnitude among Hispanics. The Ala12Ala genotype was inconsistently associated with diabetes status in Hispanics, and among NHWs, there were no diabetic subjects with the Ala12Ala genotype.

When we considered the association of T2DM with the *PPAR-γ* gene using family-based association methods, we did not find any significant association in NHWs or Hispanics for increasing copies of the Ala12 allele or Pro12 allele overall (Table 3 for NHWs, Ala12 and Hispanic data not shown). We then stratified our analyses by tertiles of dietary intake and physical activity. In the NHWs, having more copies of the Pro12 allele was associated with T2DM in those subjects with low levels of physical activity (P = .006) as well as in those in the upper tertile of PUFA intake (P = .034) (Table 3). We then conducted GEE analyses to test for interaction of this effect by including an interaction term in the model. This also allowed us to calculate measures of association (OR) to further describe the relationship. Similar to the family-based methods, there was no association between the Pro12 allele and T2DM in the GEE analysis. However, the interaction term for physical activity and the Pro12 allele in association with T2DM was statistically significant (P = .022). Based on these findings, we eliminated the interaction term and stratified the GEE analysis by high and low tertiles of diet and physical activity similar to the analyses carried out in the family-based model. We found having more copies of the Pro12 allele was associated with T2DM among those with low physical activity (OR, 2.37; 95% CI 1.14-4.94). There was no statistically significant interaction for PUFA intake and the Pro12 allele in the GEE analysis (see Table 4). We did not find any other associations in NHWs and there was no significant modification by diet or physical activity between the *PPAR-γ* gene and T2DM in Hispanics.

4. Discussion

Although this study did not find any association between the Ala12 allele of the Pro12Ala polymorphism and T2DM in either Hispanics or NHWs, we did find that with increasing copies of the Pro12 allele, NHWs were more likely to have T2DM if they were physically inactive. Numerous studies have considered the *PPAR-γ* gene and T2DM or insulin sensitivity [7,10,12-14,34-36]; however, few have considered such associations among Hispanics [37], and we are aware of only one study that considered physical activity [19].

Strengths of the present study include the use of both the family-based association method and GEE models to analyze the data as well as consideration of environmental factors as potential moderators of the association between the *PPAR-γ* gene and T2DM. Both the family-based association method and GEE models have different strengths: The family-based method tests for linkage as well as association, whereas the GEE analysis tests only for association; furthermore, the family-based method controls for any false associations that may be due to population stratification. The GEE model, however, is more powerful because it includes both parents and offspring, whereas the family-based method uses only the offspring in the analysis; furthermore, the GEE model allows us to test for "true" interactions within the model and, thus, does not limit power by necessitating stratification. There-

Table 4
Association between the *PPAR-γ* gene Pro12 allele and T2DM

	N	OR[a] (95% CI)	*P*[b]
Overall			
Pro12 allele	566	1.02 (0.73-1.43)	
SFA × Pro12 allele interaction term[a]			.52
High SFA fat tertile	194	1.37 (0.69-2.70)	
Low SFA fat tertile	189	1.01 (0.50-2.04)	
PUFA × Pro12 allele interaction term[a]			.91
High PUFA fat tertile	193	1.28 (0.66-2.49)	
Low PUFA fat tertile	185	1.30 (0.67-2.53)	
PUFA/SFA ratio × Pro12 allele interaction term[a]			.46
High PUFA/SFA tertile	191	1.07 (0.57-2.07)	
Low PUFA/SFA tertile	187	1.51 (0.76-3.03)	
Physical activity × Pro12 allele interaction term[a]			.02
High physical activity tertile	185	0.64 (0.30-1.38)	
Low physical activity tertile	189	2.37[c] (1.14-4.94)	

Data are results of GEE models overall, with interaction terms, stratified by high and low tertiles of the dietary factors and physical activity among NHWs from the GENI study.

[a] Odds ratio comparing possessing 1 copy of the Pro12 allele to 0 copies or possessing 2 copies to 1 copy.

[b] P value for the interaction term.

[c] After controlling for sex and age: OR, 2.54; 95% CI, 1.24-5.21.

fore, finding an interaction between low physical activity and the Pro12 allele in association with T2DM in the GEE model as well as an association between T2DM and the Pro12 allele when we stratified by physical activity in both the FBAT and GEE models gives us confidence that this association is present among this sample. It is important to point out that without consideration of physical activity, we would not have detected a significant association between the Pro12 allele and T2DM.

The previous studies that have considered the association of T2DM and both the Ala12 allele as well as the Pro12 allele have not been consistent. This variation in results may be due to the use of only one modeling tool as well as lack of consideration of potential environmental moderators. For example, a recent study from the San Luis Valley Diabetes Study did not find any association of the Pro12Ala polymorphism with insulin resistance measured by the homeostasis model assessment of insulin resistance among Hispanic and NHW women or men [37]. These results are similar to our study for the main effects of the Ala12 allele, which is not surprising because this study used subjects from the same population group as the present study. The other study that considered Hispanics also did not find the Ala12 allele to be associated with T2DM [31]; thus, our results among Hispanics corroborate the previous work among this group. The positive findings we did find for T2DM and the Pro12 allele depended on physical activity levels; because the Moffett et al [37] and the Cole et al [31] studies did not consider physical activity in their analysis, we could not make such a comparison. The same potential problems of comparison may explain some of the inconsistencies in the literature, as numerous studies have found an association between these alleles and T2DM [7,10,34] as well as the opposite effect of improved insulin sensitivity or decreased risk for T2DM [12-14,35,36] or no association at all [37].

There is one study we are aware of by Franks et al [19] that considered physical activity and fasting insulin levels among Pro12 homozygotes and Ala12 carriers. They did not find any correlation between physical activity and fasting insulin in either group; however, when they considered both physical activity and dietary fat (eg, PUFA/SFA ratio), they found their effects to be additive. Specifically, among those homozygous for the Pro12 allele, they found those with low physical activity and low PUFA/SFA ratios to have higher fasting insulin levels than those with high physical activity and high PUFA/SFA ratios [19]. Because of power issues, we could not consider interactions among both diet and physical activity; however, the physical activity results are in the same direction as ours, with greater fasting insulin (in our case, T2DM) associated with the Pro12 allele if the subject reported low physical activity. The mechanism for these associations is proposed by Franks et al to include increased energy flux among active people promoting improved transportation of PUFAs to *PPAR-γ*. Because PUFAs act as ligands for *PPAR-γ*, they would potentially increase *PPAR-γ* activity and this could then increase insulin sensitivity. Although we did not find consistent associations between the Pro12 allele and T2DM when we considered dietary PUFA intake, this mechanism is still plausible among our sample.

Studies that have considered interactions of the Ala12 and Pro12 alleles and diet have found higher PUFA/SFA ratios to be associated with lower fasting insulin levels in Ala12 carriers [18]. Although we did not find associations to vary by the PUFA/SFA ratio, we did find the Pro12 allele to be associated with T2DM among those with higher PUFA intake; however, these results were not corroborated by the GEE analysis and thus may be due to chance. A study carried out among participants in the Quebec Family Study found that saturated fat and total fat were more associated with components of the metabolic syndrome among Pro12 homozygotes than among those with the Ala12 allele. They did not find associations for PUFAs, but similar to our study, the Pro12 allele was modified by dietary factors [32]. Overall, the interpretation of the studies considering dietary factors is difficult and could be due to primary differences in the analytic strategies and study populations. For example, we found different results for association of the Pro12 allele and T2DM by PUFA intake when we used different modeling methods. Finding such differences in the same population group suggests that different modeling methods can give very different outcomes. So it is not surprising that when different study populations are combined with different analytical techniques there are so many inconsistencies in the literature.

In conclusion, using 2 different analysis methods, we found a significant association for the Pro12 allele of the *PPAR-γ* gene and T2DM among NHWs with low physical activity. These results reinforce the need to consider the environment when assessing the genetic epidemiology of complex phenotypes.

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References

[1] Centers for Disease Control (CDC). National diabetes surveillance system. US Department of Health and Human Services; 2004. www.cdc.gov/diabetes/statistics/index.htm.
[2] Elbein S. The genetics of human noninsulin-dependent (type 2) diabetes mellitus. J Nutr 1997;127:1891S-6S.
[3] Bartsocas C, Leslie RD. Genetics of diabetes mellitus. Am J Med Genet 2002;115:1-3.
[4] Auwerx J. PPAR gamma, the ultimate thrifty gene. Diabetologia 1999; 42:1033-49.
[5] Kliewer S, Xu HE, Lambert MH, Willson TM. Peroxisome proliferator–activated receptors: from genes to physiology. Recent Prog Horm Res 2001;56:239-63.

[6] Hara K, Tobe K, Okada T, Kadowaki H, Akanuma Y, Ito C, et al. A genetic variation in the PGC-1 gene could confer insulin resistance and susceptibility to type II diabetes. Diabetologia 2002;45:740-3.
[7] Evans D, de Heer J, Hagemann C, Wendt D, Wolf A, Beisiegel U, et al. Association between the P12A and c1431t polymorphisms in the peroxisome proliferator activated receptor gamma (PPARgamma) gene and type 2 diabetes. Exp Clin Endocrinol Diabetes 2001; 109:151-4.
[8] Andruliontye L, Zacharova J, Chiasson JL, Laasko M, STOP-NIDDM Study Group. Common polymorphisms of the PPAR-gamma2 (Pro12Ala) and PGC-1alpha (Gly482Ser) genes are associated with the conversion from impaired glucose tolerance to type 2 diabetes in the STOP-NIDDM trial. Diabetologia 2004;47:2176-84.
[9] Stumvoll M, Stefan N, Fritsche A, Madaus A, Tschritter O, Koch M, et al. Interaction effects between common polymorphisms in PPARgamma2 and insulin receptor substrate 1 (Gly972Arg) on insulin sensitivity. J Mol Med 2002;80:33-8.
[10] Lindi V, Uusitupa MIJ, Lindstrom J, Louheranta A, Eriksson JG, Valle TT, et al. Association of the Pro12Ala polymorphism in the PPAR-γ gene with 3-year incidence of type 2 diabetes and body weight change in the Finnish diabetes prevention study. Diabetes 2002;51:2581-6.
[11] Kao W, Coresh J, Shuldiner AR, Boerwinkle E, Bray MS, Brancati FL. Pro12Ala of the peroxisome proliferator–activated receptor-2 gene is associated with lower serum insulin levels in nonobese African Americans. Diabetes 2003;52:1568-72.
[12] Ek J, Anderson G, Urhammer SA, Hansen L, Carstensen B, Borch-Johnsen K, et al. Studies of the Pro12Ala polymorphism of the peroxisome proliferator–activated receptor-gamma2 (PPAR-gamma2) gene in relation to insulin sensitivity among glucose tolerant Caucasians. Diabetologia 2001;44:1170-6.
[13] Li S, Chen W, Srinivasan SR, Boerwinkle E, Berenson GS. The peroxisome proliferator–activated receptor-gamma2 gene polymorphism (Pro12Ala) beneficially influences insulin resistance and its tracking from childhood to adulthood: the Bogalusa Heart Study. Diabetes 2003;52:1265-9.
[14] Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, et al. The common PPAR gamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. Nat Genet 2000; 26:76-80.
[15] van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. Diabetes Care 2002;25:417-24.
[16] Manco M, Calvani M, Mingrone G. Effects of dietary fatty acids on insulin sensitivity and secretion. Diabetes Obes Metab 2004; 6:402-13.
[17] Pan X, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537-44.
[18] Luan J, Browne PO, Harding AH, Halsall DJ, O'Rahilly S, Krishna VK, et al. Evidence for gene-nutrient interaction at the PPAR γ locus. Diabetes 2001;50:686-9.
[19] Franks P, Luan J, Browne PO, Harding AH, Rahilly SO, Chatterjee VKK, et al. Does peroxisome proliferator–activated receptor γ geneotype (Pro12Ala) modify the association of physical activity and dietary fat with fasting insulin level? Metabolism 2004;53:11-6.
[20] Damcott C, Moffett SP, Feingold E, Barmada MM, Marshal JA, Hamman RF, et al. Genetic variation in fatty acid–binding protein-4 and peroxisome proliferator–activated receptor gamma interactively influence insulin sensitivity and body composition in males. Metabolism 2004;53:303-9.
[21] O'Connell JR, Weeks DE. PedCheck: a program for identification of genotype incompatibilities in linkage analysis. Am J Hum Genet 1998;63:259-66.
[22] Kriska A, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, et al. Development of a questionnaire to examine the relationship of physical activity and diabetes in Pima Indians. Diabetes Care 1990; 13:401-11.
[23] Lynch J, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R, et al. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non–insulin-dependent diabetes mellitus in middle-aged men. Arch Intern Med 1996; 156:307-14.
[24] Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453-69.
[25] Block G, Woods M, Potosky A, Clifford D. Validation of a self-administered diet history questionnaire using multiple diet records. J Clin Epidemiol 1990;43:1327-35.
[26] Mayer-Davis EJ, Vitolins MZ, Carmichael SL, Hemphill S, Tsaroucha G, Rushing J, et al. Validity and reproducibility of a food frequency interview in a multi-cultural epidemiology study. Ann Epidemiol 1999;9:314-24.
[27] Horvath S, Xu X, Laird NM. The family based association test method: strategies for studying general genotype-phenotype associations. Eur J Hum Genet 2001;9:301-6.
[28] Spielman R, McGinnis RE, Ewens WJ. Transmission test for linkage disequillibrium: the insulin gene region and insulin dependent diabetes mellitus (IDDM). Am J Hum Genet 1993;52:506-16.
[29] Rabinowitz D, Laird N. A unified approach to adjusting association tests for population admixture with arbitrary pedigree structure and arbitrary missing marker information. Hum Hered 2000;50:211-23.
[30] Lake SL, Blacker D, Laird NM. Family-based tests of association in the presence of linkage. Am J Hum Genet 2000;67:1515-25.
[31] Cole S, Mitchell BD, Hsueh WC, Pineda P, Beamer PA, Shuldiner AR, et al. The Pro12Ala variant of peroxisome proliferator–activated receptor-gamma2 (PPAR-γ2) is associated with measures of obesity in Mexican Americans. Int J Obes 2000;24:522-4.
[32] Robitaille J, Despres JP, Perusse L, Vohl MC. The PPAR-gamma P12A polymorphism modulates the relationship between dietary fat intake and components of the metabolic syndrome: results from the Quebec Family Study. Clin Genet 2003;63:109-16.
[33] WHO. Obesity: preventing and managing the global epidemic. Geneva: WHO Division of Noncommunicable Diseases; 1998.
[34] Pisabarro RE, Sanguinetti C, Stoll M, Prendez D. High incidence of type 2 diabetes in peroxisome proliferator–activated receptor gamma2 Pro12Ala carriers exposed to a high chronic intake of trans fatty acids and saturated fatty acids. Diabetes Care 2004;27:2251-2.
[35] Ghoussaini M, Meyre D, Lobbens S, Charpentier G, Clement K, Charles MA, et al. Implication of the Pro12Ala polymorphism of the PPAR-gamma 2 gene in type 2 diabetes and obesity in the French population. BMC Med Genet 2005;6:11.
[36] Deeb S, Fajas L, Nemoto M, Pihlajamaki J, Mykkanen L, Kuusisto J, et al. Nature Gen. A Pro12Ala substitution in PPARγ2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. Nat Genet 1998;20:284-7.
[37] Moffett S, Feingold E, Barmada MM, Damcott CM, Marshall JA, Hamman RF, et al. The C161→T polymorphism in peroxisome proliferator–activated receptor gamma, but not P12A, is associated with insulin resistance in Hispanic and non-Hispanic white women: evidence for another functional variant in peroxisome proliferator–activated receptor gamma. Metabolism 2005;54:1552-6.