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Original Research Article

Lack of Genetic Associations of PPAR-γ and PGC-1α with Alzheimer's Disease and Parkinson's Disease with Dementia

Nobuto Shibata[a] Yumiko Motoi[b, d] Hiroyuki Tomiyama[b, c]
Tohru Ohnuma[a] Bolati Kuerban[a] Katrin Tomson[a, e] Miwa Komatsu[a]
Hiromi Shimazaki[a] Nobutaka Hattori[b, c] Heii Arai[a]

Departments of [a]Psychiatry, [b]Neurology and [c]Neuroscience for Neurodegenerative Disorders, Juntendo University School of Medicine, and [d]Department of Diagnosis, Prevention and Treatment of Dementia, Graduate School of Juntendo University, Tokyo, Japan; [e]Doctoral School of Behavioural, Social and Health Sciences, University of Tartu, Tartu, Estonia

Key Words

PPAR-γ · PGC-1α · Apolipoprotein E · Polymorphism · Alzheimer's disease · Parkinson's disease · Dementia

Abstract

Background and Aims: Similar clinical and pathological features have been observed in Alzheimer's disease (AD) and Parkinson's disease with dementia (PDD). Both the peroxisome proliferator-activated receptor-γ (PPAR-γ) gene and the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) gene are candidates modifying the risk for both diseases. The aim of this study was to clarify whether common single nucleotide polymorphisms (SNPs) of the PPAR-γ gene and the PGC-1α gene affect the onset of AD and PDD genetically. ***Methods:*** Four exonic SNPs of both genes (rs1801282 and rs3856806 of the PPAR-γ gene, rs3736265 and rs8192678 of the PGC-1α gene) were genotyped in 171 AD patients, 136 age-matched controls and 53 PDD patients. Haplotype analysis and logistic regression analysis with apolipoprotein E (APO E) status were performed for AD. ***Results:*** There was no statistical difference between AD cases and controls for the 4 SNPs, nor was there any statistical difference between PDD cases and controls for the 4 SNPs. We could not find any synergetic associations between these SNPs, APO E4 and AD. ***Conclusions:*** The 4 SNPs studied here did not influence the risk for AD in a Japanese population. As the number of PDD cases was small, comprehensive genetic studies considering diabetes would be needed.

Nobuto Shibata, MD, PhD
Department of Psychiatry
Juntendo University School of Medicine
2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421 (Japan)
E-Mail nshibata@juntendo.ac.jp

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders, and the onsets of the diseases are known to be affected by genetic and environmental factors. Similar clinical and pathological features have been observed in AD and PD [1, 2]. One of the most frequent nonmotor symptoms in PD patients is dementia. PD with dementia (PDD) is supposed to have a more similar pathophysiological background with AD than PD. While apolipoprotein E4 (APO E4) is recognized as a genetic risk factor for familial and sporadic AD, the association between APO E4 and PDD has not been fully elucidated [3].

The peroxisome proliferator-activated receptor-γ (PPAR-γ) is a ligand-activated transcriptional factor and influences the expression or activity of various genes, including glucose homeostasis, energy metabolism and inflammation [4]. PPAR-γ agonists have been reported to provide neuroprotective effects against neurodegenerative diseases, including AD and PD [5, 6]. These effects were surmised to result from anti-inflammatory actions of PPAR-γ [4]. A recent study showed that PPAR-γ affects amyloidogenic pathways and reduces amyloid β-stimulated inflammatory responses in primary astrocytes [6]. In addition, PPAR-γ also reduces amyloid deposition by repressing β-site amyloid precursor protein-cleaving enzyme-1 (BACE1) promoter activity [7]. These pieces of evidence have suggested that PPAR-γ could be a candidate gene for AD. The abundance of PPAR-γ in basal ganglia supports the association between PD and PPAR-γ. PPAR-γ agonists also rescue dopaminergic neurons in the PD model by inhibition of microglial activation [8]. There is increasing evidence that antioxidant mechanisms by PPAR-γ are also important for PD pathogenesis [9, 10].

The Pro12Ala polymorphism (rs1801282) of the PPAR-γ gene has been reported to reduce the transcriptional activity of PPAR-γ [11]. It has been shown to be functional and to play potential roles in the AD pathogenesis [11, 12]. Although several genetic studies on the polymorphism and the risk for AD have been issued, the associations are in debate. There have been few genetic studies on the polymorphism of the gene and PD.

The peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a metabolic coactivator playing a critical role in the control of glucose, lipid and energy metabolism. PGC-1α also induces mitochondrial biogenesis and exerts neuroprotective effects against several neurodegenerative diseases [13]. A number of studies reported that PGC-1α expressions were decreased in the AD brain [14]. Upregulation of PGC-1α protects against neurotoxicity induced by amyloid β_{1-42} [15, 16]. These pieces of evidence also suggest that PGC-1α plays an important role in the pathophysiology of AD. Many researches showed that there are links between PD and type 2 diabetes mellitus (T2DM) with insulin resistance [17, 18]. Insulin resistance was considered to be associated with mitochondrial dysfunction [19]. Polymorphisms in the PGC-1α gene have been associated with an increased risk for T2DM [20]. It was also shown that overexpression of PGC-1α has the potential to protect against dopaminergic cell loss induced by the mitochondrial toxin rotenone [21]. Converging data implicated that PGC-1α plays a major role in the PD pathogenesis.

Only a few pilot studies investigated the genetic association between the PGC-1α gene and AD, and there are few reports on the PGC-1α polymorphisms and PD. In this study, we tested whether common single nucleotide polymorphisms (SNPs) of the PPAR-γ gene and the PGC-1α gene affect the onset of AD and PDD genetically.

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Materials and Methods

DNA was extracted from white blood cells using a standard method. Our sporadic Japanese AD cases were obtained from the Department of Psychiatry, Juntendo University Hospital, Tokyo, Japan, and the Department of Psychiatry, Juntendo Koshigaya Hospital, Saitama, Japan. All the AD cases were diagnosed according to the NINCDS-ADRDA criteria and none had a familial history of AD. Japanese PDD cases were recruited from the Department of Neurology, Juntendo University Hospital. All the PDD cases were diagnosed using the UK PD Society Brain Bank clinical diagnostic criteria, and the scores of the Mini-Mental State Examination were under 24. The control cases were healthy volunteers with no history of dementia or other neuropsychiatric diseases.

The mean age of the AD group [n = 171 (male = 82, female = 89), age (mean ± SD) = 66.1 ± 10.1 years] was not significantly different from that of the control group [n = 136 (male = 63, female = 73), age = 63.8 ± 6.7 years]. However, the mean age of the PDD group [n = 53 (male = 32, female = 21), age = 60.4 ± 12.5 years] was significantly lower than that of the control group. The purpose and significance of this study were explained in detail to each patient and his/her family, and all subjects provided informed consent. The study protocols were approved by the Ethics Committee of the Juntendo University School of Medicine.

Information on the SNPs was obtained from the SNP database established by the National Center for Biotechnology Information. Two SNPs each of the PGC-1α gene and the PPAR-γ gene were genotyped using TaqMan technology on an ABI7500 system (Applied Biosystems, Carlsbad, Calif., USA). All probes and primers were designed by the Assay-by-Design service of Applied Biosystems. A standard PCR was carried out using the TaqMan Universal PCR Master Mix reagent kit in a 10-μl volume. Hardy-Weinberg equilibrium tests were performed for all SNPs. APO E genotypes for all the samples were determined according to a previous report [22]. Differences in the genotypic frequencies were evaluated using a case-control study design and applying Fisher's exact probabilities test.

Linkage disequilibrium (LD) between the SNPs as well as a haplotype analysis were performed using SNPAlyse version 5.1 (Dynacom, Yokohama, Japan). LD, denoted as D', was calculated from the haplotype frequency using the expectation-maximization algorithm. SNPs were considered to be in LD if D' was greater than 0.75. The individual haplotypes were tested for association by grouping all others together and applying the 2 tests with 1 degree of freedom. p values were calculated on the basis of 10,000 replications, and all p values reported are two-tailed. A logistic regression analysis was performed to estimate the relationship between the 4 SNPs of the PPAR-γ gene and the PGC-1α gene, APO E status and AD onset using SPSS software version 17.0 for Windows (Chicago, Ill., USA). A p value of <0.05 was considered statistically significant.

Results

The 4 SNPs of the PPAR-γ gene and the PGC-1α gene were found to be in Hardy-Weinberg equilibrium. LD examination showed strong LD between rs1801282 and rs3856806 on the PPAR-γ gene in our Japanese cases. We also found that both rs3736265 and rs8192678 of the PGC-1α gene were in the same LD. The genotypic frequencies of the 4 SNPs are shown in table 1. There was no statistical difference between AD cases and controls for the 4 SNPs, nor was there any statistical difference between PDD cases and controls for the 4 SNPs. The haplotype frequencies on the 2 genes of the AD group did not differ from those of the control group (tables 2, 3). The multiple regression analysis, which analyzed the simultaneous effect of APO E and the 4 SNPs on AD onset, only detected an association between APO E4 and the risk for AD (table 4).

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Table 1. Genotypic frequencies of the SNPs of the PPAR-γ and PGC-1α genes

SNP	Genotype	AD patients	PDD patients	Controls	χ^2	p value
rs1801282 (PPAR-γ) Pro12Ala	C/C	154		128	1.95	0.37
	C/G	16		7		
	G/G	1		1		
rs3856806 (PPAR-γ) His449His	C/C	123		87	3.86	0.15
	C/T	40		45		
	T/T	8		4		
rs3736265 (PGC-1α) Thr612Met	A/A	9		7	0.53	0.77
	A/G	50		45		
	G/G	112		84		
rs8192678 (PGC-1α) Gly482Ser	C/C	53		38	0.38	0.83
	C/T	84		71		
	T/T	34		27		
rs1801282 (PPAR-γ) Pro12Ala	C/C		49	128	0.51	0.78
	C/G		3	7		
	G/G		1	1		
rs3856806 (PPAR-γ) His449His	C/C		40	87	4.16	0.12
	C/T		10	45		
	T/T		3	4		
rs3736265 (PGC-1α) Thr612Met	A/A		3	7	1.91	0.39
	A/G		23	45		
	G/G		27	84		
rs8192678 (PGC-1α) Gly482Ser	C/C		19	38	1.74	0.42
	C/T		27	71		
	T/T		7	27		

Table 2. Case-control haplotype analysis for the 2 PPAR-γ SNPs

Haplotype	Overall	AD group	Control group	χ^2	p value	Permutation p value
C-C	0.81	0.82	0.80	0.48	0.49	0.51
C-T	0.14	0.12	0.17	2.14	0.14	0.16
G-T	0.03	0.04	0.03	0.50	0.48	0.51

Rare haplotypes with frequencies less than 1% are not shown. Each nucleotide on the haplotypes represents the SNPs in rs1801282 and rs3856806.

Table 3. Case-control haplotype analysis for the 2 PGC-1α SNPs

Haplotype	Overall	AD group	Control group	χ^2	p value	Permutation p value
G-T	0.45	0.44	0.46	0.14	0.71	0.74
G-C	0.34	0.36	0.32	0.74	0.39	0.35
A-C	0.21	0.20	0.22	0.30	0.58	0.57

Rare haplotypes with frequencies less than 1% are not shown. Each nucleotide on the haplotypes represents the SNPs in rs3736265 and rs8192678.

Table 4. Multiple regression analysis for the effect of PPAR-γ and PGC-1α SNPs and APO E on AD

	B	SE	Wald	p value	Exp(B)	95% CI of Exp(B)	
						min	max
APO E	2.35	0.77	9.39	0.002*	10.44	2.33	46.79
rs1801282 (PPAR-γ)	–1.23	1.58	0.61	0.44	0.29	0.01	6.50
rs3856806 (PPAR-γ)	0.85	0.69	1.50	0.22	2.33	0.60	9.05
rs3736265 (PGC-1α)	–0.12	0.58	0.04	0.84	0.89	0.29	2.75
rs8192678 (PGC-1α)	–0.22	0.37	0.35	0.56	0.81	0.39	1.65

* $p < 0.05$.

Discussion

Alzheimer's Disease

To date, this is the first study to clarify genetic associations between common exonic SNPs of the PPAR-γ and PGC-1α genes and AD in a Japanese population. We failed to show a genetic association between the 4 SNPs and the onset of the disease. The 2 SNPs on each gene studied here were in the same LD; haplotype analysis could not detect any positive findings. Recently, a genetic association between the PPAR-γ Pro12Ala polymorphism and AD was studied in several populations [23]. Two studies have shown that the polymorphism modifies the risk for late-onset AD [24, 25]. Scacchi et al. [26] reported that positive associations were observed only in AD patients aged 80 years or older. Compared with this, our case-control data set consisted of younger patients. Many studies have shown that the Pro12Ala polymorphism affects the risk for T2DM. Moreover, it was observed that the cognitive decline of a demented population with DM is influenced by this polymorphism [27]. Helisalmi et al. [28] have shown that the genetic risk of AD was not directly associated significantly with the polymorphism. Although our negative results are partially due to the difference in age, we suppose that the Pro12Ala polymorphism does not have a direct impact on the onset of AD. We also showed genotype data of rs3856806, which is a silent mutation and is in the same LD as the Pro12Ala polymorphism. Our haplotype analysis could not detect a genetic association between the 2 mutations and AD. Although the results were in accordance with previous studies of a Caucasian population [28], further genetic studies including several ethnic groups are needed.

One genetic association study analyzing 8 SNPs and AD has been reported previously [29]. We confirmed that rs8192678 (Gly482Ser) and rs3736265 (Thr612Met) are not associated with the disease. For rs8192678, our results were consistent with the former report. Although rs3736265 has not been previously analyzed in AD cases, our LD analysis revealed that the SNP was in the same LD as rs8192678. This suggested that the 2 SNPs genotyped here did not have effects on the risk for AD.

Parkinson's Disease

To date, this is the first study to clarify the genetic association between SNPs of the PPAR-γ gene and PDD. Despite the small number of PDD cases, we could not find any associations between the 2 SNPs of the PPAR-γ gene and PDD. Recent studies suggested that diabetes is associated with an increased risk of PD. A number of reports proposed that insulin resistance, the main cause for T2DM, is mediated through mitochondrial dysfunctions. Mitochondrial dysfunctions are also surmised to be a pathological feature of PD. While cognitive decline among T2DM patients is supposed to be associated with the Pro12Ala polymorphism,

its modification seemed complicated [30]. The current cohort was too small to perform a multifactorial analysis taking into account the polymorphism, T2DM and PDD. However, these detailed researches would clarify the pathological significance of the polymorphism in PDD.

We found one pilot study that tested the relationship between SNPs on the PGC-1α gene and PD. Although the authors observed potential associations between some SNPs on the gene and the risk or age of onset of the disease, rs8192678 was not found to be associated [31]. They did not show any LD or haplotype analysis of the PGC-1α gene from their Caucasian samples. A meta-analysis has indicated that rs8192678 was associated with the risk for T2DM in an Asian population [20]. The size of the PGC-1α gene is approximately 150 kb and is not fully clarified for PDD. We showed that the 2 exonic SNPs did not affect the risk for PDD. Our study could not cover the entire gene region. As some pieces of evidence showed that the polymorphisms of the PGC-1α gene might affect PD [31], comprehensive genetic studies covering the PGC-1α gene should be performed for both PDD and PD without dementia.

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Disclosure Statement

We have no potential conflicts.

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