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Multiple candidate gene analysis identifies α-*synuclein* as a susceptibility gene for sporadic Parkinson's disease

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Parkinson's disease (PD), one of the most common human neurodegenerative diseases, is characterized by the loss of dopaminergic neurons in the substantia nigra of the midbrain. PD is a complex disorder with multiple genetic and environmental factors influencing disease risk. To identify susceptible genes for sporadic PD, we performed case–control association studies of 268 single nucleotide polymorphisms (SNPs) in 121 candidate genes. In two independent case–control populations, we found that a SNP in α-*synuclein* (*SNCA*), rs7684318, showed the strongest association with PD ($P = 5.0 \times 10^{-10}$). Linkage disequilibrium (LD) analysis using 29 SNPs in a region around rs7684318 revealed that the entire *SNCA* gene lies within a single LD block ($D' > 0.9$) spanning ~120 kb. A tight LD group ($r^2 > 0.85$) of six SNPs, including rs7684318, associated most strongly with PD ($P = 2.0 \times 10^{-9}$–1.7×10^{-11}). Haplotype association analysis did not show lower *P*-values than any single SNP within this group. SNCA is a major component of Lewy bodies, the pathological hallmark of PD. Aggregation of SNCA is thought to play a crucial role in PD. *SNCA* expression levels tended to be positively correlated with the number of the associated allele in autopsied frontal cortices. These findings establish *SNCA* as a definite susceptibility gene for sporadic PD.

INTRODUCTION

Sporadic Parkinson's disease (PD) (OMIM no. 168600) is the second most common neurodegenerative disease following Alzheimer's disease. PD is late onset and progressive, affecting 1–2% of persons older than 65 years. Clinical features of PD include resting tremor, bradykinesia, rigidity and postural instability. The disease is pathologically characterized by the loss of dopaminergic neurons in the substantia nigra and the presence of intracellular inclusions known as Lewy bodies. Various medical managements are available for PD, including drugs (l-dopa, dopamine agonists, anti-cholinergic drugs, etc.) and surgery (thalamotomy, pallidotomy, deep brain stimulation, etc.) (1). These treatments improve PD symptoms, but do little to deter disease progression. Identifying risk factors for PD can be helpful in delaying disease onset and slowing its progression.

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PD is a complex common disease, caused by multiple genetic and environmental factors (2). The contribution of genetic factors to sporadic PD is indicated by several findings. First, ~10% of patients with PD have a positive family history (3). Secondly, a recent large-scale survey in Iceland showed that the risk ratio for PD was increased in related individuals (6.7 for siblings, 3.2 for offspring and 2.7 for nephews and nieces of patients with PD) (4). Thirdly, a twin study using [^{18}F]dopa PET showed that the concordance rate for PD, including subclinical cases, is approximately three times higher in monozygotic twins (55%) than in dizygotic twins (18%) (5).

Causal genes for Mendelian-inherited PD have been reported, including *α-synuclein* [4q21, autosomal dominant (AD)] (6), *parkin* [6q25.2–27, autosomal recessive (AR)] (7), *UCH-L1* (4p14, AD) (8), *PINK1* (1p36, AR) (9), *DJ-1* (1p36, AR) (10), *LRRK2/dardarin* (12q12, AD) (11,12) and *NR4A2/Nurr1* (2q22–23, AD) (13).

Many case–control association studies using single nucleotide polymorphisms (SNPs) in candidate genes have been reported, but few consistent findings have been obtained (2). This is due, in part, to limited numbers of available samples, target genes and/or genetic markers. Since 2001, genome-wide, non-parametric linkage analysis of PD families has revealed significant linkage in multiple chromosomal regions (14–17), leading to the identification of *tau* (18) and *FGF20* (19) as susceptibility genes.

To date, polymorphisms that influence PD as strongly as *APOE-ε4* influences Alzheimer's disease have not been identified. Through extensive candidate gene association studies, we have established *α-synuclein* (*SNCA*) as a definite susceptibility gene for sporadic PD.

RESULTS

Screening of SNPs in candidate genes for PD

We selected candidate genes from the literature describing genetic, pathological and biochemical findings in PD, as well as genes that participate in the proposed mechanisms for PD. Finally, we picked up 121 genes relevant to familial PD, Lewy bodies, dopaminergic neurons, cytokines and trophic factors, mitochondrial functions, oxidative stress, proteasome function, autophagy, endoplasmic reticulum-associated degradation (ERAD) and toxins. One to seven SNPs per gene (268 SNPs total) were selected from the dbSNP, JSNP and Celera Discovery System databases.

In the initial screen, we genotyped 190 patients and 190 controls (Supplementary Material, Table S1). To avoid false negatives, we set the α-value at 0.05 in the first screen. From 268 SNPs, 22 SNPs in 16 genes showed association with PD ($P < 0.05$) in genotype frequency, allele frequency, dominant model or recessive model. We genotyped the 22 qualifying SNPs in a replication panel of 692 patients and 748 controls and tested again for association. This independent test revealed that SNP0070 (rs7684318 C/T) was prominently associated with PD ($P = 5.0 \times 10^{-10}$ for allele frequency) (Table 1). We corrected the α-value to 0.00019 after Bonferroni's correction (tests for 268 SNPs). The remaining 21 SNPs did not show P-values lower than 0.00019 (data not shown). SNP0070 is located in intron 4 of the *α-synuclein* (*SNCA*) gene on chromosome 4q21. SNCA is a primary component of intracellular inclusions called Lewy bodies, which are considered to be the pathological hallmark of PD (20). Aggregation of SNCA is thought to play a crucial role in the pathogenesis of PD (21). The allele C frequency of SNP0070 was higher in PD (0.67) than in controls (0.57) (Table 1). The association of SNP0070 was significant in genotype frequency, allele frequency, dominant model and recessive model. Of the two disease models, allele C of SNP0070 was more significantly associated in the recessive model than in the dominant model (Table 1).

Linkage disequilibrium (LD) mapping and search for susceptibility SNPs

We performed LD mapping in a 430 kb region around SNP0070. This region contains two genes: *SNCA* and *MMRN1*. Using SNP0070 and 28 additional SNPs in this region, we genotyped 134 control subjects and constructed an LD map based on pairwise D' and r^2 (Fig. 1) (Supplementary Material, Table S2). Three LD blocks were observed on the basis of D' ($D' > 0.9$). The entire *SNCA* gene was included in a block containing SNP0070 (block 2). The *MMRN1* gene was in another LD block, indicating that *MMRN1* does not correlate with the SNP0070 association (Fig. 2).

To search for the most strongly associated SNP(s) in the region, we next performed association studies with these 29 SNPs (Fig. 2; Table 2). We found significant associations for SNPs in block 2, but not in blocks 1 and 3. Block 2, thought to be a susceptibility block for PD, was further analyzed on the basis of r^2-values. Of the 19 SNPs in block 2, 16 belonged to three groups with high pairwise r^2 (>0.85) and the remaining three did not belong to any group (Fig. 1; Table 2) (Supplementary Material, Table S2). Six SNPs in group 1, including originally screened SNP0070 and five additional SNPs (0203, 0204, 0205, 0207 and 0209), showed prominent association with PD ($P = 2.0 \times 10^{-9}$–1.7×10^{-11}, allele 1 versus allele 2) (Fig. 2; Table 2). Population attributable risk (PAR) (22) of SNP0070 was 42.5% in the dominant model and 18.5% in the recessive model.

We next performed haplotype analysis using six representative SNPs in block 2 (Table 3). Six common haplotypes (>1% of PD and controls) covered >90% of the population haplotypes in both PD and controls. The major haplotypes 1 and 2 showed significant associations; however, their P-values were not lower than that of any single SNP in group 1. Therefore, the presence of hidden SNP(s) with a lower P-value than group 1 seemed unlikely, as was the possibility that the haplotype(s) is implicated in PD susceptibility. These findings establish the six SNPs in group 1 as the strongest susceptibility SNPs. All showed stronger associations in the recessive model than in the dominant model, similar to the originally screened SNP0070 (Table 4).

Taken together, our genetic analyses indicate that *SNCA* is a definite susceptibility gene for sporadic PD and that multiple SNPs in group 1 are susceptibility SNPs, likely in a recessive model.

Table 1. Association of SNP0070 in *SNCA* between cases and controls

	Genotype				Allele			*P*-value (χ^2-test)			
	CC	CT	TT	Total	C	T	Total	Genotype	Allele	Dominant[a] model	Recessive[b] model
First screen											
Case	87 (0.46)	87 (0.46)	14 (0.07)	188	261 (0.69)	115 (0.31)	376	3.4×10^{-4}	1.8×10^{-4}	1.8×10^{-4}	1.1×10^{-2}
Control	62 (0.33)	85 (0.46)	39 (0.21)	186	209 (0.56)	163 (0.44)	372				
Replication											
Case	298 (0.44)	307 (0.45)	75 (0.11)	680	903 (0.66)	457 (0.34)	1360	1.3×10^{-6}	4.2×10^{-7}	1.5×10^{-3}	9.0×10^{-7}
Control	233 (0.31)	387 (0.52)	126 (0.17)	746	853 (0.57)	639 (0.43)	1492				
Total											
Case	385 (0.44)	394 (0.45)	89 (0.10)	868	1164 (0.67)	572 (0.33)	1736	2.7×10^{-9}	5.0×10^{-10}	5.7×10^{-6}	2.8×10^{-8}
Control	295 (0.32)	472 (0.51)	165 (0.18)	932	1062 (0.57)	802 (0.43)	1864				

Frequencies of genotypes and alleles are in parentheses.
[a]Genotype CC+CT versus TT.
[b]Genotype CC versus CT+TT.

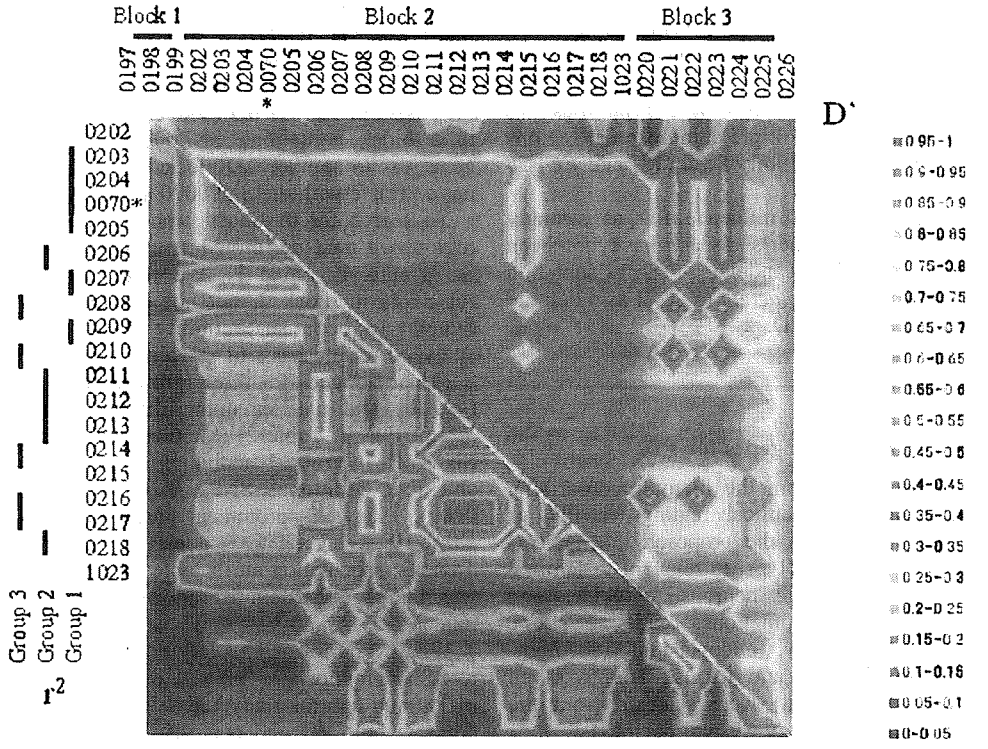

Figure 1. LD structure of the susceptibility region for sporadic PD. Pairwise LD between SNPs, as measured by D' in 134 controls, is graphically indicated. The region spanning 430 kb around the originally screened SNP0070(*) was divided into three LD blocks ($D' > 0.9$) (upper right). On the basis of r^2, SNPs in block 2, including SNP0070, were further divided into three groups ($r^2 > 0.85$) and three solitary SNPs (lower left). The scale is nominal.

SNCA gene expression in relation to susceptibility genotypes

To examine whether the strongest associated SNPs (group 1) affect *SNCA* gene expression, we further quantified *SNCA* mRNA in autopsied frontal cortices and compared the values among the genotypes. SNP0070, in which allele C is associated with PD, was used as a representative of group 1.

The relative values of *SNCA* mRNA for all cases ($n = 21$) and all controls ($n = 18$) were 1.07 ± 0.10 and 0.95 ± 0.13, respectively, showing almost the same level ($P = 0.46$, Student's t-test). When compared among the genotypes in cases, the mean tended to decrease in the order of CC, CT and TT (Fig. 3), although the differences did not reach the significant levels ($P = 0.71$ for CC versus CT, $P = 0.16$ for CT versus TT and $P = 0.32$ for CC versus TT). Similar tendency

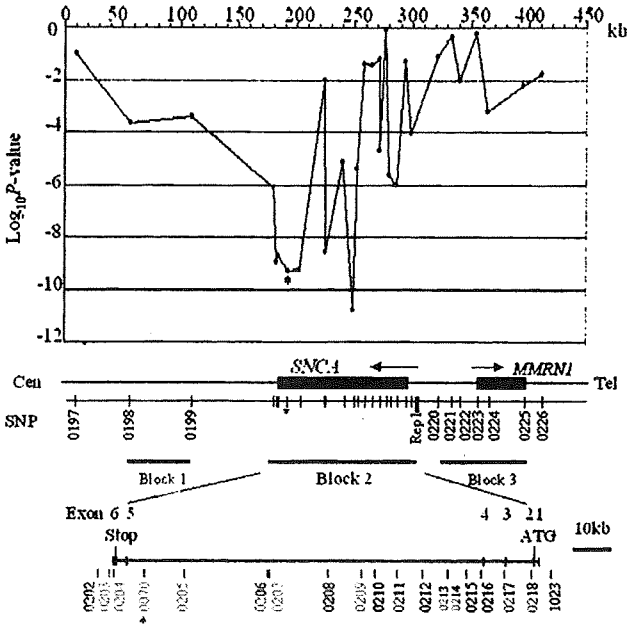

Figure 2. Genomic structure and SNPs of the susceptibility region for sporadic PD and case–control association studies (882 cases and 938 controls). Log *P*-values (allele 1 versus allele 2) are plotted against the physical location of the SNPs. The region includes two genes: *SNCA* and *MMRN1*; transcription orientation is indicated by horizontal arrows. Physical locations of SNPs are shown as axial bars with our experimental ID number. The originally screened SNP0070 is indicated by an asterisk. The location of Rep1, a well-known repeat polymorphism in the *SNCA* promoter region, is indicated by a thick bar. SNPs in block 2 are nominated in an expanded map with the exon–intron structure of *SNCA*. SNPs in group 1 are shown in red. Note that *P*-values are prominently low at the group 1 SNPs located in the 3′ region of *SNCA*. *P*-values in the region around Rep1 are far from significant when compared with those in group 1.

was observed in controls. The mean tended to decrease in the order of CC, CT and TT (Fig. 3) ($P = 0.33$ for CC versus CT, $P = 0.59$ for CT versus TT and $P = 0.54$ for CC versus TT).

These results indicate the possibility that expression of *SNCA* mRNA in the brain tends to be positively correlated with the number of PD-associated allele.

DISCUSSION

To identify susceptibility genes for PD, we performed an extensive candidate gene approach by screening 268 SNPs in 121 genes and identified a prominent association with SNP0070 (rs7684318) in the *SNCA* gene (Table 1). LD mapping localized the entire *SNCA* gene within a single LD block (Figs 1 and 2). Within this block, six SNPs including SNP0070 were in a tight LD group and most strongly associated with PD (Fig. 2; Table 2). The major allele of each SNP in group 1 was positively associated with PD, more strongly in the recessive model than in the dominant model (Table 4). Our genetic analyses establish *SNCA* as a definite susceptibility gene for PD and identify multiple SNPs in group 1 as susceptibility SNPs. Recently, Mueller *et al.* (23) reported that multiple regions of *SNCA* are associated with PD in the German population. Associated SNPs identified by Mueller *et al.* included rs356165 ($P = 1.5 \times 10^{-4}$), which corresponds to SNP0204 in our study, indicating that this SNP has a similar association in Caucasians. Pals *et al.* (24) previously reported no association of the haplotype containing rs356165 with PD in Belgian samples. This contradictory finding may be, at least in part, due to a small sample size (175 cases and 186 controls), as mentioned by the authors.

SNCA/α-synuclein was originally identified in the electric organ of the Pacific electric ray (25). SNCA is a presynaptic protein that is highly and broadly expressed in the brain, but its normal function remains unknown (21). It is a major component of Lewy bodies, the pathological hallmark of PD (20), and the aggregation of SNCA protein is thought to play a crucial role in the loss of dopaminergic neurons (21,26).

SNCA was also the first gene identified as a causative gene in familial PD. Three missense mutations in *SNCA* were reported in families with AD inheritance (6,27,28). These mutations are thought to increase the aggregation of SNCA protein. Point mutations in *SNCA* have not been identified in sporadic PD (27,29), and no SNPs have been found in the coding region, suggesting that disease-related amino acid changes in SNCA are unlikely in sporadic PD.

Genes' overdosage is a potential mechanism for the influence of *SNCA* in PD. Triplication of the *SNCA* locus has been seen in an AD PD family (30), and doubling of *SNCA* gene dosage by triplication has been shown to result in the doubling of mRNA and protein expression in blood and brain (31). Duplication of *SNCA* has also been identified as a cause of familial PD (32,33). Clinical features of patients with *SNCA* duplication resemble those of sporadic cases and are much milder than those with triplication. Taken together, these observations indicate a correlation between increased SNCA protein levels and disease risk. Identification of one or more polymorphisms related to *SNCA* expression level might reveal strong susceptibility indicators for sporadic PD. Many studies have focussed on a mixed repeat microsatellite polymorphism called Rep1 (34), because of its location in the *SNCA* promoter region. However, their significance is uncertain, possibly because of the small number of samples (35–37). Our study demonstrates that the *P*-values of SNPs around Rep1 (0218, 1023 and 0220) are less significant than that of the SNPs in group 1 (Fig. 2). In addition, we genotyped our samples for Rep1. Pairwise *D′*-values showed that Rep1 was not in block 2, but on the boundary (Supplementary Material, Table S2). *P*-value of Rep1 was 7.5×10^{-7} (Supplementary Material, Table S3), which might be explained by its intermediate correlation with the strongest susceptibility SNPs (group 1, $P = 2.0 \times 10^{-9}$–1.7×10^{-11}). Our findings suggest that *P*-value of Rep1 depends on its LD strength with SNPs in group 1. LD strength may be modified by the unstableness of microsatellite markers (38) and may vary among races (39). Taken together, these findings may also partly explain the contradictory findings of previous Rep1 association studies.

To investigate the relationship between the SNPs in group 1 and the *SNCA* expression levels, we analyzed *SNCA* mRNA expression in autopsied frontal cortices (Fig. 3). *SNCA* expression levels tended to be positively correlated with the number of the PD-associated allele, supporting the popular hypothesis that increased SNCA leads to the disease.

Table 2. Association analysis in *SNCA* and surrounding region

SNPs			LD block	Genotype							
ID (rs ID)	Alleles 12	Location	(group)	Case 11/12/22	(Total)	Control 11/12/22	(Total)	MAF Case/control	Allele 1 versus allele 2 *P*-value	OR (95% CI)	HWE Case/control
0197 (rs3733450)	TC		1	38/286/549	(873)	33/280/619	(932)	0.21/0.19	0.10	1.15 (0.97–1.36)	1.00/0.93
0198 (rs1390280)	AG		1	366/384/118	(868)	316/454/162	(932)	0.36/0.42	2.1×10^{-4}	1.29 (1.13–1.46)	0.32/1.00
0199 (rs3733449)	CT		1	117/375/374	(866)	154/451/322	(927)	0.35/0.41	3.7×10^{-4}	1.28 (1.11–1.48)	0.16/0.91
0202 (rs356221)	TA	3′-flanking	2	73/369/431	(873)	123/449/360	(932)	0.30/0.37	7.2×10^{-7}	1.42 (1.25–1.63)	0.69/0.40
0203 (rs3857053)	TC	3′-flanking	2 (1)	380/406/87	(873)	293/476/164	(933)	0.33/0.43	1.1×10^{-9}	1.53 (1.33–1.73)	0.18/0.24
0204 (rs356165)	GA	3′-UTR	2 (1)	379/399/89	(867)	289/482/159	(930)	0.33/0.43	2.0×10^{-9}	1.52 (1.33–1.74)	0.32/0.09
0070[a] (rs7684318)	CT	Intron 4	2 (1)	385/394/89	(868)	295/472/165	(932)	0.33/0.43	5.0×10^{-10}	1.54 (1.35–1.75)	0.47/0.35
0205 (rs3775424)	CT	Intron 4	2 (1)	87/406/376	(869)	166/477/288	(931)	0.33/0.43	5.4×10^{-10}	1.52 (1.34–1.75)	0.16/0.22
0206 (rs3775426)	CT	Intron 4	2 (2)	56/350/456	(862)	53/324/555	(932)	0.27/0.23	0.0098	1.22 (1.05–1.41)	0.35/0.59
0207 (rs3796661)	CT	Intron 4	2 (1)	91/367/382	(840)	154/482/296	(932)	0.33/0.42	2.7×10^{-9}	1.52 (1.31–1.76)	0.90/0.08
0208 (rs3775435)	GA	Intron 4	2 (3)	157/434/272	(863)	115/439/375	(929)	0.43/0.36	7.3×10^{-6}	1.36 (1.18–1.56)	0.53/0.48
0209 (rs2737029)	TC	Intron 4	2 (1)	84/377/402	(863)	156/480/297	(933)	0.32/0.42	1.7×10^{-11}	1.60 (1.40–1.83)	0.81/0.12
0210 (rs3775442)	TC	Intron 4	2 (3)	158/438/274	(870)	114/440/378	(932)	0.43/0.36	4.2×10^{-6}	1.37 (1.19–1.58)	0.50/0.46
0211 (rs3756055)	GA	Intron 4	2 (2)	50/339/481	(870)	49/319/565	(933)	0.25/0.22	0.042	1.17 (1.00–1.37)	0.38/0.72
0212 (rs3775446)	TG	Intron 4	2 (2)	50/340/480	(870)	49/317/565	(931)	0.25/0.22	0.034	1.19 (1.01–1.38)	0.36/0.67
0213 (rs3756056)	CT	Intron 4	2 (2)	50/340/482	(872)	48/323/557	(928)	0.25/0.23	0.062	1.16 (0.99–1.34)	0.37/0.97
0214 (rs894278)	GT	Intron 4	2 (3)	156/438/275	(869)	117/441/375	(933)	0.43/0.36	1.9×10^{-5}	1.34 (1.18–1.52)	0.46/0.52
0215 (rs1812923)	CA	Intron 4	2	74/383/413	(870)	92/392/447	(931)	0.31/0.31	0.79	1.01 (0.89–1.16)	0.30/0.71
0216 (rs2298728)	AG	Intron 4	2 (3)	163/432/274	(869)	117/435/380	(932)	0.44/0.36	2.2×10^{-6}	1.38 (1.22–1.56)	0.80/0.72
0217 (rs3796667)	AT	Intron 3	2 (3)	159/430/271	(860)	114/428/383	(925)	0.44/0.36	9.2×10^{-7}	1.41 (1.23–1.61)	0.66/0.80
0218 (rs2035268)	TG	Intron 2	2 (2)	475/339/54	(868)	556/326/51	(933)	0.26/0.23	0.049	1.16 (0.99–1.37)	0.59/0.79
1023 (rs1023777)	CT	5′-flanking	2	66/318/464	(848)	86/433/411	(930)	0.27/0.33	9.3×10^{-5}	1.33 (1.15–1.55)	0.31/0.08
0220 (rs2736994)	GA		3	542/263/22	(827)	529/292/33	(854)	0.19/0.21	0.081	1.16 (0.98–1.38)	0.17/0.41
0221 (rs11097239)	CA		3	245/437/182	(864)	272/431/226	(929)	0.46/0.48	0.48	1.05 (0.92–1.19)	0.67/0.04
0222 (rs1899389)	AG		3	592/245/29	(866)	586/297/46	(929)	0.18/0.21	0.009	1.25 (1.05–1.46)	0.64/0.34
0223 (rs2289515)	AT		3	180/436/238	(854)	221/423/267	(911)	0.47/0.48	0.6	1.03 (0.90–1.18)	0.49/0.04
0224 (rs3775464)	GA		3	109/414/346	(869)	95/385/449	(929)	0.36/0.31	5.9×10^{-4}	1.28 (1.11–1.46)	0.43/0.40
0225 (rs1246270)	GA		3	372/394/84	(850)	474/372/81	(927)	0.33/0.29	0.0061	1.21 (1.05–1.40)	0.19/0.56
0226 (rs3822098)	CT		3	50/300/514	(864)	59/376/494	(929)	0.23/0.27	0.017	1.21 (1.04–1.40)	0.54/0.30

MAF, minor allele frequency. When the odds ratio (OR) is less than 1, an inverted score is indicated.
[a]Originally screened SNP.

Table 3. Haplotype association analysis using representative SNPs in block 2

Haplotypes	Representative SNP (group)						Haplotype frequency		*P*-value
	202	0070 (1)	0206 (2)	0214 (3)	0215	1023	Case	Control	
1	A	C	T	G	A	T	0.39	0.33	4.4×10^{-5}
2	T	T	T	T	A	C	0.24	0.3	5.0×10^{-6}
3	A	C	C	T	C	T	0.24	0.21	0.071
4	A	T	T	T	C	T	0.03	0.06	3.3×10^{-4}
5	T	T	T	T	C	T	0.02	0.03	0.083
6	T	T	T	G	A	T	0.01	0.02	0.62

Table 4. Association of the SNPs in group 1 of block 2

SNP	Allele	Genotype						Dominant model (MM + Mm versus mm)		Recessive model (MM versus Mm + mm)	
		Case			Control						
	M/m	MM	Mm	mm	MM	Mm	mm	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95%CI)
0203	T/C	380	406	87	293	476	164	3.0×10^{-6}	1.95 (1.45–2.52)	1.0×10^{-7}	1.68 (1.41–2.07)
0204	G/A	379	399	89	289	482	159	2.7×10^{-5}	1.81 (1.36–2.38)	3.0×10^{-8}	1.72 (1.43–2.13)
0070[a]	C/T	385	394	89	295	472	165	5.7×10^{-6}	1.90 (1.44–2.53)	2.8×10^{-8}	1.71 (1.42–2.06)
0205	T/C	376	406	87	288	477	166	1.8×10^{-6}	1.98 (1.45–2.61)	6.0×10^{-8}	1.69 (1.40–2.05)
0207	T/C	382	367	91	296	482	154	5.3×10^{-4}	1.66 (1.25–2.16)	3.0×10^{-9}	1.78 (1.47–2.16)
0209	C/T	402	377	84	297	480	156	1.4×10^{-5}	1.89 (1.41–2.51)	1.5×10^{-10}	1.86 (1.55–2.27)

M and m are major allele and minor allele, respectively. CI, confidence interval.
[a]Originally screened SNP.

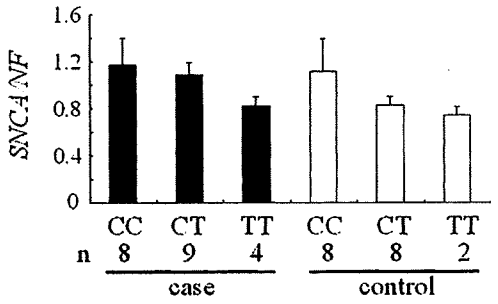

Figure 3. *In vivo* expression of *SNCA* mRNA in relation to susceptibility genotypes. SNP0070 (C/T) is used as a representative of group 1. *SNCA* expression levels in autopsied frontal cortices of cases (solid bar; 8 CC, 9 CT and 4 TT) and controls (open bar; 8 CC, 8 CT and 2 TT). Relative *SNCA* mRNA levels (normalized to *neurofilament L, NF*) are indicated. In cases, mean ± SEM of CC, CT and TT were 1.17 ± 0.23, 1.08 ± 0.11 and 0.82 ± 0.08, respectively. In controls, mean ± SEM of CC, CT and TT were 1.11 ± 0.28, 0.83 ± 0.07 and 0.75 ± 0.07, respectively.

The PD-associated alleles may positively correlate with the basal transcription level of *SNCA* and/or the induction of *SNCA* expression by certain stimulators, for example, oxidative stress.

Other possible functional effects of associated SNPs include alternative splicing, which may result in a protein isoform that aggregates more readily. The C-terminal region of SNCA is rich in acidic amino acid residues, and its truncation promotes aggregation *in vitro* (40,41). The known splice variant *SNCA112* lacks exon 5, which encodes 28 amino acids (10 of which are acidic) in frame. Thus, SNCA112 may also promote aggregation. We investigated *SNCA112* mRNA expression in frontal cortices using splice variant-specific primers, but observed little difference among the three genotypes (data not shown).

In summary, our study establishes *SNCA* as a susceptibility gene for sporadic PD. Focussed investigations of SNCA function will further enhance our understanding of how genetic factors contribute to the complex etiology of PD.

MATERIALS AND METHODS

Subjects

We recruited 882 unrelated sporadic PD patients (age, 64.9 ± 9.8; male/female ratio, 0.79) and 938 unrelated controls (age, 45.3 ± 16.3; male/female ratio, 1.10). The diagnosis of idiopathic PD was based on the presence of two or more of the cardinal features of PD (tremor, rigidity, bradykinesia and postural instability), according to the criteria for sporadic PD (42). Patients were evaluated by the certified neurologists specializing in PD. The average age of onset was 57.4 ± 10.9 years. Forty-two patients showed early onset of PD (<40 years) and 51 patients had a positive family history of PD. Patients who carried *parkin* mutations were excluded. All patients and controls were of Japanese ancestry. Informed consent was obtained from each individual, and approval for the study was obtained from the University Ethical Committees.

SNP genotyping

Genomic DNA was extracted from whole blood using FlexGene (Qiagen). SNP information was obtained from the dbSNP (http://www/ncbi.nlm.nih.gov/SNP/), JSNP (http://snp.ims.u-tokyo.ac.jp/) (43) and Celera Discovery System

(http://myscience.appliedbiosystems.com/) databases. We genotyped SNPs using the Invader assay (Third Wave Technologies), TaqMan (Applied Biosystems) or direct sequencing using an ABI3730 capillary sequencer (Applied Biosystems). Rep1 genotyping and allele designations followed those described previously (35). The Rep1 region was amplified using FAM5′-CCTGGCATATTTGATTGCAA-3′ and 5′-GACTGGCCCAAGATTAACCA-3′ as primers and analyzed using ABI3730 capillary sequencer.

Statistical analysis

SNPAlyze software (DYNACOM, Japan) was used for the case–control study (χ^2-test), calculation of odds ratio and its 95% CI (Bootstrap method), haplotype analysis (Expectation–Maximization algorithm) and pairwise LD analysis (Lewontin's coefficient D' and standardized coefficient r).

Real-time RT–PCR

Autopsied frontal cortices were obtained from the Brain Bank for Aging Research (Tokyo Metropolitan Geriatric Hospital/Tokyo Metropolitan Institute of Gerontology) and from the Department of Neurology, Juntendo University School of Medicine. The samples contained 21 cases [age, 82.6 ± 7.1 (SD) years; 11 males and 10 females] with Lewy body pathology defined by the third Consensus Guideline for Dementia with Lewy Bodies (44), comprising PD with and without dementia and dementia with Lewy bodies, and 18 control subjects (age, 81.2 ± 5.2; 12 males and six females) without parkinsonism or dementia and without neurodegenerative pathological changes. Total RNA was extracted from tissues using RNeasy (Qiagen), and cDNA was prepared using Superscript reverse transcriptase (Invitrogen). Real-time RT–PCR was carried out on ABI PRISM 7900 sequence detection system (Applied Biosystems) using SYBR Premix Ex Taq (TAKARA, Japan). First-strand cDNA was amplified using primers specific for *SNCA* (forward: 5′-GCAGAAGCA GCAGGAAAGAC-3′; reverse: 5′-CTGGGCTACTGCTGTC ACAC-3′; product size: 159 bp) and *NF* (*neurofilament L*, forward: 5′-AGAACGCTGAGGAATGGTTC-3′; reverse: 5′-CTGGTGAAACTGAGTCGGGT-3′; product size: 391 bp). A single band of the expected size was amplified from cDNA samples, but not from RNA samples. For quantification, we used a relative standard curve method. Standard curves of *SNCA* and *NF* were generated from the amplification of diluted series of cDNA from cortices. *SNCA* expression levels were normalized to those of *NF*. One of the experimental samples was used as the calibrator. Each of the normalized *SNCA* values was divided by the calibrator normalized *SNCA* value to generate the relative expression levels. The values were determined in triplicate. Reproducibility of the results was confirmed by repeating cDNA synthesis and real-time PCR twice for seven samples, and similar results were obtained.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

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Conflict of Interest statement. None declared.

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症例報告

反復する無自覚性低血糖の治療にPioglitazoneが有効であった筋強直性ジストロフィーの1例

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要旨：筋強直性ジストロフィー（DM1）の20歳女性が，傾眠と易疲労，突然の応答の悪さに気づかれた．食前食後の血糖測定で無自覚性低血糖の反復をみとめた．75g経口糖負荷試験（OGTT）では，空腹時の血糖値，血中インスリン値（IRI）は正常であったが，IRIは糖負荷60分後に最高528μIU/mlまで上昇し，120分後血糖は57mg/dlに低下した．インスリン過分泌による低血糖症と診断し，pioglitazone内服治療を開始した．治療から2週後と10カ月後のOGTTでは，インスリン分泌は抑制され，低血糖はなかった．非糖尿病のDM1患者の反復する無自覚性低血糖にpioglitazoneが有効であった．

（臨床神経，49：641—645，2009）

Key words：筋強直性ジストロフィー，反復性無自覚性低血糖，インスリン過分泌，Pioglitazone，75g経口糖負荷試験

はじめに

筋強直性ジストロフィー（DM1）では，糖負荷によりいちじるしく血中インスリン値（IRI）が上昇する耐糖能異常があり，インスリン受容体の異常によるインスリン抵抗性が原因とされる[1)2)]．Pioglitazoneは，sulfonylurea薬に代表されるインスリン分泌促進薬とことなり，インスリン抵抗性を改善させ，血糖を降下させる[3)]．糖尿病を合併したDM1患者へのpioglitazone治療は，高血糖も高インスリン血症も改善する[4)]．

無自覚性低血糖は，インスリンの相対的，もしくは絶対的過剰状態が原因で，動悸，振戦，不安症状，発汗，空腹感などの自律神経症状を欠いたまま，中枢神経系の糖欠乏による頭痛，行動変化，錯乱，疲労，意識障害，痙攣などの症状が現れる現象である[5)6)]．非糖尿病のDM1患者がインスリン過分泌による無自覚性低血糖をくりかえし，pioglitazone治療が有効であったことを報告する．

症　例

患者：20歳　女性．

主訴：傾眠傾向，易疲労，会話中の突然の応答低下．

既往歴：19歳，右チョコレート嚢胞摘除術．20歳，歯髄炎．過去に糖尿病の指摘なし．

家族歴：父親は消息不明．同胞は弟1人で，精神運動発達の遅滞をみとめる．

現病歴：出生時3,170g，満期産であった．一人歩きは1歳6～7カ月であった．小学校は障害児学級に通学した．小学校高学年で握った手を開けないことに気づかれた．高校は養護学校に進学し，在学中に大学病院を受診した．精神運動発達遅滞，前腕や下腿の筋力低下，ミオトニアなどを指摘された．末梢血白血球でミオトニンプロテインキナーゼ遺伝子の非翻訳領域のCTGリピート数が約830回に延長し，DM1と診断された．19歳頃，疲れやすいため車椅子を購入した．20歳，屋外で車椅子を使用するようになった．日中の眠気が強く，一日18時間ぐらい眠っている日もあった．会話中に，突然，ボーっとし，話しかけても返事をしないことがあるのに家族が気付いた．応答が悪い時でも開眼し，眠っていなかった．家族は，会話に集中できていないと思っていた．

現症：血圧110/64，脈拍72回/分，整，体温35.8度，胸部腹部に異常なし．黄疸なし．意識清明で，自発的に会話することは少なかった．食事はほぼ一定して十分量を摂取した．間食が多かった．Body mass indexは17.1で，過去6カ月に体重減少はなく，46.6kgであった．軽度の白内障があった．高口蓋をみとめた．前腕と下腿の筋力低下，深部反射低下，胸鎖乳突筋の萎縮，両手の把握ミオトニアと叩打ミオトニアをみとめた．

検査所見：血液検査ではHb 9.4g/dl，MCV 77.1fl，血清鉄20μg/dl，UIBC 391μg/dl，TIBC 411μg/dlと鉄欠乏性貧血をみとめた．一般生化学検査では，肝機能，甲状腺機能をふくめ異常なかった．空腹時血糖76mg/dl，HbA_{1c} 4.7%，脳性ナト

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（受付日：2009年4月28日）

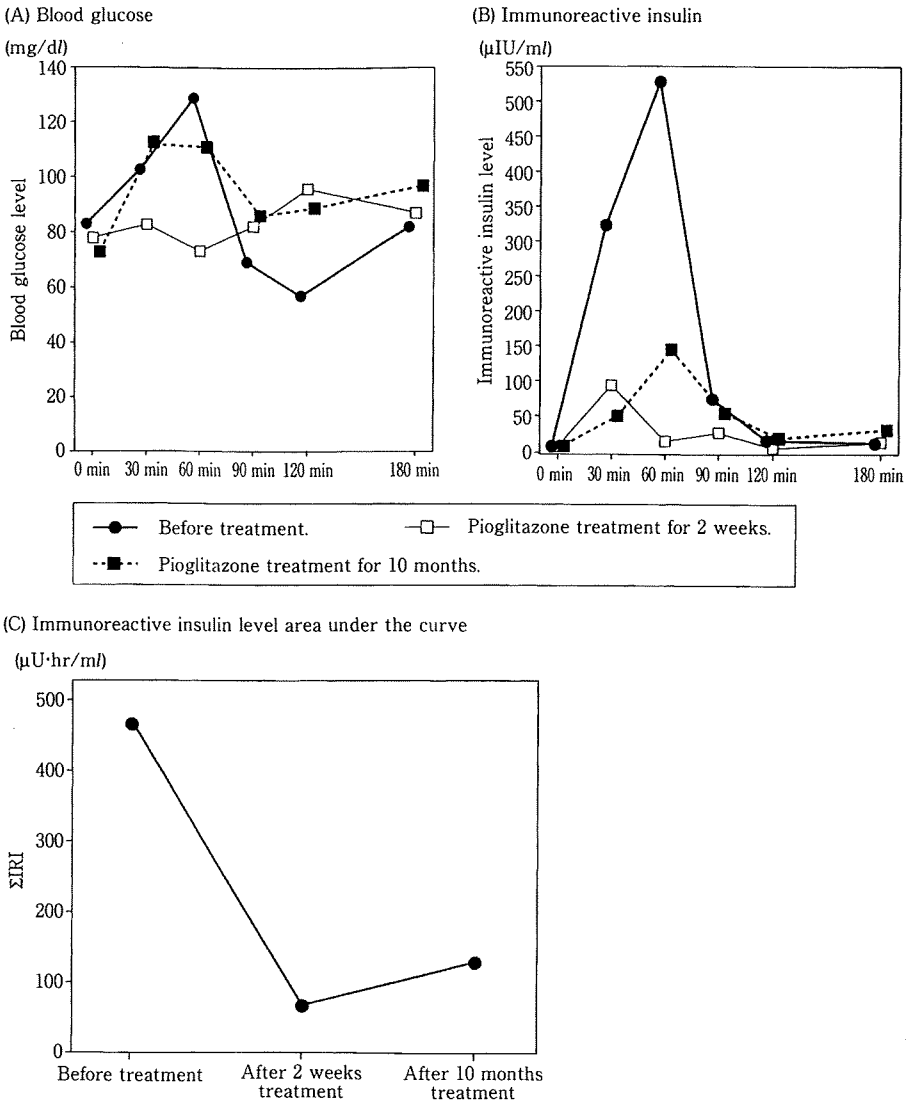

Fig. 1 Blood glucose level (A), immunoreactive insulin (IRI) level (B), and IRI area under the curve of the OGTT (ΣIRI) (C) on a 75 g oral glucose tolerance test (OGTT) in the present patient. Before treatment, IRI increases from 30 minutes to 60 minutes after glucose loading, and blood glucose level at 120 minutes decreases to 57 mg/dl. During pioglitazone treatment, ΣIRI decreases. After 2 weeks of treatment, blood glucose level at 120 minutes is lower than fasting blood glucose level, but does not represent hypoglycemia. After 10 months of treatment, blood glucose level after glucose loading exceeds fasting blood glucose level. Pioglitazone treatment does not cause hypoglycemia but improves blood glucose level at 120 minutes.

リウム利尿ペプチド（BNP）は4.0g/mlで正常であった．血中オレキシンは測定しなかった．心電図，心エコー，ホルター心電図は正常で，胸部X線写真では心拡大はなかった．腹部CTでは腫瘍性病変はなかった．呼吸機能検査では座位の肺活量が2.51Lであった．覚醒時，睡眠中とも，酸素飽和度は95%以上であった．嚥下造影検査では誤嚥はなかった．頭部MRIでは，びまん性に脳萎縮をみとめたが，信号異常はなかった．脳波に異常はなかった．ウェクスラー成人知能評価尺度・改訂版では，言語性IQ 55，動作性IQ 75，全IQ 61であった．

会話中の応答の悪さのくりかえしが低血糖による意識障害の可能性を考え，毎食前と毎食後2時間の血糖を4日間検査した．朝食後の血糖で測定限界（20mg/dl）以下が1回，夕食前の血糖で44mg/dlが1回あった．いずれも発汗や動悸，手指振戦など交感神経症状はなく，傾眠でもなく，医師や看護師には応答の変化はわからなかった．高血糖はみとめなかった．

75g経口糖負荷試験（OGTT）では，空腹時血糖83mg/dl，空腹時IRI 5.96μIU/mlで，インスリン抵抗性の評価指数（HOMA-IR：homeostasis model assessment for insulin resistance）[7]は1.22と正常であった．しかし，60分後にIRI 528 μIU/mlと最高値をとり，120分後の血糖は57mg/dlに低下

した(Fig. 1)．糖負荷後120分までのIRI曲線下面積(Σ IRI)は469.8μU・hr/mlであった．蓄尿できず，尿中C-ペプチドは検査できなかった．

経過：当院倫理委員会の承認の下，本人と家族の同意をえて，入院観察下でpioglitazone (Actos®)の治療を開始した．最初の1週間はpioglitazone 15mgを朝食後に内服し，その後，30mgに増量し，維持量とした．治療開始前後に，栄養指導や運動療法などはおこなわなかった．

Pioglitazone治療開始から21日間，毎食前と毎食後2時間の血糖を検査した．低血糖は治療開始6日後に1回，7日後に2回，10日後に1回おこり，いずれのときも傾眠はなく，低血糖を示唆する変化はなかった．治療開始11日目から21日目までは低血糖はなかった．治療開始から2週後のOGTTでは，IRIは糖負荷30分後に93.6μIU/mlで最高になり，120分後の血糖は96mg/dlであった(Fig. 1)．糖負荷60分後の血糖は73mg/dlで，糖負荷前の78mg/dlよりも低値であった．Σ IRIは67.4μU・hr/ml，HOMA-IRは1.00であった．

Pioglitazone治療中，家族からみて，会話中に応答が悪くなることは減った．しかし，傾眠と易疲労は変化なかった．治療開始8カ月後，pioglitazoneの副作用の可能性がある腹部膨満感を訴えた．対処治療薬を追加し，治療を継続した．

Pioglitazone治療開始から10カ月後，毎食前と毎食後2時間の血糖を4日間測定した．低血糖はなかった．OGTTでは，IRIが60分後に145.0μIU/mlと最高になり，120分後の血糖は111mg/dlであった(Fig. 1)．糖負荷後の血糖が糖負荷前の血糖73mg/dlより低下することはなかった．Σ IRIは129.4μU・hr/ml，HOMA-IRは1.08であった．尿中C-ペプチドは32.6μg/日で正常であった．

なお，BNP，胸部X線写真，心電図は変化なく，浮腫や肝機能障害，腎機能障害は生じなかった．

考　察

本患者は無自覚性低血糖を反復した非糖尿病のDM1患者である．DM1患者では，FBSやHOMA-IRが正常であっても，インスリン過分泌や耐糖能常をみとめることがあり[8]，OGTTではDM1患者の49%に，糖負荷によって上昇した血糖が，一度下がり，ふたたび上がる，二峰性の血糖変化をみとめる[9]．DM1患者は糖負荷後の急激なインスリン過分泌のため低血糖が誘発されることがある[10]が，その頻度は不明である．インスリノーマのためインスリン過分泌をみとめたDM1患者の報告はある[11]が，本患者の空腹時血糖，空腹時IRIは正常で，インスリノーマは否定された．

Pioglitazoneは，脂肪細胞の分化を促進し，小型脂肪細胞を増加させることで，アディポネクチン分泌とインスリン依存性糖輸送活性を増加させ，インスリン抵抗性を改善する[3]．われわれはこれまでに，糖尿病を合併したDM1患者へのpioglitazone治療を報告した[4]．この報告では，治療前にインスリン過分泌（Σ IRI ≧250μU・hr/ml）があったDM1患者4人は治療中のΣ IRIが低下し，インスリン分泌不良（Σ IRI ≦150μU・hr/ml）があった患者4人は治療中のΣ IRIが増加した．いずれの患者も高血糖が改善した．Pioglitazone治療はDM1患者のインスリン抵抗性を改善することによって，糖尿病を合併したDM1患者の血糖を改善させると考察した．本患者は非糖尿病のDM1患者で，治療前のΣ IRIが469.8μU・hr/mlであり，糖の利用が上昇したとき低血糖をくりかえす病態が考えられた．Pioglitazone治療によって，本患者のインスリン抵抗性が改善し，糖負荷後のインスリン過分泌が抑制されたことで低血糖が改善したと考えた．α-グルコシダーゼ阻害薬で血糖の吸収を遅らせ，インスリン過分泌を抑制する治療も考えられるが，インスリン抵抗性による病態であることを考慮するとpioglitazone治療が適切であると考えた．

Pioglitazoneは健常者に対する臨床第I相試験で危惧すべき副作用がなく[12]，非糖尿病患者のメタボリック症候群や高血圧の治療にも使われることがある[13][14]．しかしながら，非糖尿病のDM1患者へのpioglitazone治療の有害事象は不明である．インスリン感受性の改善によるインスリン作用の増大が，低血糖を発生させる可能性もあるため，治療開始時には入院で慎重に観察する必要があると考えた．また，一般にpioglitazoneの効果発現は緩徐であり，効果の安定には3カ月から6カ月程度要する[3]．非糖尿病のDM1患者へのpioglitazone治療中は定期的に評価をおこない，有害事象に対処しながら適切な維持量を検討する必要があると考えた．

本患者は低血糖時に自律神経性反応が欠如しており，無自覚性低血糖と診断した．無自覚性低血糖は，1型糖尿病患者のインスリン治療中に合併することが多く，インスリノーマでの報告も散見される[6][15]．無自覚性低血糖は自律神経ニューロパチーとはことなる機能障害で，反復する低血糖に対する膵α細胞からのグルカゴン分泌の低下とエピネフリン反応の減弱が原因と考えられており，一定期間，低血糖を回避することによって回復する[5][6]．DM1患者では糖負荷後のグルカゴンの分泌は健常者よりも上昇することが多く[16]，また，DM1患者のエピネフリン反応については不明である．本患者で無自覚性低血糖が出現した機序は不明であるが，上記の機序を考えると，無自覚性低血糖が現れるまでには，相当，低血糖をくりかえしたと推定された．

DM1では，しばしば傾眠をみとめ，その原因として肺胞低換気やREM睡眠異常などがうたがわれている[17]~[19]．本患者は低血糖による中枢神経異常が現われていた可能性は否定できないが，pioglitazone治療で傾眠や易疲労は改善しておらず，これらの症状はDM1による過眠症や筋力低下が原因であると考えた．会話中の応答の低下は，pioglitazone治療中は軽減しており，無症候性低血糖の影響があったと考えるが，低血糖による意識障害があったのかは不明であった．

本患者は，空腹時血糖やHbA1cは正常で，低血糖時に自律神経性反応がなく，精神運動発達遅滞のため，応答の悪さなどの変化は家族にしかわからなかった．DM1患者では，低血糖をうたがって食前食後の血糖測定やOGTTをおこなわなければ，反復する低血糖や高インスリン血症に対する治療が遅れる可能性があった．今後，他のDM1患者で無自覚性低血糖

を評価し，pioglitazoneの有効性について検討したい．

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Abstract

Successful treatment of recurrent hypoglycemia by pioglitazone in a patient with myotonic dystrophy

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A 20 year-old woman with myotonic dystrophy type 1 (DM1) presented with fatigue, daytime somnolence, and sudden poor responsiveness. Blood glucose was measured before and after each meal for 4 days, and hypoglycemia was confirmed twice, although neither perspiration nor palpitations occurred in the hypoglycemic state. On a 75 g oral glucose tolerance test (OGTT), fasting blood glucose level was 83 mg/dl, and fasting blood immunoreactive insulin (IRI) level was 5.96 μIU/ml. However, IRI increased to 528 μIU/ml at 60 minutes and blood glucose decreased to 57 mg/dl at 120 minutes of the OGTT. The patient was diagnosed with reactive hypoglycemia due to excessive insulin secretion. Oral administration of pioglitazone improved the excessive insulin secretion as assessed by OGTT. After starting treatment, hypoglycemia was not detected either pre- or post-prandially. After 10 months of treatment, blood glucose level after glucose loading was higher than fasting blood glucose level during OGTT, and the IRI area under the curve of the OGTT decreased. We considered that hypoglycemia unawareness resulted from recurrent hypoglycemic episodes in this patient. Pioglitazone was effective in improving hyperinsulinemia and reactive hypoglycemia in nondiabetic DM1.

(Clin Neurol, 49: 641—645, 2009)

Key words: Myotonic dystrophy, recurrent hypoglycemia unawareness, hyperinsulinemia, pioglitazone, 75-g oral glucose tolerance test

脊柱後彎と食道裂孔ヘルニアがレボドパ吸収に影響したパーキンソン病の82歳女性例

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短　報

脊柱後彎と食道裂孔ヘルニアがレボドパ吸収に影響したパーキンソン病の82歳女性例

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要旨：パーキンソン病の82歳女性．66歳から高度の脊柱後彎．82歳から体幹屈曲が悪化し，易転倒が出現．Levodopa 100mg/carbidopa 10mg合剤2錠を空腹時に内服後4時間までの評価では，レボドパ血中濃度は二峰性に推移し，濃度変化に遅れてパーキンソニズムが変動した．体幹屈曲は変化なかった．食道造影と上部消化管内視鏡で食道裂孔ヘルニアと食道の蛇行をみとめ，食道での薬剤通過障害がうたがわれた．同量の薬剤を，飲水量を増やして内服し，内服後，体幹を伸展させた．レボドパ血中濃度は一峰性になり，ピーク値は上昇し，体幹屈曲とパーキンソニズムが改善した．体幹の姿勢異常がレボドパの吸収に影響していたと考えられた．

（臨床神経，49：493—496, 2009）
Key words：パーキンソン病，体幹屈曲，脊柱後彎，食道裂孔ヘルニア，薬物吸収

はじめに

パーキンソン病（PD）における体幹屈曲は不安定な歩行の原因となり[1]，レボドパで改善せず治療に難渋することが多い[2]．一般にPD患者が空腹時にレボドパを内服すると，すみやかに吸収され，血中濃度は一峰性に変化する[3]．レボドパ血中濃度と臨床症状の変化から個々の患者のレボドパ効果の閾値をある程度推測することが可能である[3]．レボドパ血中濃度変化から上部消化管での通過障害によるレボドパの吸収障害をうたがったPD患者において，内服時の飲水をうながし伸展位をとることで体幹屈曲とパーキンソニズムの改善をみとめた例を報告する．

症　例

症例：82歳，女性．
主訴：転倒が増えた．
家族歴・生活歴：特記事項なし．
既往歴：66歳頃から脊柱後彎．
現病歴：68歳，書字で手がふるえた．75歳，PDと診断され，levodopa 100mg/carbidopa 10mg合剤（LD-CD合剤）を1日300mg分3食後服用し，振戦は改善した．77歳，すくみ足が出現した．Droxidopa 200mg，pergolide 500μgを併用したが効果なかった．82歳，体幹屈曲が出現した．歩行が不安定になり，月に1度程度の転倒をくりかえした．右上肢に静止時振戦をみとめ，歩行時は両上肢に出現した．LD-CD合剤を300mgから600mg分3食後服用へ増量したが効果なかった．

現症：身長140cm，体重47kg．一般身体所見では，高度の脊柱後彎をみとめた．意識清明で，脳神経系では眼球運動をふくめ異常なかった．筋力低下はなく，腱反射は正常で，病的反射はみとめなかった．左上肢優位に両上肢に歯車様の，左下肢に鉛管様の筋強剛をみとめた．頸部，体幹に筋強剛はみとめなかった．右上肢に静止時振戦をみとめた．立位で上体は体幹軸から90°前屈した．歩行開始時にすくみ足をみとめ，奇異性歩行をみとめた．歩行中，体幹屈曲のため前方への視野が制限され，姿勢は不安定であった．突進現象はなかった．運動失調や感覚障害はなかった．Hoehn-Yahr重症度IV度で，明らかなウェアリング・オフ現象やジスキネジーはみとめなかった．

検査所見：一般血液生化学検査，尿検査は異常なかった．単純X線で脊柱は粗鬆化し，第10胸椎の圧迫骨折をみとめた．同部位で脊椎は接線方向から45°前屈した．頭部CTで脳実質内異常はみとめなかった．

経過：起床後空腹時にLD-CD合剤100mgを2錠内服させ，村田らの方法[4]で，内服後240分までに7回，レボドパの血中濃度を測定し，同時にパーキンソニズムを評価した（L-dopa test）．臥位から立位までの時間（起立動作時間）は内服後60分まで改善し，120分後に悪化したが，240分後にふたたび改善した．振戦はUnified Parkinson Disease Rating Scaleに準じて評価したが，改善はみとめなかった．体幹屈曲は変化なかった．血中濃度は，内服後30分（5.1nmol/ml）と180

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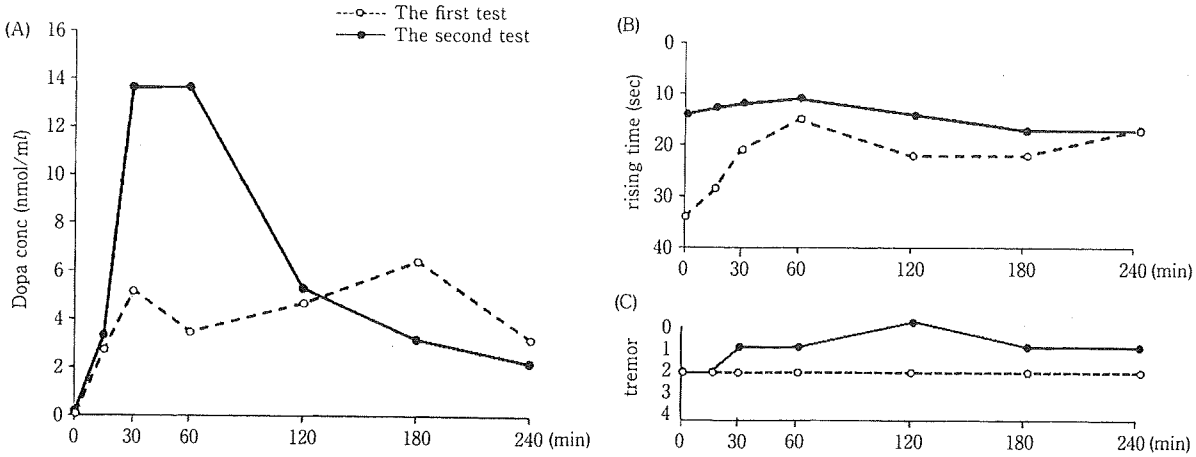

Fig. 1　Plasma levodopa concentration and the change of symptoms were assessed until 240 minutes after administering levodopa (200mg) plus carbidopa (20mg) after overnight fasting (L-dopa test). (A) shows the plasma levodopa concentration, (B) shows the rising time, which represents the time required to assume the upright position from the supine position, and (C) shows the severity of tremor. The relative values rate the aggravation in symptoms on a scale of 0 to 4. Dotted lines represent the results of the first L-dopa test and solid lines represent the results of the second test. In the second test, the patient was instructed to stretch her back after consuming the tablets with a lot of water. At the first test, plasma levodopa concentration shows a bimodal peak with respect to the improvement in the rising time. At the second test, plasma levodopa concentration shows a single peak, and the symptoms improved considerably more than that observed in the first test.

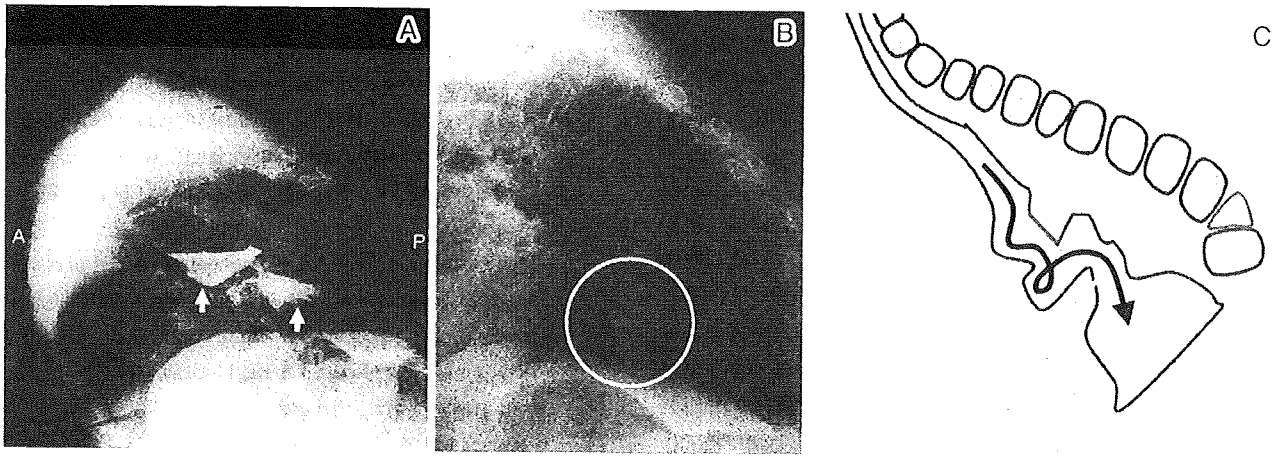

Fig. 2　The lateral X-ray films show the contrast media (A: arrow) or the contrast capsule (B: circle) that were located in the esophagus. C: the montage of the patient's esophagus; the arrow indicates the path of entry of the tablets into the stomach. The contrast media remains in the esophagus during the esophagography procedure (more than 5 min). The contrast capsule reaches the stomach after 15 min. These data support the fact that the LD-CD tablet remains in the esophagus after swallowing.

分（6.3nmol/ml）にピークを示した（Fig. 1 点線）．薬物吸収量の目安となる area under the curve（AUC）は 19.6nmol/ml・hr であった．

L-dopa test で二峰性の血中濃度変化であったことから，薬剤の消化管での停留をうたがい食道造影検査をおこなった．造影剤は食道内に貯留し（Fig. 2A），伸展姿勢になると貯留は解消した．X 線不透過マーカー（SITZMARKS®）の内服では，食道内の造影剤貯留部位にマーカーが停留した（Fig. 2B）．上部消化管内視鏡では，食道の蛇行と食道裂孔ヘルニアをみとめた．食道憩室やアカラシアはみとめなかった．

食道での薬剤の通過を改善させるために，初回の L-dopa test の 2 倍量の水（約 200ml）で LD-CD 合剤 100mg を 2 錠内服し，内服後数分は，体幹を伸展するように指導し，2 回目の L-dopa test をおこなった．起立動作時間，振戦が 120 分後を

ピークに改善し，体幹屈曲も改善した．レボドパ血中濃度は60分後に13.7nmol/mlまで上昇し，一峰性の変化となった(Fig. 1実線)．AUCは31.9nmol/ml・hrと初回より増加した．

考　察

PD患者での食道裂孔ヘルニアの合併頻度は32.6%で，同年代の正常対照者の7.6%よりも高く，腹筋の緊張や消化管の蠕動運動低下が原因とされる[5][6]．また，高度の脊柱後彎は背部から腹腔を圧迫し，食道裂孔ヘルニアの原因となる[7]．本症例は食道裂孔ヘルニアのため，咽頭から胃までの距離が短縮したことで，食道の蛇行をきたし，さらに体幹屈曲のため食道が水平に近くなったと考えられた．

本例の初回のL-dopa testでは，レボドパ血中濃度は内服30分後のピークの後，60分後から180分後まで緩やかに上昇した．LD-CD合剤が食道に留まっている様子はとらえられていないが，食道内の造影剤貯留像とX線不透過マーカーの停留像から，内服したLD-CD合剤の一部は，食道内の蛇行した部位に留まり，徐々に小腸上部の吸収部位に到達したと推定した．

2回目のL-dopa testの血中濃度変化から，内服方法の変更によって薬剤の食道での通過が改善し，全量がすみやかに吸収され，初回より効果があったと考えられた．2回目にはじめて改善した体幹屈曲はレボドパ非依存性であるとされるが，レボドパの追加で改善した報告もある[8]．レボドパ治療時には吸収量の不足のために体幹屈曲が改善しない可能性を考慮する必要がある．

胃排出時間の延長，胃酸度の低下などによりレボドパ吸収障害がおこりうることが報告されている[9]．本報告は脊柱後彎と食道裂孔ヘルニアにともなう食道蛇行もレボドパ吸収障害をおこしうることを明らかにした．脊柱後彎の強いPD患者では，レボドパ効果が不十分なばあいに食道通過障害によるレボドパ吸収障害が出現している可能性があることをうたがうべきである．診断的治療として内服時の飲水量増加と伸展姿勢が有用であると考えた．

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Abstract

Severe kyphosis and esophagus hiatal hernia affected on the levodopa absorption of a patient with Parkinson's disease

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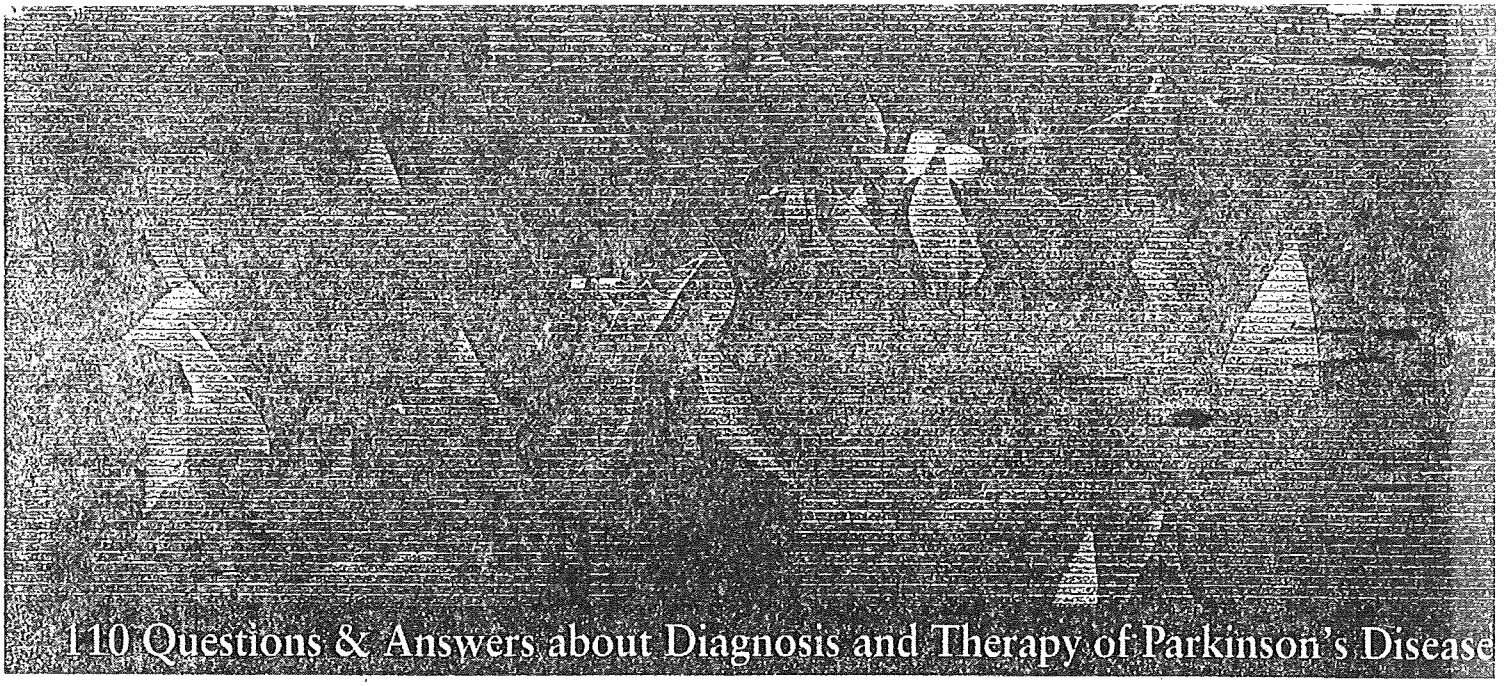
An 82 year-old woman with Parkinson's disease complained of a tendency to fall. She has had an extensive kyphosis since she was 66 years old. Over the last 6 months, she has repeatedly fallen. Even though she took anti-parkisonian drugs, she had also developed camptocormia. Her plasma levodopa concentration was analyzed for 4 hrs after administrating an oral dose of levodopa (200 mg) plus carbidopa (20 mg) at the time of fasting. The change in the plasma levodopa concentration showed bimodal peaks. The physical symptoms depended on the plasma concentration and improved twice. Esophageal tortuosity and esophageal hiatal hernia were detected by esophagography and upper gastric endoscopy. Such physical symptoms were speculated to have been caused by the transit disturbance of the drug in the gastrointestinal duct. During a second analysis of the plasma levodopa concentration, the patient was instructed to keep extending her back after consuming the same dose of drugs but with a greater amount of water than in the first analysis. A single and a higher peak were observed for the plasma levodopa concentration, and the physical symptoms, including camptocormia and parkinsonism, were improved. Hunched posture could influence the absorption of antiparkinsonian drugs.

(Clin Neurol, 49: 493—496, 2009)

Key words: Parkinson's disease, camptocormia, kyphosis, esophageal hiatal hernia, drug absorption



パーキンソン病診療 Q&A 110

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58 ゾニサミドはどのような場合に使用するのがよいか，また，なぜ効くのか，その使い方も説明してください．

ゾニサミドは元々抗てんかん薬（エクセグラン）で，偶然の臨床経験から抗パーキンソン作用が見出され，2009年3月，抗パーキンソン病薬（トレリーフ）として，認可された．抗パーキンソン病薬としては25mg 1日1回投与のみが認可されている．

1 ゾニサミドの抗パーキンソン効果

進行期パーキンソン病（PD）患者が偶然てんかん発作を併発し，抗てんかん薬としてゾニサミドを投与したところ，てんかん発作の消失とともにPD症状が著明に改善したことをきっかけに抗PD効果が発見されたことから，治験はすべて進行期の患者でL-dopa併用下で行われた．したがって，現在臨床的なエビデンスがあるのは，L-dopa併用の進行期PD患者での効果のみである．

抗PD薬としての認可までに3つの二重盲検試験（第II相，第IIb/III相，第III相）が行われた．第II相は50mg，100mg，200mg，偽薬の4群比較（合計136人），第IIb/III相は25mg，50mg，100mg，偽薬の4群比較（合計347人），第III相は25mg，50mg，偽薬の3群比較（合計185人）である．いずれもL-dopa併用でなんらかの問題点が出現しているPD患者が対象で平均罹患期間は7.5～10年，Yahr重症度はon 2.5，off 3.5程度である．on時の運動症状の指標であるUPDRS IIIは第II相の50mg群，IIb/IIIの25mg，50mg，IIIの25mgで有意に改善した．ADLの指標であるUPDRS IIについては，第II相では50mg群でon時off時とも，第III相では25mg群でoff時のスコアがそれぞれ有意に改善，第IIb/III相では50mg，100mg群でoff時間が1.5時間前後有意に短縮した．UPDRS IIIが30%以上改善した患者の割合（responder rate）は第3相では25mg群で41.0%，50mgで45.8%で，IIb/IIIもほぼ同様の結果であった．

これらの試験ではいずれも90%以上がドパミン受容体作動薬を服用し，ほぼ半数がMAOB阻害薬を併用していた．

進行期ですでに様々な薬剤を使用しているPD患者にゾニサミドを加えることで運動症状やADLがon時のみならずoff時も著明に改善している一方，副作用の発現率はきわめて低く，25～50mg群では偽薬群と同程度であった．認可された25mg群では5%以上の発現率の項目はなく，これまでの25～200mgのすべての治験での合計でも，眠気（10.4%），食欲不振（8.6%），悪心（6.2%），気力低下（5.2%），幻覚（5.2%）であった．特に進行期に問題となる不随意運動の出現率の低さは特筆すべきで，むしろ不随意運動の改善例も認められた．

2 抗パーキンソン病薬ゾニサミドの作用機序

ゾニサミドはチロシン水酸化酵素活性亢進を介してのドパミン合成亢進作用，ドパミン遊離促進作用，MAO活性阻害作用をもつがこの他，多機能製剤とよばれるように，Naチャンネル阻害作用，T型Caチャンネル阻害作用，グルタミン酸遊離抑制作用，GABAトランスポーター（GAT1）抑制作