Pro12Ala polymorphism in PPAR- γ 2 and dementia in Chinese nonagenarians/centenarians

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Abstract We examined the existence of a relationship between polymorphism and dementia in subjects aged 90 years and above. The sample included 732 unrelated Chinese nonagenarians/centenarians (aged 90–108 years, mean age 93.68 years; 67.5% women). The Pro12Ala variant was examined using polymerase chain reaction restriction fragment length polymorphism. Cognitive function was measured with 30-item mini-mental state examination. The genotype frequencies of the Pro12Ala polymorphism were 0% Ala12Ala, 9.1% Pro12Ala, and 90.9% Pro12Pro. The prevalence rates of dementia were 64.9% in the whole sample (45.0% for men and 74.5% for women). In both men and women, between subjects with and without 12Ala carriers, there was no significant difference in cognitive function scores and also no significant difference in prevalence of dementia; there was no significant difference in frequency of 12Ala carriers between subjects with and without dementia. Multiple logistic regression was performed by adjusting clinical factors that are thought to be associated with cognitive function or

with 12Ala carriers. We found that 12Ala is not a risk factor for dementia. We found that Pro12Ala polymorphism in PPAR- γ 2 was not directly correlated with dementia among Chinese nonagenarians and centenarians.

Keywords Pro12Ala polymorphism · PPAR- γ 2 · Dementia · Nonagenarians and centenarians

Introduction

Dementia is a common and multifactorial disorder in which multiple genes are likely to be involved concurrently (Katsel et al. 2007; Poorkaj et al. 2001; Silberfeld et al. 2002). Pathophysiology of dementia depends on a variety of interrelated factors, in which the genetic determinant must be prominent in the development of dementia in view of the heritability of cognitive function. Peroxisome proliferator-activated receptors gamma (PPAR- γ) gene, as a candidate gene, seems to attract particular interest in relation to dementia (Santos et al. 2005).

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-dependent transcription factors (Issemann and Green 1990). So far, three PPAR distinct isoforms, PPAR- α , PPAR- β/δ , and PPAR- γ , have been identified and cloned. PPAR- γ is mostly

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expressed in adipose tissues, and it controls adipocyte differentiation and lipid storage (Forman et al. 1997; Kliewer et al. 1995; Tontonoz et al. 1994), affects the action of insulin, and regulates glucose homeostasis (Berger and Moller 2002; Spiegelman 1998). Pro12Ala polymorphism in PPAR- γ 2 may therefore have important consequences related to obesity, insulin resistance, and type 2 diabetes mellitus (McIntyre et al. 2007; Watson and Craft 2003; Watson et al. 2005).

A close association between cognitive impairment and Pro12Ala polymorphism in PPAR- γ 2 has already been highly reported in prospective and cross-sectional observational studies, but the role of Pro12Ala polymorphism in PPAR- γ in the pathogenesis of cognitive impairment and dementia remains equivocal (Johnson et al. 2008; Scacchi et al. 2007; West et al. 2008; Yaffe et al. 2008; Yen et al. 1997). Common in each of these studies, however, was the relatively young age of the participants. The average age of each population was under 80 years. However, dementia is a major component of age-related deterioration and differs in younger subjects in aspects of etiology, presentation, treatment, and outcome (Jama et al. 1996). Moreover, Pro12Ala polymorphism in PPAR- γ 2 has been shown to exert an impact on longevity and the very-elderly population (aged 90 years and above) has a higher allele frequency of Ala12 than those aged 60 years and above (Barbieri et al. 2004). Mortality tends to remove those with dementia who are non-Ala12 carriers. As a result, the relationship between Pro12Ala polymorphism in PPAR- γ 2 and dementia in the very-elderly population might be different from that in people aged 60 years and above.

In addition, the prevalence of Ala12 allele varied greatly among different ethnic populations, with the prevalence being much lower in Asians than in Caucasians (Chuang et al. 2001; Tai et al. 2004). The relationship between Pro12Ala polymorphism in PPAR- γ 2 and dementia in the very-elderly population might be different from that in old people aged 60 years and above, and the allele frequency of Ala12 in PPAR- γ 2 varies greatly in different ethnic populations. However, up to date, there has been no relevant evidence from the very-elderly population and no relevant data from the Chinese population. Therefore, the present study explored the association of dementia with Pro12Ala polymorphism in PPAR- γ 2 among Chinese nonagenarians/centenarians.

Methods

Study subjects

Subjects were recruited as part of the “Project of Longevity and Aging in Dujangyan” (PLAD). PLAD was performed in DuJiangYang (located outside the urban area of Chengdu, China, with 2,311,709 inhabitants, 870 subjects were found to be aged 90 years or more, women 67.4%). In April 2005, 870 subjects aged 90 years or more were recruited from this population. The study protocol was approved by the Research Ethics Committee of the Sichuan University. Informed consent was obtained from all participants and their legal proxies. Trained personnel visited all study participants at their homes for data collection, e.g., biological specimen collection and anthropometric measurements. Socio-demographic characteristics and lifestyle habits were collected by using a general questionnaire. We excluded the subjects who did not complete the 30-item mini-mental state examination (MMSE) and who had no biological specimen available for genotype typing. Twenty-one men and 26 women were found to be ineligible for the study because they had already died or moved away from the area. Of 262 men and 561 women who were interviewed, five men and 41 women did not complete the MMSE, 23 men and 35 women had no biological specimen for genotype typing, and four men and nine women both did not complete the MMSE nor did they have biological specimen available. Overall, we included a total of 732 participants (238 men and 494 women).

Assessment of cognitive function

Dementia is defined as a score below 18 on the MMSE (Tombaugh and McIntyre 1992). This score has been shown to be 80% to 90% sensitive and 80% to 100% specific for a diagnosis of dementia (Langley 2000; Tombaugh and McIntyre 1992). In the MMSE, we categorized subjects according to the following: dementia (scores of 0–18), mild cognitive impairment (scores of 19–24), and normal cognitive functions (scores of 25–30). To minimize error and assure reliability, we (1) reviewed the MMSE procedure and grading system outlined in a short booklet and video, (2) observed a geriatrician conducting the MMSE procedure on residents not part of the study for

training purposes, and (3) was supervised when conducting the MMSE on residents not part of the study. The MMSE test was thereafter applied to the consented study subjects.

Measurement of genotype typing

Genomic DNA was isolated from whole blood drawn from antecubital vein using commercial DNA isolation kits from QIAGEN (Chatsworth, CA, USA), according to standard procedures. Genotyping of the PPAR- Γ Pro12Ala was carried out by a polymerase chain reaction (PCR) restriction fragment length polymorphism detection method. The PCR conditions and primers used were those previously indicated by Meirhaeghe et al. (2007). Briefly, genomic leukocyte DNA was amplified by PCR using the forward 5-TCT GGG AGA TTC TCC TAT GG-3 and reverse 5-CCC AAT AGC CGT ATC TGG AAG G-3, which introduced a *Sau96I* restriction site only when the GC substitution at nucleotide 80 is present. The amplified product was 99 bp. The PCR conditions were as follows: an initial denaturation step at 94°C for 5 min, followed by 37 cycles of denaturation at 94°C for 35 s, annealing at 52°C for 35 s, and extension at 72°C for 35 s, with a final extension of 10 min at 72°C. The PCR reaction product was digested at 37°C for overnight (at least 10 h) with *Sau96I* (New England Biolabs, Beverly, MA, USA), using the buffer recommended by the manufacturer, generating two fragments of 80 and 19 bp, respectively, when the G allele is present.

Assessment of covariates

The baseline examination included information on age (years), educational levels (illiteracy, primary school, secondary school, college, and post-graduate), fasting plasma glucose (FPG), serum uric acid ($\mu\text{mol/L}$), serum lipid/lipoprotein [including total cholesterol (Yilmaz et al.), triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol], systolic BP (mm Hg), diastolic BP (mm Hg), sleep duration per day, sleep quality, and body mass index (BMI, kg/m^2). BMI is calculated as body weight in kilograms divided by height in meters squared. Right arm blood pressure was measured in the sitting or recumbent position twice to the nearest 2 mm Hg using a standard mercury sphygmomanometer (phases I and V of Korotkoff) by trained nurses or

physicians. The mean value of two measurements was used to calculate systolic and diastolic blood pressure. FPG, serum uric acid, and lipid/lipoprotein levels were determined by standard laboratory techniques (performed by technician in biochemistry laboratory of Sichuan University). The other covariates were collected by using a general questionnaire. The survey also determined a history of diagnosis or treatment for type 2 diabetes mellitus over the prior 3 years. Sleep quality was assessed using a relevant questionnaire with scores of 1 to 4 being very unsatisfactory, generally unsatisfactory, generally satisfactory, and very satisfactory, respectively. Therefore a higher score represented better sleep quality.

Statistical analysis

All statistical analyses were performed with the SPSS for Windows software package, version 11.5 (SPSS Inc, Chicago, IL, USA). We analyzed data in men and women separately because there are differences in cognitive function scores and in the prevalence rates of dementia between men and women. In addition, previous study showed that among nonagenarians and centenarians, cognitive impairment in women with risk factors (any except age-related deterioration) was more insensitive (Corrada et al. 2008). χ^2 or Fisher's exact test (where an expected cell count was <5) were used for categorical variables and unpaired Student's *t* test for continuous variables; baseline characteristics were compared between those with and without prevalent dementia and between those with and without 12Ala carriers. Wald Chi-square test was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of 12Ala carriers as a function of increased cognitive impairment. Multiple logistic regression models were used to adjust for factors associated with cognitive function, Pro12Ala polymorphism in PPAR- γ 2, and all the covariates. *P* value <0.05 was considered to be statistically significant, and all of the *P* values have been two-sided.

Results

Seven hundred thirty-two subjects (mean age 93.68 years, standard deviation 3.43 years, aged 90–108 years), including 494 (67.49%) women, and 76 centenarians were included in the present study. The prevalence rates

Table 1 Baseline characteristics according to dementia ($n=732$)

Characteristics	Dementia		Non-dementia		χ^2 or t		df		P value	
	Men ($n=107$)	Women ($n=368$)	Men ($n=131$)	Women ($n=126$)	Men	Women	Men	Women	Men	Women
Age (years)	93.27 $\pm$ 3.05	94.03 $\pm$ 3.55	92.89 $\pm$ 2.84	93.18 $\pm$ 3.19	0.96	2.50	223	239	0.34	0.013
Genotype distribution										
Pro/Pro	97/107	337/368	115/131	115/126						
Pro/Ala	10/107	31/368	16/131	11/126	0.49	0.01	1	1	0.480	0.975
Score on MMSE	12.04 $\pm$ 4.43	11.49 $\pm$ 4.35	21.67 $\pm$ 2.66	20.42 $\pm$ 2.16	19.77	30.10	166	430	<0.001	<0.001
Triglycerides (mmol/L)	1.13 $\pm$ 0.53	1.28 $\pm$ 0.73	1.22 $\pm$ 0.51	1.17 $\pm$ 0.55	1.35	1.66	216	273	0.179	0.099
Total cholesterol (mmol/L)	4.11 $\pm$ 0.78	4.22 $\pm$ 0.84	4.02 $\pm$ 0.80	4.20 $\pm$ 0.89	0.88	0.18	221	197	0.378	0.855
HDL (mmol/L)	1.50 $\pm$ 0.32	1.60 $\pm$ 0.87	1.50 $\pm$ 0.36	1.70 $\pm$ 0.73	0.20	1.09	226	181	0.846	0.235
LDL (mmol/L)	2.27 $\pm$ 0.59	2.28 $\pm$ 0.60	2.18 $\pm$ 0.54	2.41 $\pm$ 1.88	1.19	0.71	212	128	0.252	0.278
FPG (mmol/L)	4.53 $\pm$ 1.41	4.44 $\pm$ 4.35	4.58 $\pm$ 1.65	4.35 $\pm$ 4.35	0.26	0.68	226	237	0.793	0.496
Serum uric acid (μ mol/L)	323.88 $\pm$ 89.88	312.30 $\pm$ 86.92	344.77 $\pm$ 91.09	309.68 $\pm$ 69.30	1.68	0.34	225	256	0.095	0.738
Systolic BP (mm Hg)	136.18 $\pm$ 19.48	140.95 $\pm$ 23.33	141.43 $\pm$ 22.48	140.88 $\pm$ 26.45	1.91	0.03	231	207	0.057	0.977
Diastolic BP (mm Hg)	72.91 $\pm$ 10.80	73.09 $\pm$ 12.42	72.15 $\pm$ 12.13	72.75 $\pm$ 11.81	0.51	0.27	230	226	0.610	0.785
BMI	19.32 $\pm$ 3.28	21.07 $\pm$ 9.15	19.11 $\pm$ 4.64	18.75 $\pm$ 3.13	0.39	1.07	223	340	0.257	0.286
Sleep duration per day	11.43 $\pm$ 2.58	11.51 $\pm$ 1.90	11.02 $\pm$ 1.95	10.76 $\pm$ 5.14	1.05	2.35	229	247	0.296	0.020
Sleep quality	1.59 $\pm$ 0.86	1.62 $\pm$ 0.81	1.47 $\pm$ 0.73	1.75 $\pm$ 0.93	1.11	1.57	203	246	0.267	0.118
Educational levels										
Illiteracy	61/107	345/368	30/129	96/126	29.20	19.57	4	4	<0.001	<0.001
Primary school	33/107	16/368	62/129	15/126						
Secondary school	10/107	6/368	27/129	10/126						
College and post-graduate	3/107	1/368	10/126	5/126						
Diabetes	1/63	6/214	1/88	0/77	0.057	2.204	1	1	0.662	0.155

Baseline characteristics were compared between those with and without prevalent cognitive impairment using χ^2 or Fisher's exact test (where an expected cell count was <5) for categorical variables and unpaired Student's t test for continuous variables. In the testing, a P value <0.05 was considered to be statistically significant

MMSE mini-mental state examination, BMI body mass index, FPG fasting plasma glucose, HDL high-density lipoprotein, LDL low-density lipoprotein, BP blood pressure

of dementia were 64.9% in the whole sample (45.0% for men and 74.5% for women). Difference between men and women was significant ($P<0.001$). In order to examine the association of the main demographic and clinical characteristics with dementia, demographic and clinical characteristics grouped by dementia and not dementia are presented in Table 1.

The genotype frequencies of the Pro12Ala polymorphism were 0% Ala12Ala, 9.1% Pro12Ala, and 90.9% Pro12Pro in the whole sample; 0% Ala12Ala,

10.9% Pro12Ala, and 89.1% Pro12Pro in men; and 0% Ala12Ala, 8.5% Pro12Ala, and 91.5% Pro12Pro in women (difference between men and women was insignificant, $P=0.294$). Demographic and clinical characteristics grouped by Pro12Ala polymorphism are presented in Table 2.

To examine the association of dementia with Pro12Ala polymorphism, the MMSE scores and prevalence of dementia grouped by their Pro12Ala genotype are given in Table 2, and prevalence of

Table 2 Characteristics of subjects with different PPAR- γ 2 Pro12Ala genotypes

Characteristics	Pro/Pro		Pro/Ala		χ^2 or t		df		P value	
	Men ($n=212$)	Women ($n=452$)	Men ($n=26$)	Women ($n=42$)	Men	Women	Men	Women	Men	Women
Age (years)	92.97 $\pm$ 2.93	93.85 $\pm$ 3.53	93.85 $\pm$ 3.43	93.38 $\pm$ 2.90	1.25	0.99	29	53	0.220	0.327
Cognitive impairment	97/212	337/452	10/26	31/42	0.50	0.01	1	1	0.480	0.915
Score on MMSE	17.41 $\pm$ 5.90	13.72 $\pm$ 5.56	16.77 $\pm$ 6.67	14.29 $\pm$ 5.07	0.47	0.56	30	51	0.643	0.497
Triglycerides (mmol/L)	1.18 $\pm$ 0.51	1.24 $\pm$ 0.65	1.23 $\pm$ 0.58	1.42 $\pm$ 1.01	0.40	1.13	27	41	0.694	0.264
Total cholesterol (mmol/L)	4.12 $\pm$ 0.79	4.23 $\pm$ 0.85	4.05 $\pm$ 0.78	4.08 $\pm$ 0.85	0.39	1.05	29	45	0.697	0.297
HDL (mmol/L)	1.49 $\pm$ 0.35	1.64 $\pm$ 0.78	1.54 $\pm$ 0.33	1.55 $\pm$ 0.68	0.63	0.76	29	47	0.536	0.451
LDL (mmol/L)	2.24 $\pm$ 0.56	2.33 $\pm$ 1.12	2.18 $\pm$ 0.61	2.23 $\pm$ 0.55	0.29	1.00	28	71	0.776	0.319
FPG (mmol/L)	4.51 $\pm$ 1.46	4.43 $\pm$ 1.38	4.96 $\pm$ 2.13	4.25 $\pm$ 1.34	1.02	0.80	26	44	0.319	0.428
Serum uric acid (μ mol/L)	336.76 $\pm$ 92.46	310.10 $\pm$ 82.77	322.67 $\pm$ 115.80	329.26 $\pm$ 81.49	0.58	1.39	27	44	0.57	0.172
Systolic BP (mm Hg)	138.95 $\pm$ 21.39	141.07 $\pm$ 23.99	140.04 $\pm$ 20.98	139.49 $\pm$ 20.88	0.25	0.46	32	50	0.805	0.649
Diastolic BP (mm Hg)	72.77 $\pm$ 11.77	73.25 $\pm$ 12.14	70.27 $\pm$ 9.35	70.32 $\pm$ 13.30	1.25	1.36	36	46	0.221	0.180
BMI	19.42 $\pm$ 4.20	20.93 $\pm$ 2.45	17.50 $\pm$ 2.35	20.22 $\pm$ 2.97	3.51	2.80	49	51	<0.001	0.007
Sleep duration per day	11.44 $\pm$ 2.52	11.36 $\pm$ 4.97	11.17 $\pm$ 2.34	10.85 $\pm$ 2.19	0.56	0.66	30	49	0.577	0.510
Sleep quality	1.53 $\pm$ 0.79	1.71 $\pm$ 0.91	1.44 $\pm$ 0.77	1.80 $\pm$ 0.84	0.56	0.68	30	49	0.577	0.497
Educational levels										
Illiteracy	80/210	408/452	11/26	33/42						
Primary school	86/210	24/452	9/26	7/42						
Secondary school	34/210	144/52	3/26	2/42						
College and post-graduate	10/210	6/452	3/26	0	2.60	9.37	4	4	0.626	0.06
Diabetes	0/20	5/266	2/129	1/25	0.309	0.509	1	1	0.752	0.420

Baseline characteristics were compared between different PPAR- γ 2 Pro12Ala genotypes using χ^2 or Fisher's exact test (where an expected cell count was <5) for categorical variables and unpaired Student's t test for continuous variables. In the testing, a P value <0.05 was considered to be statistically significant

MMSE mini-mental state examination, BMI body mass index, FPG fasting plasma glucose, HDL high-density lipoprotein, LDL low-density lipoprotein, BP blood pressure

Ala12 carriers grouped by dementia and non-dementia are given in Table 1. In both men women, between subjects with and without 12Ala carriers, there was no significant difference in cognitive function scores nor in the prevalence of dementia; there was also no significant difference in frequency of 12Ala carriers between subjects with and without dementia.

Finally, the Ala12 allele was not associated significantly with the risk of dementia in long-lived subjects. This association was confirmed in four logistic models: unadjusted; adjusted for covariates, which might be associated with cognitive function; adjusted for covariates, which might be associated with Pro12Ala; adjusted made with all the covariates. The ORs were all found to be insignificant (Table 3).

Table 3 Effect of PPAR- γ 2 Pro12Ala genotype on cognitive impairment in long-lived subjects

Characteristics	Pro/Pro		Pro/Ala		OR		95% CI	
	Men (<i>n</i> =212)	Women (<i>n</i> =452)	Men (<i>n</i> =26)	Women (<i>n</i> =42)	Men	Women	Men	Women
No. of risk/case	97/212	337/452	10/26	31/42				
Unadjusted					1.60	1.08	0.33, 7.67	0.51, 2.12
Model 1					1.41	1.13	0.27, 7.46	0.53, 2.40
Model 2					1.68	1.10	0.31, 9.21	0.51, 2.03
Model 3					1.83	1.25	0.32, 10.52	0.57, 2.77

Adjusted multiple logistic regression was used to adjust for covariates

OR odds ratio, *Unadjusted* Wald Chi-square test with *df*=1 was used, *Model 1* adjustment made with covariates which might be associated with cognitive function at baseline ($P<0.05$ shown in Table 1), *Model 2* adjustment made with covariates which might be associated with Pro12Ala ($P<0.05$ shown in Table 2), *Model 3* adjustment made with all the covariates

Discussion

In the cross-sectional observations, in community-dwelling Chinese nonagenarians/centenarians, there were a high prevalence rate of dementia (64.9%) and a low prevalence rate of 12Ala carriers (0% Ala12Ala, 9.1% Pro12Ala, and 90.9% Pro12Pro). There were no significant differences in both cognitive function scores and prevalence of dementia between subjects with and without 12Ala carriers; there was also no difference in the prevalence of 12Ala carriers between subjects with and without dementia.

To the best of our knowledge, there are only three studies, which examined the association between Pro12Ala polymorphism in PPAR- γ 2 and dementia in humans. Two of these studies took place in USA and the other took place in UK (Johnson et al. 2008; West et al. 2008; Yaffe et al. 2008). West et al. reported that although female Ala carriers were found to be associated with a reduced risk of type 2 diabetes mellitus, there was an increased risk of cognitive impairment in individuals once diabetes has developed. Moreover, male Ala carriers were found to have a greater risk of dementia (West et al. 2008). Wendy et al. concluded that the risk of cognitive decline is greater when 12Ala carriers developed type 2 diabetes mellitus (Johnson et al. 2008). Yaffe et al. concluded that carriers of the PPAR- γ 2 Ala allele have better performance in two tests of cognitive function, and there was a reduced risk of cognitive decline over time (Yaffe et al. 2008). All of these showed that Pro12Ala polymorphism in PPAR- γ 2 is associated

with dementia, but the impact of 12Ala carriers on dementia is indefinable. The results of our study showed that in community-dwelling Chinese nonagenarians/centenarians, there was no relationship between Pro12Ala polymorphism in PPAR- γ 2 and dementia. Our results not only provided relevant evidence in Chinese population but also provided evidence in the very-elderly population.

PPAR- γ has previously been reported as associated with BMI (Masud et al. 2003) and not associated with BMI (Dahlman and Arner 2007). In our study, Ala carriers have lower BMI, which is associated with a reduced risk of type 2 diabetes mellitus in the general population. This information could suggest PPAR- γ is associated with BMI, and Ala carriers are associated with a reduced risk of type 2 diabetes mellitus. However, our study found that PPAR genotype was not associated with type 2 diabetes mellitus. It has been confirmed that subjects with type 2 diabetes mellitus had a higher mortality rate than those without. In nonagenarians/centenarians, mortality removed the subjects with type 2 diabetes mellitus and Pro/Pro and the association between Pro12Ala polymorphism with type 2 diabetes mellitus.

It has been confirmed that there were more 12Ala carriers in the nonagenarian/centenarian group than in the general population (Barbieri et al. 2004). Dementia is a major component in age-related deterioration and the prognosis of dementia (Jama et al. 1996). Mortality in the nonagenarian/centenarian group might tend to remove those with dementia and those who lack the 12Ala gene. Therefore, it is reasonable to believe that mortality in the nonagenarian/centenarian

group may alter the association between dementia and Pro12Ala Polymorphism in PPAR- γ 2. In addition, the prevalence of Ala12 allele varied greatly in different ethnic populations, with the prevalence rate being much lower in Asians than in Caucasians (Chuang et al. 2001; Tai et al. 2004). Therefore, ethnicity might also be an influencing factor. However, these issues require further investigation.

There are potential limitations to this study. Firstly, the number of 12Ala carriers was only 68, and this small sample of 12Ala carriers may weaken statistical efficacy. Secondly, we did not include insulin resistance or serum insulin levels as baseline characteristics; thus, we were unable to show the role of insulin resistance in the relationship between polymorphism in PPAR- γ and dementia. Thirdly, we did not perform adjustment for other potential confounders, such as socio-economic status and family history of depression. Finally, we did not evaluate several confounding variables such as smoking and daily alcohol consumption, as there were a considerable number of subjects who quit drinking and/or smoking in their eighties, which could have influenced the study outcome.

In conclusion, we demonstrated that there was no association between the Pro12Ala variant of PPAR- γ 2 gene and dementia in Chinese nonagenarians/centenarians.

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Conflicts of interest None.

References

- Barbieri M, Bonafe M, Rizzo MR, Ragno E, Olivieri F, Marchegiani F, Franceschi C, Paolisso G (2004) Gender specific association of genetic variation in peroxisome proliferator-activated receptor (PPAR) γ -2 with longevity. *Exp Gerontol* 39:1095–1100
- Berger J, Moller DE (2002) The mechanisms of action of PPARs. *Annu Rev Med* 53:409–435
- Chuang LM, Hsiung CA, Chen YDI, Ho LT, Sheu WHH, Pei D, Nakatsuka CH, Cox D, Pratt RE, Lei HH, Tai TY (2001) Sibling-based association study of the PPAR γ (2) Pro12Ala polymorphism and metabolic variables in Chinese and Japanese hypertension families: a SAPHIRE study. *J Mol Med* 79:656–664
- Corrada MM, Brookmeyer R, Berlau D, Paganini-Hill A, Kawas CH (2008) Prevalence of dementia after age 90: results from the 90+ study. *Neurology* 71:337–343
- Dahlman I, Arner P (2007) Obesity and polymorphisms in genes regulating human adipose tissue. *Int J Obes* 31:1629–1641
- Forman BM, Chen J, Evans RM (1997) Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors α and δ . *Proc Natl Acad Sci U S A* 94:4312–4317
- Issemann I, Green S (1990) Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature* 347:645–650
- Jama JW, Launer LJ, Witteman JC, den Breeijen JH, Breteler MM, Grobbee DE, Hofman A (1996) Dietary antioxidants and cognitive function in a population-based sample of older persons. The Rotterdam study. *Am J Epidemiol* 144:275–280
- Johnson W, Harris SE, Starr JM, Whalley LJ, Deary IJ (2008) PPARG Pro12Ala genotype and risk of cognitive decline in elders? Maybe with diabetes. *Neurosci Lett* 434:50–55
- Katsel P, Li C, Haroutunian V (2007) Gene expression alterations in the sphingolipid metabolism pathways during progression of dementia and Alzheimer's disease: a shift toward ceramide accumulation at the earliest recognizable stages of Alzheimer's disease? *Neurochem Res* 32:845–856
- Kliwer SA, Lenhard JM, Willson TM, Patel I, Morris DC, Lehmann JM (1995) A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor γ and promotes adipocyte differentiation. *Cell* 83:813–819
- Langley LK (2000) Cognitive assessment of older adults. In: Kane RL (ed) *Assessing older persons*. Oxford University Press, Oxford, pp 65–128
- Masud S, Ye S, Group SAS (2003) Effect of the peroxisome proliferator activated receptor- γ gene Pro12Ala variant on body mass index: a meta-analysis. *J Med Genet* 40:773–780
- McIntyre RS, Soczynska JK, Woldeyohannes HO, Lewis GF, Leiter LA, MacQueen GM, Miranda A, Fulgosi D, Konarski JZ, Kennedy SH (2007) Thiazolidinediones: novel treatments for cognitive deficits in mood disorders? *Expert Opin Pharmacother* 8:1615–1628
- Meirhaeghe A, Boreham CA, Murray LJ, Richard F, Davey Smith G, Young IS, Amouyel P (2007) A possible role for the PPARG Pro12Ala polymorphism in preterm birth. *Diabetes* 56:494–498
- Poorkaj P, Grossman M, Steinbart E, Payami H, Sadovnick A, Nochlin D, Tabira T, Trojanowski JQ, Borson S, Galasko D, Reich S, Quinn B, Schellenberg G, Bird TD (2001) Frequency of tau gene mutations in familial and sporadic cases of non-Alzheimer dementia. *Arch Neurol* 58:383–387
- Santos MJ, Quintanilla RA, Toro A, Grandy R, Dinamarca MC, Godoy JA, Inestrosa NC (2005) Peroxisomal proliferation protects from beta-amyloid neurodegeneration. *J Biol Chem* 280:41057–41068
- Scacchi R, Pinto A, Gambina G, Rosano A, Corbo RM (2007) The peroxisome proliferator-activated receptor γ

- (PPAR-gamma2) Pro12Ala polymorphism is associated with higher risk for Alzheimer's disease in octogenarians. *Brain Res* 1139:1–5
- Silberfeld M, Rueda S, Krahn M, Naglie G (2002) Content validity for dementia of three generic preference based health related quality of life instruments. *Qual Life Res* 11:71–79
- Spiegelman BM (1998) PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. *Diabetes* 47:507–514
- Tai ES, Corella D, Deurenberg-Yap M, Adiconis X, Chew SK, Tan CE, Ordovas JM (2004) Differential effects of the C1431T and Pro12Ala PPARgamma gene variants on plasma lipids and diabetes risk in an Asian population. *J Lipid Res* 45:674–685
- Tombaugh TN, McIntyre NJ (1992) The mini-mental state exam: a comprehensive review. *J Am Geriatr Soc* 40:922–935
- Tontonoz P, Hu E, Spiegelman BM (1994) Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell* 79:1147–1156
- Watson GS, Craft S (2003) The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. *CNS Drugs* 17:27–45
- Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, Fishel MA, Kulstad JJ, Green PS, Cook DG, Kahn SE, Keeling ML, Craft S (2005) Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry* 13:950–958
- West NA, Haan MN, Morgenstern H (2008) The PPAR-gamma Pro12Ala polymorphism and risk of cognitive impairment in a longitudinal study. *Neurobiol Aging*. doi:[10.1016/j.neurobiolaging.2008.06.005](https://doi.org/10.1016/j.neurobiolaging.2008.06.005)
- Yaffe K, Kanaya AM, Lindquist K, Hsueh WC, Cummings SR, Beamer B, Newman A, Rosano C, Li R, Harris T (2008) PPAR-gamma Pro12Ala genotype and risk of cognitive decline in elders. *Neurobiol Aging* 29:78–83
- Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Roth J, Shuldiner AR (1997) Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. *Biochem Biophys Res Commun* 241:270–274