Table 2 Summary of multiple system atrophy patients with dementia

Case	Gender	Onset age	Disease duration	Initial symptom	ICARS	MMSE	Frontal lobe atrophy	WMH severity	H/M ratio (early/delayed)
1	F	71	2	Ataxia	32	23	+	–	1.88/1.72
2	F	52	2	Ataxia	45	24	+	–	1.73/1.43
3	F	54	3	Ataxia	33	22	+	–	2.04/2.29
4	M	53	3	Ataxia	49	21	+ +	–	1.61/1.38
5	M	62	5	Ataxia	53	20	+	–	1.82/2.09
6	F	58	6	Ataxia	90	23	+ + +	–	1.34/1.04
7	M	59	7	Ataxia	71	21	+ +	–	1.43/1.13
8	F	58	3	Dementia	23	18	+ + +	+	2.06/1.58
9	M	64	4	Dementia	94	9	+ +	+ +	1.47/1.21
10	F	69	6	Dementia	34	18	+ + +	+ + +	2.38/2.37

Gradings of frontal lobe atrophy were estimated qualitatively; +: slight, + +: moderate, + + +: severe. white matter hyperintensities (WMH) severity ratings were attained according to the Fazekas scale; –: grade 0, +: grade 1, + +: grade 2, + + +: grade 3; ICARS, International Cooperative Ataxia Rating Scale; MMSE, Mini Mental State Examination; H/M, heart to mediastinum.

impairment and disorientation in the same three patients were more severe than seen in the other seven patients.

Representative cases

Case 7

The patient was a 66-year-old man with no family history of neurological disease and no history of major illness. He presented initially with gait disturbance and orthostatic hypotension at age 59 years and was diagnosed with MSA by a neurologist. The following year, he gradually developed dysarthria, ataxia and neuropathic bladder, and his family detected cognitive impairment. At age 62 years, he was admitted to our hospital, where he presented with ataxia, extrapyramidal signs, and dysautonomia. ICARS score was 36 points and MMSE score was 24 points. At age 65 years, his ICARS score was 71 points, MMSE score was 21 points, and intelligence quotient was 71 (VIQ 83, PIQ 60) with the Wechsler adult intelligence scale-revised (WAIS-R) and 10 points in frontal assessment battery. His lowest scored category in MMSE and WAIS-R was attention, calculation, and verbal frequency. MRI study disclosed typical findings of MSA such as severe cerebellar and pontine atrophy with the so-called 'hot cross bun sign' and moderate frontal lobe atrophy [Correction added after online publication 31 March 2009: in the preceding sentence, 'burn' was corrected to 'bun']. ^{99}mTc-ECD SPECT image revealed moderate decline of rCBF in the frontal lobe (Fig. 1). H/M ratio in ^{123}I-MIBG cardiac scintigraphy was 1.43/1.13 (early/delayed phase). Symptoms continued to progress gradually and he became bed-ridden at age 65 years.

Case 9

The patient was a 75-year-old man with no family history of neurological disease who had a several-year history of diabetes mellitus. At age 69, he had developed episodic memory impairment and disorientation; he was diagnosed with DAT by a neurologist. At this time, mild bilateral temporal atrophy was detected by MRI, whereas no cerebellar or pontine atrophy was evident. At age 70, gait disturbance gradually developed and he was admitted to our hospital. He was diagnosed with MSA based on the presence of severe ataxia, parkinsonism, and dysautonomia. He showed severe episodic memory impairment, disorientation, and constructional apraxia. MRI revealed typical MSA findings and moderate fronto-temporal lobe atrophy. Furthermore, there were moderate leukoaraiosis in deep white matter around anterior and posterior horn of lateral ventricles. ^{99}mTc-ECD SPECT image revealed severe decline of rCBF in the frontal and temporal lobes (Fig. 2). His ICARS score was 80 points. With cognitive assessment, he was found to have an MMSE score of 15 points and WAIS-R IQ of 62 (VIQ 76, PIQ 54). His lowest scored category in MMSE and WAIS-R was not only attention, calculation, and verbal fluency, but also severe disorientation. His symptoms progressed gradually and he became bedridden at age 72 years. At that time, ICARS score was 94 points and MMSE score was 9 points. H/M ratio in ^{123}I-MIBG cardiac scintigraphy was 1.46/1.12 (early/delayed phase). His symptoms continued to progress gradually and he died suddenly at age 73 years.

Discussion

In this study, we documented dementia in a significant proportion of patients with MSA in our hospital. Dementia is included in exclusion criteria in the consensus criteria for MSA. Of our patients, 10 (17%) were diagnosed with dementia. We classified two types of MSA with dementia. One group (cases 1–7) had

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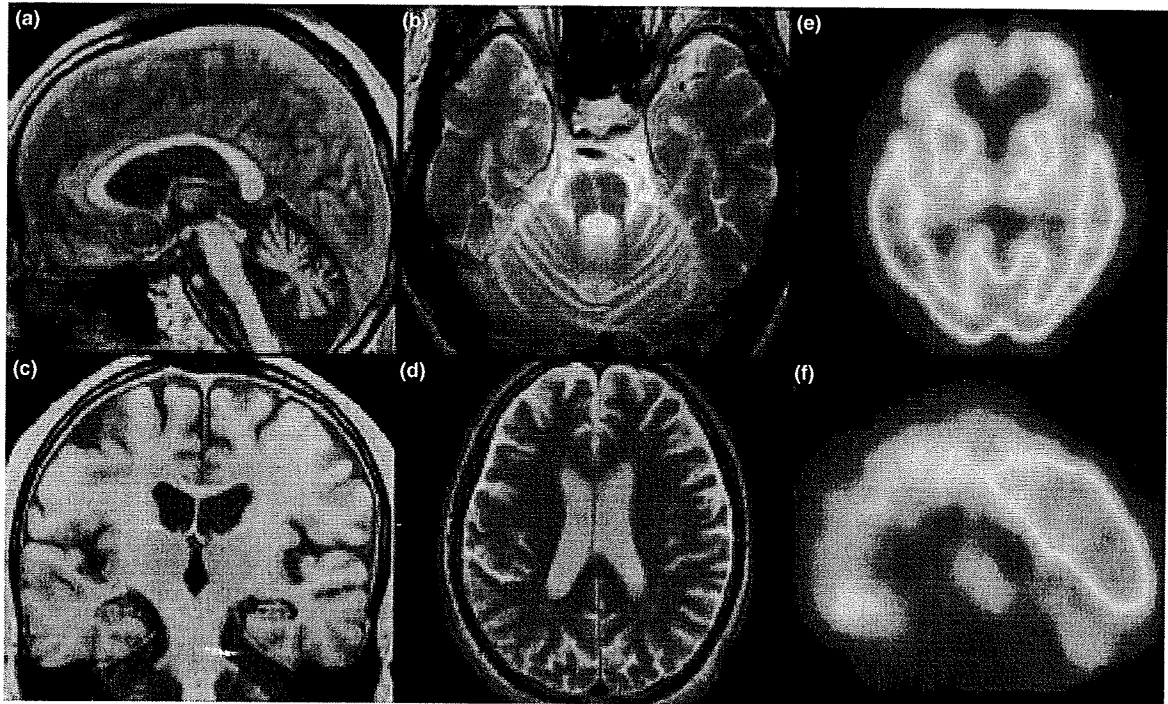

Figure 1 Neuroimaging studies at case 7. (a–d) Magnetic resonance imaging (MRI) revealed severe cerebellar and pontine atrophy with the so-called 'hot cross bun sign,' moderate fronto-temporal lobe atrophy [Correction added after online publication 31 March 2009: in the preceding sentence, 'burn' was corrected to 'bun']. White matter lesions were not noted. (e, f) 99mTc-ECD SPECT image showed moderate decline of regional cerebral blood flow in the frontal and temporal lobes. (a, c) T1 weighted MRI image. (b, d) T2 weighted MRI image.

dementia that was preceded by development of ataxia. The other three patients (cases 8–10) developed dementia before onset of ataxia. The common characteristics of cognitive impairment in each type of MSA with dementia included frontal executive dysfunction, findings similar to those of previous studies [10–15]. The latter type of dementia (cases 8–10) was diagnosed as DAT before criteria were reached for MSA. According to qualitative analyses of MRI, these patients showed more severe disorientation and more severe cerebral atrophy, with cerebral white matter lesions more prominent than in the other type of patient.

Moreover, we found that the patients with MSA and dementia had significantly reduced ^{123}I-MIBG cardiac uptake compared with the patients without dementia. Recent studies have reported that H/M ratio of ^{123}I-MIBG cardiac scintigraphy is a useful diagnostic tool for LBDs based on evidence of post-ganglionic cardiac sympathetic denervation in these patients [19–22]. Although MSA is also an α-synucleinopathy, H/M ratio of ^{123}I-MIBG cardiac scintigraphy in patients with MSA has been reported predominantly to be in the normal range. These published results support the hypothesis that post-ganglionic cardiac sympathetic denervation might be evident in MSA patients with dementia. However, it has not yet been clarified whether decreased cardiac uptake of MIBG is associated with neuropathological changes of the central nervous system and neuropsychological state. We have found that reduction of cardiac MIBG uptake might be associated with neuropsychological state in patients with PD [23]. Nagayama *et al.* [24] has reported a MSA case with reduction of MIBG uptake and Lewy body pathology. However, it has not been described whether the MSA case had dementia. In our study, whilst there was no neuropathological examination, we could not diagnose any type of dementia in these cases neuropathologically.

Recent studies reported that there are neuropathological changes in patients with MSA and dementia [25–27]. These reports described autopsy cases with remarkable frontal lobe atrophy, in which GCI were abundant in the deep layer of the cortex and were even more abundant in the white matter of the frontal and parietal lobes. Piao *et al.* [28] emphasized that α-synuclein and phosphorylated tau co-occurred in certain brain regions in two cases of combined MSA and AD. Moreover, only a few reports have described the

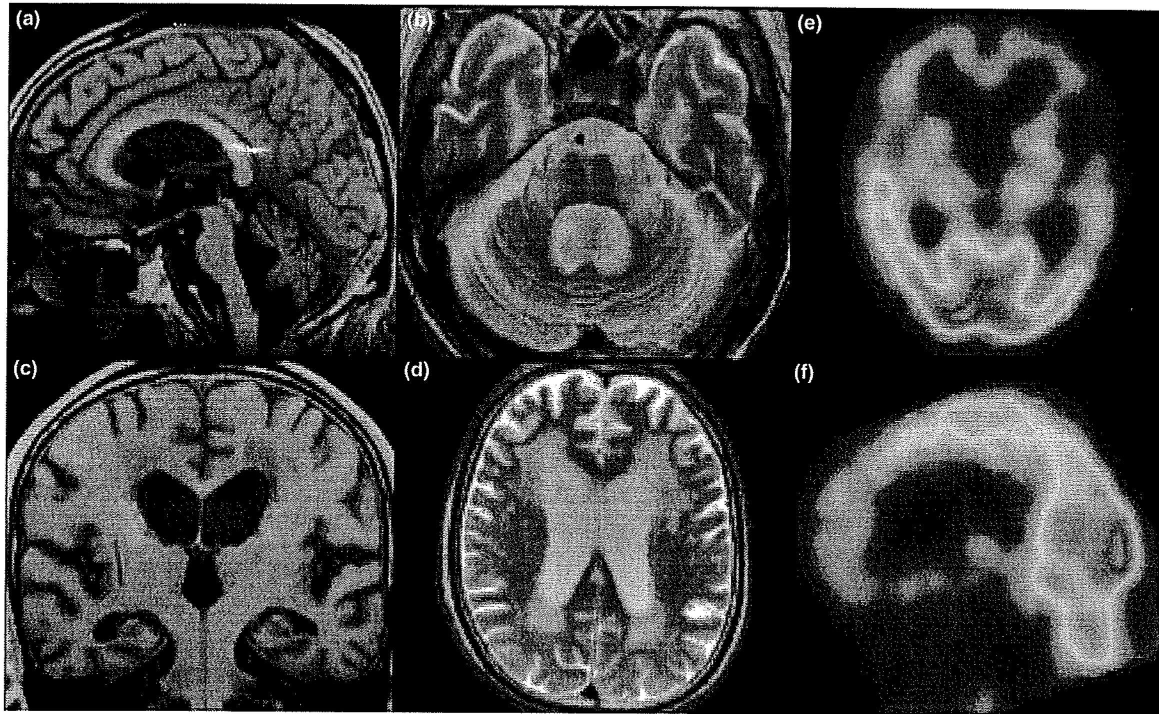

Figure 2 Neuroimaging studies at case 9. (a–d) Magnetic resonance imaging (MRI) revealed severe cerebellar and pontine atrophy with the so-called 'hot cross bun sign,' severe fronto-temporal lobe atrophy and moderate white matter lesions [Correction added after online publication 31 March 2009: in the preceding sentence, 'burn' was corrected to 'bun']. (e, f) 99mTc-ECD SPECT image showed severe decline of regional cerebral blood flow in the frontal and temporal lobes. (a, c) T1 weighted MRI image (b, d) T2 weighted MRI image.

co-existence of GCIs and Lewy bodies [29,30]. Neuropathological findings associated with dementia in patients with MSA are thought to be varied. As far as we know, patients with MSA whose dementia preceded motor dysfunction have not been described to date. As autopsy was not performed in any of the cases, we could not clarify the neuropathological correlates of dementia in our series. Therefore, neuropathological examination is necessary to clarify a new subtype of MSA. Thus, further study including postmortem neuropathological examination is needed.

In conclusion, dementia in patients with MSA may be more common than previously thought. Etiology of cognitive decline in these patients may be varied, with heterogeneous underlying pathogenetic processes.

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Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease

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To identify susceptibility variants for Parkinson's disease (PD), we performed a genome-wide association study (GWAS) and two replication studies in a total of 2,011 cases and 18,381 controls from Japan. We identified a new susceptibility locus on 1q32 ($P = 1.52 \times 10^{-12}$) and designated this as *PARK16*, and we also identified *BST1* on 4p15 as a second new risk locus ($P = 3.94 \times 10^{-9}$). We also detected strong associations at *SNCA* on 4q22 ($P = 7.35 \times 10^{-17}$) and *LRRK2* on 12q12 ($P = 2.72 \times 10^{-8}$), both of which are implicated in autosomal dominant forms of parkinsonism. By comparing results of a GWAS performed on individuals of European ancestry, we identified *PARK16*, *SNCA* and *LRRK2* as shared risk loci for PD and *BST1* and *MAPT* as loci showing population differences. Our results identify two new PD susceptibility loci, show involvement of autosomal dominant parkinsonism loci in typical PD and suggest that population differences contribute to genetic heterogeneity in PD.

Parkinson's disease (MIM168600) is one of the most common neurodegenerative diseases worldwide, affecting 1–2% of individuals aged ≥65 years[1]. Clinical features of PD result primarily from loss of dopaminergic neurons in the substantia nigra. Various medical treatments improve PD symptoms but do little to deter disease progression. Identifying genetic risk factors for PD will be helpful in elucidating the pathogenesis of the disease. Linkage studies have been successful in mapping genes for mendelian forms of parkinsonism: *SNCA* (encoding α-synuclein)[2] and *LRRK2* (refs. 3,4) in autosomal dominant forms, and *PARK2* (encoding parkin), *PINK1*, *PARK7* (encoding DJ-1) and *ATP13A2* in autosomal recessive forms[5,6]. However, mendelian forms of parkinsonism are rare compared to the far more common typical PD, a complex disorder caused by multiple genetic and environmental factors[7]. Association studies have evaluated variants in many candidate genes for PD[7], but only a few, such as common variants of *SNCA*[8–10] and rare mutations of *GBA*[11], have been identified as PD-susceptibility genes with genome-wide significance. Recently, GWASs in PD have provided association evidence at several loci, but not at the genome-wide significant level[12–14].

We conducted a GWAS and two subsequent replication studies for PD to identify further common variants that contribute to disease. In the GWAS stage, we genotyped 561,288 SNPs on autosomal and sex chromosomes using the HumanHap550 array (Illumina). The GWAS stage included 1,078 PD cases and 2,628 controls in the Japanese population (**Supplementary Note**). After SNP and sample quality control analyses, we used genotype data from 435,470 SNPs in 988 cases and 2,521 controls in the GWAS analysis (see Online Methods).

We tested for association between each SNP and PD using the Cochran-Armitage trend test with 1 d.f. The quantile-quantile plot showed a close match to test statistics expected under the null distribution (genomic inflation factor $\lambda = 1.055$ for PD) (**Fig. 1a,b**). This indicates minimal overall inflation of genome-wide statistical results due to population stratification and also reveals a number of SNPs whose P values exceed those expected under the null hypothesis. Seventeen SNPs showed $P < 5 \times 10^{-7}$, the threshold for genome-wide significance suggested by the Wellcome Trust Case Control Consortium[15] (**Fig. 1c**). All these SNPs were located on 4q22, a region harboring *SNCA* that was previously identified by us and others as a definite susceptibility gene for PD[8–10].

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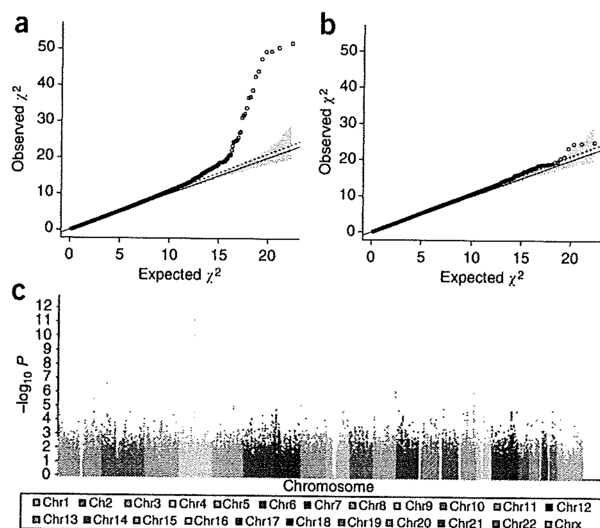

Figure 1 Genome-wide association results from the discovery phase. **(a)** Quantile-quantile plot for test statistics (Cochran-Armitage trend test) for 435,470 SNPs passing quality control. The solid line represents concordance of observed and expected values. Slope of the dashed line represents the genomic inflation factor (λ = 1.055). The shaded region is the 95% concentration band formed by calculating, for each order statistic, the 2.5th and 97.5th percentiles of the respective distribution under the null hypothesis. **(b)** Quantile-quantile plot for test statistics (Cochran-Armitage trend test) after the removal of the four loci with strong associations in this study (1q32, 4p15, 4q22 and 12q12). **(c)** Manhattan plot presenting the *P* values across the genome. The $-\log_{10} P$ (Cochran-Armitage trend test) from 435,470 SNPs in 988 Parkinson's disease cases and 2,521 controls is plotted according to its physical position on successive chromosomes.

For fast-track replication, we selected the 337 most associated SNPs ($P \leq 0.000533$) from analysis of GWAS data and genotyped them in a sample set of replication 1, which consisted of 612 cases and 14,139 controls from Japan (**Supplementary Note**). Thirty-two SNPs showed association of $P < 0.05$ in replication 1 (**Supplementary Fig. 1**). Combined analyses of the GWAS and replication 1 showed that 12 SNPs in 3 loci (1q32, 4p15 and 4q22) surpassed $P < 5 \times 10^{-7}$. Furthermore, we found association signals ($P = 3.06 \times 10^{-6}$, OR = 1.36) on 12q12, harboring *LRRK2*, which is a causative gene for autosomal dominant parkinsonism (**Table 1**).

In replication 2, we tested 24 SNPs at these four loci for association with PD. An independent sample set (321 cases and 1,614 controls) recruited from Japan was used in replication 2 (**Supplementary Note**). Association evidence was again found at these four loci: 1q32, $P = 2.80 \times 10^{-4}$, OR = 1.37; 4p15, $P = 7.70 \times 10^{-3}$, OR = 1.26; 4q22, $P = 0.02$, OR = 1.22; and 12q12, $P = 6.43 \times 10^{-4}$, OR = 1.57 (**Table 1**). The disease associations on 1q32 and 12q12 exceeded the conservative Bonferroni-corrected threshold for significance ($P = 0.0021$; calculated as 0.05/24). All the SNPs showed allele frequency differences in the same direction in the GWAS, replication 1 and replication 2. Furthermore, combined analysis of the GWAS and two replication stages provided strong evidence of association in the four regions with a significance level of $P = 2.72 \times 10^{-8}$ or less (**Table 1**).

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We identified two new susceptibility loci with genome-wide significance on 1q32 and 4p15, which have not been reported to be associated with PD in previous studies[12–14]. On 1q32, seven SNPs (rs16856139, rs823128, rs823122, rs947211, rs823156, rs708730 and rs11240572) reached $P < 5 \times 10^{-7}$ in the overall analysis (**Fig. 2a**). rs947211 showed the strongest association to PD ($P = 1.52 \times 10^{-12}$, OR = 1.30) and is located 8.5 kb upstream of *RAB7L1* and 5.6 kb downstream of *SLC41A1*. Linkage disequilibrium (LD) analysis revealed that SNPs with significant associations to PD lie within several LD blocks containing the following five genes: *SLC45A3*, *NUCKS1*, *RAB7L1*, *SLC41A1* and *PM20D1* (also called *FLJ32569*) (**Table 1** and **Fig. 2a**). Three genes (*NUCKS1*, *RAB7L1* and *SLC41A1*) were contained in the same LD block as rs947211. rs947211 was weakly correlated with the other six SNPs (r^2 = 0.07–0.25), and we observed residual association signals when rs947211 and each of the other six SNPs were paired in conditional analyses of our overall data. This result suggests that this locus has multiple independent association signals (**Supplementary Table 1**). These data provide the first evidence, to our knowledge, of an association between 1q32 and PD susceptibility, and we designated this region as *PARK16*.

On 4p15, four SNPs (rs11931532, rs12645693, rs4698412 and rs4538475) reached $P < 5 \times 10^{-7}$ in the combined analysis (**Fig. 2b**). These four SNPs showed strong disease association with almost the same significance levels (ranging from $P = 3.94 \times 10^{-9}$ to $P = 1.78 \times 10^{-8}$, all OR = 1.24); among them, rs4538475 was the most strongly associated. The four SNPs were located from intron 8 to 4.1 kb downstream of *BST1* (bone marrow stromal cell antigen). LD analysis revealed that the four SNPs were correlated with $r^2 > 0.78$ and lie within a 15 kb LD block containing a single gene, *BST1*.

The remaining two intervals (4q22 and 12q12) harbored genes previously found to be causal for autosomal dominant forms of parkinsonism, specifically, *SNCA* and *LRRK2*, respectively. On 4q22, seven SNPs (rs3733449, rs11931074, rs3857059, rs2736990, rs3796661, rs6532194 and rs12233759) throughout the *SNCA* region showed genome-wide significant association in the combined analysis (**Fig. 2c**). The most significantly associated SNPs, rs11931074 ($P = 7.35 \times 10^{-17}$, OR = 1.37) and rs3857059 ($P = 5.68 \times 10^{-16}$, OR = 1.36), are approximately 35.7 kb apart, located 7.2 kb downstream from and in intron 4 of *SNCA*, respectively. The entire *SNCA* gene was divided into two LD blocks at intron 4. Both SNPs were positioned on the 3′ side of the LD block and showed a high degree of LD ($r^2 = 0.98$). Three SNPs (rs2736990, rs3796661 and rs6532194) were moderately correlated with rs11931074 (r^2 = 0.81, 0.76 and 0.63, respectively). The remaining two SNPs (rs3733449 and rs12233759) were weakly correlated with rs11931074 (r^2 = 0.05 and 0.24, respectively), and residual association signals were marginally observed when rs11931074 and each of these two SNPs were paired in conditional analyses of our overall data (**Supplementary Table 1**). These data confirm *SNCA* as a susceptibility gene for PD.

On 12q12, five SNPs (rs1994090, rs7304279, rs4768212, rs2708453 and rs2046932) surpassed $P < 5 \times 10^{-7}$ in the overall analysis (**Fig. 2d**). The five SNPs showed strong disease association with almost the same significance (ranging from $P = 2.72 \times 10^{-8}$ to $P = 1.09 \times 10^{-7}$, OR = 1.37–1.39); among them, rs1994090 was the most strongly associated to PD. These five SNPs were located from intron 2 of *SLC2A13* to 38.4 kb upstream of *LRRK2*. These SNPs were highly correlated with $r^2 > 0.83$ and were positioned within several LD blocks defined by the method of Gabriel *et al.*[16]. This is the first evidence that common variants proximal to *LRRK2* are associated with PD at genome-wide significance level.

Variants with the highest significance at the four loci detected in this study were common SNPs with risk allele frequencies of 0.50 (rs947211 on 1q32), 0.38 (rs4538475 on 4p15), 0.58 (rs11931074 on 4q22) and 0.08 (rs1994090 on 12q12) (**Table 1**). Population attributable risks for rs947211, rs4538475, rs11931074 and rs1994090 were estimated to be 13%, 8%, 18% and 3%, respectively.

Table 1 Summary of association results for representative SNPs that characterize the association of Parkinson's disease with 1q32 (*PARK16*), 4p15 (*BST1*), 4q22 (*SNCA*) and 12q12 (*LRRK2*)

			Allele	GWAS			Replication 1			GWAS + Replication 1		Replication 2			GWAS + Replication 1+2	
Locus	SNP	Pos (Mb)	Minor/major	MAF Case / Ctrl	P_{trend}	OR (95% CI)	MAF Case / Ctrl	P_{trend}	OR (95% CI)	P_{cmh}	OR (95% CI)	MAF Case / Ctrl	P_{trend}	OR (95% CI)	P_{cmh}	OR (95% CI)
New PD loci																
1q32 (*PARK16*)	rs16856139	203.91	T/C	0.10 / 0.14	2.55×10^{-6}	1.50 (1.26–1.77)	0.11 / 0.13	0.067	1.19 (0.99–1.44)	2.15×10^{-6}	1.35 (1.19–1.54)	0.10 / 0.13	0.015	1.42 (1.07–1.88)	1.02×10^{-7}	1.36 (1.22–1.53)
	rs823128	203.98	G/A	0.10 / 0.14	2.09×10^{-5}	1.43 (1.21–1.69)	0.11 / 0.13	0.0056	1.31 (1.08–1.59)	4.67×10^{-7}	1.38 (1.22–1.57)	0.09 / 0.14	0.0028	1.53 (1.16–2.03)	4.88×10^{-9}	1.41 (1.26–1.58)
	rs823122	203.99	C/T	0.10 / 0.14	7.98×10^{-5}	1.39 (1.18–1.64)	0.11 / 0.13	0.013	1.27 (1.05–1.54)	3.87×10^{-6}	1.34 (1.18–1.52)	0.09 / 0.14	0.0034	1.52 (1.15–2.01)	5.22×10^{-8}	1.37 (1.22–1.54)
	rs947211	204.02	A/G	0.43 / 0.48	1.15×10^{-4}	1.23 (1.11–1.37)	0.42 / 0.50	1.35×10^{-6}	1.35 (1.19–1.52)	1.12×10^{-9}	1.28 (1.18–1.38)	0.42 / 0.50	2.80×10^{-4}	1.37 (1.16–1.63)	1.52×10^{-12}	1.30 (1.21–1.39)
	rs823156	204.03	G/A	0.13 / 0.17	1.20×10^{-5}	1.40 (1.20–1.62)	0.14 / 0.17	0.012	1.25 (1.05–1.48)	6.45×10^{-7}	1.33 (1.19–1.49)	0.12 / 0.17	0.0013	1.52 (1.17–1.95)	3.60×10^{-9}	1.37 (1.23–1.52)
	rs708730	204.04	G/A	0.14 / 0.18	2.60×10^{-5}	1.37 (1.18–1.59)	0.15 / 0.17	0.022	1.22 (1.03–1.44)	2.89×10^{-6}	1.30 (1.17–1.46)	0.12 / 0.18	0.0019	1.48 (1.15–1.89)	2.43×10^{-8}	1.33 (1.21–1.48)
	rs11240572	204.07	A/C	0.13 / 0.16	1.66×10^{-4}	1.34 (1.15–1.56)	0.13 / 0.16	0.016	1.24 (1.04–1.48)	9.78×10^{-6}	1.30 (1.16–1.46)	0.12 / 0.17	0.0024	1.49 (1.15–1.92)	1.08×10^{-7}	1.33 (1.20–1.48)
4p15 (*BST1*)	rs11931532	15.33	T/C	0.45 / 0.40	2.75×10^{-4}	1.22 (1.09–1.35)	0.47 / 0.42	1.86×10^{-4}	1.26 (1.11–1.42)	2.02×10^{-7}	1.23 (1.14–1.34)	0.47 / 0.41	0.0077	1.26 (1.06–1.49)	5.13×10^{-9}	1.24 (1.15–1.33)
	rs12645693	15.34	G/A	0.45 / 0.40	3.06×10^{-4}	1.21 (1.09–1.35)	0.47 / 0.42	3.00×10^{-4}	1.25 (1.11–1.41)	3.42×10^{-7}	1.23 (1.14–1.33)	0.47 / 0.41	0.0077	1.26 (1.06–1.49)	8.65×10^{-9}	1.24 (1.15–1.33)
	rs4698412	15.35	A/G	0.38 / 0.33	5.28×10^{-5}	1.25 (1.12–1.40)	0.40 / 0.35	4.91×10^{-4}	1.24 (1.10–1.40)	1.03×10^{-7}	1.25 (1.15–1.35)	0.38 / 0.34	0.055	1.19 (1.00–1.42)	1.78×10^{-8}	1.24 (1.15–1.33)
	rs4538475	15.35	A/G	0.41 / 0.36	4.05×10^{-5}	1.25 (1.12–1.40)	0.43 / 0.38	3.48×10^{-4}	1.25 (1.10–1.41)	5.98×10^{-8}	1.25 (1.15–1.35)	0.42 / 0.37	0.022	1.22 (1.03–1.46)	3.94×10^{-9}	1.24 (1.16–1.34)
Loci located in or near autosomal dominant parkinsonism genes																
4q22 (*SNCA*)	rs11931074	90.86	G/T	0.32 / 0.42	6.17×10^{-13}	1.50 (1.34–1.68)	0.36 / 0.42	2.12×10^{-5}	1.31 (1.16–1.48)	2.19×10^{-16}	1.41 (1.30–1.53)	0.38 / 0.43	0.034	1.21 (1.01–1.44)	7.35×10^{-17}	1.37 (1.27–1.48)
	rs3857059	90.89	A/G	0.32 / 0.41	1.17×10^{-12}	1.49 (1.34–1.67)	0.36 / 0.42	6.92×10^{-5}	1.29 (1.14–1.45)	1.54×10^{-15}	1.40 (1.29–1.52)	0.38 / 0.43	0.041	1.20 (1.01–1.43)	5.68×10^{-16}	1.36 (1.26–1.46)
	rs894278	90.95	G/T	0.43 / 0.38	7.68×10^{-5}	1.24 (1.11–1.37)	0.39 / 0.38	0.46	1.05 (0.93–1.18)	4.77×10^{-4}	1.15 (1.07–1.25)	0.42 / 0.37	0.020	1.22 (1.03–1.45)	3.28×10^{-5}	1.17 (1.09–1.25)
	rs6532194	91.00	C/T	0.31 / 0.40	6.93×10^{-11}	1.44 (1.29–1.61)	0.36 / 0.41	0.0014	1.22 (1.08–1.39)	1.77×10^{-12}	1.35 (1.24–1.46)	0.37 / 0.41	0.040	1.21 (1.01–1.44)	4.15×10^{-13}	1.32 (1.22–1.42)
12q12 (*LRRK2*)	rs1994090	38.71	G/T	0.11 / 0.08	4.45×10^{-5}	1.43 (1.20–1.70)	0.10 / 0.08	0.018	1.26 (1.04–1.54)	3.06×10^{-6}	1.36 (1.20–1.55)	0.12 / 0.08	0.0019	1.51 (1.16–1.97)	2.72×10^{-8}	1.39 (1.24–1.56)
	rs7304279	38.75	T/C	0.11 / 0.08	5.17×10^{-5}	1.42 (1.20–1.69)	0.10 / 0.08	0.026	1.25 (1.03–1.52)	5.10×10^{-6}	1.35 (1.19–1.54)	0.12 / 0.09	0.0022	1.50 (1.15–1.95)	5.06×10^{-8}	1.38 (1.23–1.55)
	rs4768212	38.76	C/T	0.11 / 0.08	3.98×10^{-5}	1.43 (1.20–1.70)	0.10 / 0.08	0.057	1.21 (0.99–1.48)	1.10×10^{-5}	1.34 (1.18–1.52)	0.12 / 0.08	0.0020	1.51 (1.16–1.97)	1.09×10^{-7}	1.37 (1.22–1.54)
	rs2708453	38.76	T/G	0.11 / 0.08	7.46×10^{-5}	1.41 (1.19–1.68)	0.10 / 0.08	0.063	1.21 (0.99–1.48)	2.04×10^{-5}	1.33 (1.17–1.52)	0.13 / 0.08	6.43×10^{-4}	1.57 (1.21–2.04)	9.67×10^{-8}	1.38 (1.22–1.55)
	rs2046932	38.87	T/C	0.11 / 0.08	3.24×10^{-5}	1.44 (1.21–1.71)	0.10 / 0.08	0.039	1.23 (1.01–1.51)	5.47×10^{-6}	1.35 (1.19–1.54)	0.13 / 0.09	0.0017	1.52 (1.17–1.97)	4.34×10^{-8}	1.39 (1.23–1.56)

Nucleotide positions refer to NCBI build 36. *P* values obtained in the case-control analysis using the Cochran-Armitage trend test (1 d.f.) are listed (P_{trend}). Combined *P* values (P_{cmh}) and combined ORs of the Cochran-Mantel-Haenzel test statistics are shown. MAF, minor allele frequency.

Next, we exchanged data with colleagues performing a GWAS of PD in individuals of European ancestry[17]. Their study found a strong association at the *MAPT* (microtubule-associated protein tau) region on 17q21. We genotyped our samples for six SNPs at the *MAPT* locus to evaluate these associations in the Asian population; however, the association with *MAPT* was not replicated in our study (**Supplementary Table 2** and **Supplementary Fig. 2**). Conversely, despite strong association signals in our scan of the samples from the Asian population, the association with *BST1* on 4p15 was not detected among individuals of European ancestry[17]. In contrast, the associations we found with *PARK16* and *LRRK2* were replicated among individuals of European ancestry[17]. These data provide evidence that *PARK16* and *LRRK2*, in addition to *SNCA*, are PD risk loci common to Asian- and European-descent populations and indicate that there is population genetic heterogeneity in the *MAPT* region and 4p15 (*BST1*) for PD susceptibility.

The *PARK16* region contains functionally interesting candidate genes for PD etiology. SLC41A1 is a magnesium (Mg^{2+}) transporter[18]. It is of interest that Mg^{2+} deficiency is thought to be an environmental risk factor for the amyotrophic lateral sclerosis

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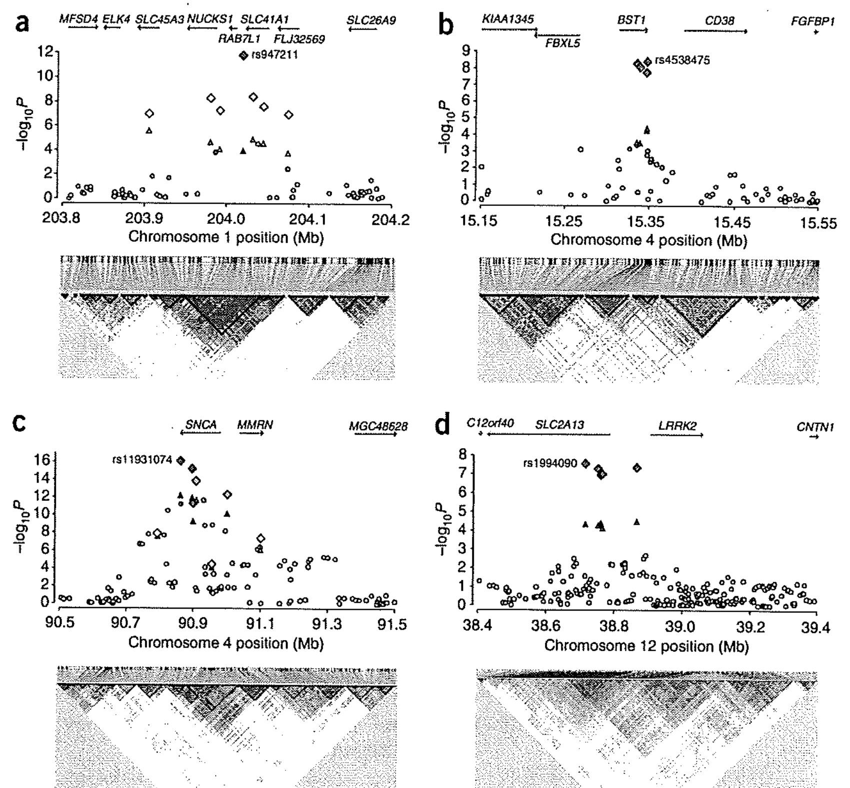

Figure 2 Regional association plots and linkage disequilibrium structure for the four PD risk loci. (**a**) 1q32 (*PARK16*). (**b**) 4p15 (*BST1*). (**c**) 4q22 (*SNCA*). (**d**) 12q12 (*LRRK2*). The $-\log_{10}$ *P* (Cochran-Armitage trend test) for association in the GWAS stage of SNPs across each region are shown as small triangles for SNPs that were selected for replication and as small circles for SNPs not selected. The $-\log_{10}$ combined *P* values (Cochran-Mantel-Haenszel test) for association in overall samples of SNPs selected for replication are shown as large diamonds. In each panel, the SNP with the most significant association in the combined analysis is listed. Proxies are indicated with colors determined from their pairwise r^2 from the JPT and CHB HapMap data (red, $r^2 > 0.8$; orange, $r^2 = 0.5$–0.8; yellow, $r^2 = 0.2$–0.5; white, $r^2 < 0.2$ or no information available). Positions are NCBI build 36 coordinates.

(ALS)-parkinsonism/dementia complex (MIM105500)[19]. Furthermore, RAB7L1 is a small GTP-binding protein that plays an important role in regulation of exo- and endocytotic pathways[20], and NUCKS1 is a nuclear protein containing several consensus phosphorylation sites for casein kinase II and cyclin-dependent kinases of unknown function[21]. We evaluated the relationships between the PD-associated SNPs and the transcript levels of genes in an available genome-wide gene expression database[22]. We found that rs947211 and ten tightly linked HapMap SNPs ($r^2 > 0.9$) were strongly associated with transcript levels of *NUCKS1* (rs947211, $P = 6.0 \times 10^{-15}$; rs823114, $P = 2.7 \times 10^{-34}$). These PD-susceptibility variants are the principal genetic determinants of variation in expression levels of *NUCKS1* (**Supplementary Fig. 3**). These data highlight *NUCKS1* as a promising candidate for association with PD that is worthy of additional follow-up.

The product of *BST1* on 4p15 catalyses formation of cyclic ADP-ribose (cADPR)[23]. cADPR mobilizes calcium (Ca^{2+}) from ryanodine-sensitive intracellular Ca^{2+} stores in the endoplasmic reticulum[24]. Disruption of Ca^{2+} homeostasis has recently been proposed as a possible cause of selective vulnerability of dopaminergic neurons in PD[25–27]. Associated SNPs in the *BST1* region may modify ADP-ribosylcyclase activity, thus leading to Ca^{2+} dyshomeostasis in dopaminergic neurons.

Two of the four susceptibility loci detected in our scan contained genes linked to autosomal dominant forms of parkinsonism. Gene overdosage is a potential mechanism for the influence of *SNCA* on PD because triplication and duplication of the *SNCA* locus has been seen in families with autosomal dominant parkinsonism[28]. SNPs with prominently low *P* values compared to other SNPs in the region were around the 3′ region of *SNCA*; these SNPs may function as enhancer or silencer elements, improve RNA stability or influence alternative splicing. The associated interval on 12q12 contains *SLC2A13* and the region upstream of *LRRK2*. Given prior evidence, *LRRK2* stands out as the most likely susceptibility gene for PD, although it remains possible that *SLC2A13*, which encodes a H^+-myoinositol cotransporter, may be the PD-related gene in this region[29]. Previous reports have investigated the association of SNPs in *LRRK2* with PD, but the results are a subject of dispute[30,31]. In the present study, it is noteworthy that the PD-associated intervals lie upstream of *LRRK2*. Increased kinase activity of mutant LRRK2 mediates neuronal toxicity[32,33]. PD-associated SNPs may play a role in transcriptional upregulation of *LRRK2*, leading to loss of dopaminergic neurons.

SNCA is a main component of Lewy bodies, a pathological hallmark of typical PD. The clinical features of individuals with *SNCA* duplication or *LRRK2* mutation similar to typical PD. 1.6% of sporadic PD cases among individuals of European ancestry have heterozygous *LRRK2* G2019S mutations[34]. These data support the close involvement of these genes with sporadic PD. Our data clearly show that the genes involved in autosomal dominant parkinsonism play a large part in the complex etiology of typical PD. Genes that cause autosomal dominant parkinsonism through their causative mutations also confer risk of typical PD through their common variants. Although further research is needed, this relationship between rare single-gene disorders and common multifactorial disorders may also be applicable for other disorders beyond PD.

Finally, *MAPT* mutations cause hereditary frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), a type of autosomal dominant parkinsonism[35], and the *MAPT* H1 haplotype has been reported to be associated with several tauopathies[36–38]. Although the *MAPT* region is divided into two major haplotypes, H1 and H2, in Europeans, the H2 haplotype is absent in East Asians. Therefore, we believe that the differences observed between our study and the findings in populations of European descent reflect population differences in the genetic heterogeneity of PD etiology, although differences in allele frequencies and LD structure and a possible difference in the effect size between the European and East Asian populations may influence the detection power of the two scans.

Further increases in sample sizes for SNP-GWAS efforts and searches for copy number variation and rare variants will reveal additional genetic risk factors and further enhance our understanding of PD.

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METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Note: Supplementary information is available on the Nature Genetics website.

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AUTHOR CONTRIBUTIONS

T. Toda conceived the study. W.S., I.M. and T. Toda designed the study. W.S., Y.N., C.I., M.K. and T.Y. performed genotyping. W.S. and T. Toda wrote the manuscript. W.S., T.K. and T. Tsunoda performed data analysis. W.S., I.M., Y.H., M.W., A.T., H.T., K.N., K.H., F.O., H.K., S.S., M.Y., N.H., M.M. and T. Toda managed Parkinson clinical information and DNA samples. M.K. and Y.N. managed DNA samples belonging to BioBank Japan. T. Toda obtained funding for the study.

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ONLINE METHODS

Study participants. For the GWAS stage, 1,078 cases and 2,628 controls were recruited from Japan through multiple institutions. Two case-control sample sets, which were independent of each other, were used in the two subsequent replication stages (replication 1 and 2): the first sample set (replication 1) consisted of 612 cases and 14,139 controls and the second set (replication 2) consisted of 321 cases and 1,614 controls, all recruited in Japan. For replication 2, we used case samples from two facilities that had not provided any case samples for GWAS and replication 1, in order to eliminate false positive association due to a slight possibility of differences in PD diagnosis among facilities. Genomic DNA was extracted using established methods and quantified using PicoGreen (Invitrogen). Details for all study panels are given in the **Supplementary Note**. Informed consent was obtained from each participant, and approval for the study was obtained from the Ethical Committees of relevant institutions (Osaka University Graduate School of Medicine, National Center Hospital of Neurology and Psychiatry, Juntendo University School of Medicine, Kagawa Prefectural Central Hospital, University of Tsukuba, Tohoku University Graduate School of Medicine and Tottori University Faculty of Medicine).

Genotyping. Genome-wide genotyping was performed using the Illumina Infinium HumanHap550 array. Cases and controls were genotyped at the Division of Clinical Genetics of Osaka University Graduate School of Medicine and at RIKEN Center for Genomic Medicine, respectively. For two subsequent replication studies (replication 1 and 2), 337 SNPs were genotyped for replication 1 and 2 samples using Illumina GoldenGate technology for the VeraCode platform (335 SNPs; cases in replication 1 and cases and controls in replication 2), TaqMan (2 SNPs; cases in replication 1 and cases and controls in replication 2) and the Illumina Infinium HumanHap610 array (337 SNPs; controls in replication 1). For the replication study of the *MAPT* locus, we selected six SNPs (rs417968, rs17690703, rs242557, rs7225002, rs183211 and rs7224296) that showed significant association, including four SNPs showing association with genome-wide significance, in samples of European ancestry. Samples with a call rate >90% in replications 1 and 2 (877 cases and 15,616 contols) were genotyped. All genotyping was done according to the manufacturer's instructions. To assess consistency across genotyping platforms, we genotyped these SNPs in 95 samples included in the GWAS. After SNP and sample quality control analyses, the mean concordance rates were 99.8% and 99.5% for GoldenGate technology and TaqMan when compared with the HumanHap550 array.

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Quality control. In the GWAS stage, case samples with a call rate <95% and control samples with a call rate <98% were excluded, according to each criterion of separate institutes which genotyped cases and controls. Remaining samples were reclustered using BeadStudio (Illumina), and genotypes of 1,012 cases and 2,573 controls were then obtained. We excluded samples with ambiguous sex (n = 18) by the check-sex function of PLINK 1.01 (ref. 39). We determined identity-by-state (IBS) similarity using PLINK 1.01, estimated the cryptic relatedness for each pair of samples, and excluded one individual from each pair of unexpected duplicates and first- or second-degree cryptic relatives (n = 55). To detect population outliers, we assessed 3,512 participants who remained after removal of samples with low call rates, ambiguous sex and familial relationships, together with 201 HapMap subjects without relationships (42 JPT, 45 CHB, 57 CEPH and 57 YRI)[40]. By computing IBS scores for 49,605 SNPs with $r^2 < 0.2$ and using multidimensional scaling, we identified three individuals who seemed to have non-Asian ancestry and excluded those from further analyses. Projection onto the two multidimensional scaling axes is shown in **Supplementary Figure 4**. We excluded SNPs with a call rate <95% in cases or controls (n = 7,927), a minor allele frequency <5% (n = 117,908) in all samples, or a P value of deviation from Hardy-Weinberg equilibrium (P_{HWE}) < 0.001 in the controls (n = 3,045). On visual inspection of the cluster plots of SNPs showing apparently strong association, we further removed 69 SNPs with poor clustering. The overall median genotype call rate for quality-controlled SNP was 99.9%. In replication 1, we excluded samples with a call rate <90%. We also removed SNPs with a call rate <95% in cases or controls, a $P_{HWE} < 0.001$ in the controls, or poor clustering of SNP plot on visual inspection. Genotypes of 279 SNPs for 559 cases and 14,026 controls were then obtained for further analyses. The overall mean genotype call rate was 99.7% for quality-controlled SNPs. In replication 2, we excluded samples with a call rate <90% and then obtained genotypes of 318 cases and 1,590 controls. All 24 SNPs showed a call rate >90% and P_{HWE} >0.001. The overall mean genotype call rate was 99.7% for quality-controlled SNPs. Associated SNPs in each interval had high call rates in each sample set (**Supplementary Table 3**). In the replication study of the *MAPT* locus, all six SNPs showed a call rate >95% and $P_{HWE} > 0.001$.

Statistical analyses. To calculate the power of our GWAS stage, we used the CaTS program[41]. The GWAS stage had 80% power to detect common alleles that confer a genotype relative risk of 1.3 and 1.43 at a significance of $P < 0.00053$ and $P < 5 \times 10^{-7}$, respectively.

To test for association of each SNP with PD, we used the Cochran-Armitage trend test with 1 d.f. We estimated the odd ratios (OR) and their 95% confidence intervals using logistic regression. Association analysis of the combined samples was conducted using the Cochran-Mantel-Haenezel method. Heterogeneity among sample sets was examined using the Breslow-Day test. There was no heterogeneity among sample sets (rs947211, P = 0.38; rs4538475, P = 0.98; rs11931074, P = 0.09; rs3857059, P = 0.08; and rs1994090, P = 0.48). SNPs with combined $P < 5 \times 10^{-7}$ were considered to have genome-wide significant evidence for association. SNPs with genome-wide significant evidence for association in the combined analysis of the GWAS and replication 1 and $P < 0.05$ in replication 2 were considered to have confirmed association with PD. To assess whether single or multiple independent association signals existed within each locus, we investigated relationships among multiple SNPs that showed association with PD in the same region ($P < 5.0 \times 10^{-7}$), using logistic regression analysis. We assessed the impact of additional SNPs by a likelihood-ratio test with 1 d.f. A significant residual association signal was defined as $P < 0.05$ in the conditional analysis. We used R 2.8.1 or PLINK 1.01 for general statistical analysis.

The quantile-quantile plot was used to evaluate overall significance of the genome-wide association results and the potential impact of population stratification. Quantile-quantile plots were depicted using the qq.chisq function of the snpMatrix package with a concentration band[15]. The inflation factor λ was calculated by dividing the mean of the lower 90% of the test statistics by the mean of the lower 90% of the expected values from a χ^2 distribution with 1 d.f. Given that the impact of population stratification was found to be minimal, all statistical results are presented without correction for λ. Haploview 4.1 was used to infer the LD structure of the genome in regions containing loci associated with disease risk[42]. The LD patterns were created from the Asian (CHB and JPT) HapMap data (minor allele frequency > 5%, genotyping rate > 95%, and $P_{HWE} > 0.001$), using the methods of Gabriel *et al.*[16].

URLs. PLINK, http://pngu.mgh.harvard.edu/~purcell/plink; R, http://www.r-project.org; SNPmatrix, http://www-gene.cimr.cam.ac.uk/clayton; HapMap, http://www.hapmap.org; Haploview, http://www.broad.mit.edu/mpg/haploview; CaTS, http://www.sph.umich.edu/csg/abecasis/CaTS/; database of expression QTL analysis, http://www.sph.umich.edu/csg/liang/imputation/.

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KEY WORD
●corticobasal degeneration ●clinical diagnostic criteria ●limb-kinetic apraxia ●akinetic-rigid sign ●asymmetry

1．高齢期のパーキンソン病の類縁疾患 5）皮質基底核変性症

中島　健二

SUMMARY

■皮質基底核変性症は，①中年以後の高齢者に発症，②緩徐な進行，③肢節運動失行，皮質性感覚障害，他人の手徴候，反射性ミオクローヌスなどの大脳皮質徴候，④無動・筋強剛やジストニアなどの錐体外路徴候，⑤著明な左右差，といった臨床的な特徴を示す疾患である．しかし，非典型的な臨床徴候を示す例も多い．いまだ根治的な治療法はなく，治療は対症療法にとどまる．

はじめに

皮質基底核変性症(corticobasal degeneration：CBD)は，Rebeiz ら(1968)により corticodentatonigral degeneration with neuronal achromasia として3例の臨床病理学的な報告がなされたことに始まる[1]．1989年になって，Gibb らは3例の臨床病理学的報告を行い，corticobasal degeneration と呼んだ[2]．その後，報告が相次ぐようになってきている．

発症年齢，罹病期間

発症年齢は40～80歳代で，平均60歳代とされ，中年以降に多い疾患である[3-6]．罹病期間は平均6年程度とされている[3-6]．

病理学的特徴

本症は，前頭・頭頂葉に強い大脳皮質萎縮とともに，黒質・淡蒼球を中心とした皮質下神経核の神経細胞が減少する．神経細胞やグリア細胞に異常リン酸化タウ蛋白が蓄積し，本症はタウオパチーに含まれる[3,7]．顕微鏡学的には，astrocytic plaque が CBD に特徴的である[3,7]．

症状

左右差のある大脳皮質徴候と錐体外路徴候を特徴とする[3,7]．

大脳皮質徴候として，肢節運動失行，観念運動失行，構成失行，他人の手徴候，把握反射，失語，半側空間無視などが認められる．これらの中でも多くみられ，特徴的な症状は肢節運動失行である[3]．

認知症は，皮質下性認知症の特徴を示すことが多いが，後に皮質性認知症が加わったり，また，初期から皮質性認知症が目立つ例もある[7]．進行すると，構音障害や嚥下障害も出現し，眼球運動障害や錐体路徴候もみられる[3,4]．

錐体外路徴候としてパーキンソニズムがみられる．なかでも，筋強剛が多く観察される[3,6]．振戦は6～8 Hz のことが多く，パーキンソン病と異なり，不規則で jerky な傾向を示す[3]．静止時振戦を示すことは少ない[7]．ミオクローヌスも振戦とともに観察される．左右差のあるジストニアもみられ，上肢優位の傾向を示す[3,4,6]．進行すると姿勢反射障害や易転倒性が生じる．

臨床検査

頭部の画像検査などでも初期には明らかでないことも多いが，進行すると左右差が観察され，

■なかしま　けんじ(鳥取大学医学部脳神経医科学講座脳神経内科分野)

表1a　難病情報センターによるパーキンソン病関連疾患(大脳皮質基底核変性症)認定基準[3)]

1　主要項目

(1) 中年期以降に発症し緩徐に進行する.

(2) 失行あるいはそのほかの大脳皮質徴候
　① 肢節運動失行があり，左右差が目立つ.
　② 肢節運動失行が明瞭でなくても，皮質性感覚障害，把握反応，「他人の手」徴候，反射性ミオクローヌスのいずれかがあり，左右差が目立つ.
　③ 観念運動失行が肢節運動失行よりも顕著な場合は，左右差は目立たないことが多い.
　④ そのほかの認知機能障害(まれに，認知症，異常行動，注意障害，失語などが早期から目立つ例がある).

(3) 錐体外路徴候
　① パーキンソニズム(無動，筋強剛，振戦)：障害は下肢よりも上肢に目立つことが多い.
　② ジストニー

(4) そのほかの神経症状
　① 偽性球麻痺(構音障害，嚥下障害)
　② 尿失禁

(5) 画像所見
CT，MRI，SPECTで，一側優位性の障害(大脳半球の萎縮または血流低下)は診断において，重要な支持的所見である．しかし，両側性あるいはびまん性に異常所見が出現する例もあるので，診断上必須所見とはしない.

(6) 除外すべき疾患
　① パーキンソン病
　② 進行性核上性麻痺
　③ 多系統萎縮症(特に線条体黒質変性症)
　④ 薬剤，脳炎，脳血管障害，外傷など
　⑤ 類似症状を呈するそのほかの疾患

(7) 判定
次の3条件を満たすものを皮質基底核変性症と診断する.
　① (1)を満たす.
　② (2)の1項目以上，および(3)の1項目以上がある.
　③ ほかの疾患を除外できる.
　注：なお，必須ではないが，画像所見によってほかの疾患を除外し，一側性優位性の障害を確認することが望ましい.

前頭葉や頭頂葉などの非対称性大脳萎縮が観察される[3,6,7)]．脳波検査においても，症候優位側との対側に優位な徐波化が観察される[3,6)]．しかし，神経症候の左右差が著しい場合であっても，画像検査などでは，びまん性の脳萎縮のみを示す場合もある[6,7)].

診断

CBDは，①中年以後の高齢者に発症し，②緩徐な進行を示し，③大脳皮質徴候として肢節運動失行，観念運動性失行，皮質性感覚障害，他人の手徴候，などが出現し，④錐体外路徴候として無動，筋強剛，ジストニアなどがみられ，

表 1b　難病情報センターによるパーキンソン病関連疾患（大脳皮質基底核変性症）認定基準[3)]

2　参考所見

大脳皮質基底核変性症（CBD）は，一側優位性が目立つ大脳半球萎縮および基底核変性を生じる神経変性疾患で，特有の大脳皮質症状と運動障害を呈する．

(1) 臨床的には，以下の所見がみられる．

① 中年期以降に発病し緩徐に進行する．

② 大脳皮質症状として，前頭・頭頂葉症状がみられる．最も頻度が高く特徴的な症状は肢節運動失行で，このほかに観念運動失行，皮質性感覚障害，把握反応，他人の手徴候，反射性ミオクローヌスなどが出現する．

③ 錐体外路症状として，パーキンソニズム（無動，筋強剛，振戦），ジストニーなどが出現する．症状は下肢よりも上肢の方が顕著なことが多い．

④ 上記神経症状には，病初期から顕著な一側優位性がみられることが多い．

⑤ 注意障害，認知症，異常行動のような精神症状は，通常，運動症状よりも遅れて出現する．

⑥ 歩行障害，偽性球麻痺（構音障害，嚥下障害）などが早期から出現するために，進行性核上性麻痺と鑑別困難な症例がある．

(2) 画像所見

CT，MRI，SPECT で，一側優位性の大脳半球萎縮または血流低下を認めた場合には，重要な支持的所見である．しかし，両側性あるいはびまん性の異常を認める例もあるので，診断上必須所見とはしない．

(3) 薬物などへの反応

L-ドパやほかの抗パーキンソン病薬への反応は不良である．抗うつ薬，ドロキシドパ，経頭蓋磁気刺激などが試みられているが，効果はあっても一時的である．

(4) 病理学的所見

前頭・頭頂葉に目立つ大脳皮質萎縮が認められ，黒質の色素は減少している．顕微鏡的には皮質，皮質下，脳幹の諸核（視床，淡蒼球，線条体，視床下核，黒質，中脳被蓋など）に神経細胞減少とグリオーシスが認められる．ピック細胞と同様の腫大した神経細胞が大脳皮質および皮質下諸核に認められる．黒質細胞には神経原線維変化がみられる．ガリアス染色やタウ染色ではグリア細胞にも広範な変性が認められ，特に astrocytic plaque は本症に特徴的である．

⑤著明な左右差を示す疾患である[3,4,6,7)]．しかし，左右差のない例，認知症が目立つ例，進行性核上性麻痺に臨床的に極めて類似した例など，非典型例も多く[3,8)]，注意を要する．

わが国では，CBD は特定疾患として指定されており，難病情報センター[3)]からその認定基準が示されている（**表 1a，b**）．また，本邦では森松らにより本症の患者数調査がなされており，その際に用いられた診断基準を**表 2** に示す[6)]．

Litvan ら (1997) は，古典的な診断基準について病理学的所見との比較検討を行い，発症後 68 カ月後の診察時で感度 48.3%，特異度 99.6 %と報告した[9)]．すなわち，診断基準に合致すれば CBD であるが，診断基準に合致しない例も約半数存在することを報告している[6,8)]．

治療

根治療法はなく，対症療法が基本である[3)]．無動・筋強剛などのパーキンソン症状に対しては，L-dopa などの抗パーキンソン病薬が投与される[3,6,7)]．しかし，著明な効果は期待し難く，効果は一時的なことが多い[3)]．ミオクローヌスに対しては，クロナゼパムなどのベンゾジアゼピン系薬剤が試みられる[3,6,7)]．

表 2　厚生科学研究事業“神経変性疾患に関する研究班(田代邦雄班長)”による大脳皮質基底核変性症(CBD)の臨床診断基準(暫定)[6]

“probable CBD”：以下の(A)(B)(C)のいずれかに該当するもの

(A)古典型：(1)～(3)のすべてを満たす
(1)緩徐進行性の神経変性疾患(画像的に他疾患を除外する)
(2)以下のaおよびbが一側優位性に出現する
a. 大脳皮質徴候として肢節運動失行
b. 錐体外路徴候として無動・筋強剛
(3)認知症は遅れて出現する
(注)CT，MRI，SPECTを含む画像検査で一側優位性の障害(大脳半球の萎縮または血流・代謝障害)は診断上，重要な支持的所見であるが，びまん性の萎縮または血流・代謝障害の例もあるので，診断上必須所見とはしない

(B)準古典型：ほぼ古典型に似るが，一部条件を満たさないもの．ただし(1)～(3)のすべてを満たす
(1)緩徐進行性の神経変性疾患(画像的に他疾患を除外する)
(2)以下のaまたは(および)bが一側優位性に出現する
a. 大脳皮質徴候として肢節運動失行が明瞭でなくても，皮質性感覚障害，把握反応，他人の手徴候，反射性ミオクローヌスのいずれかを示す．ただし，肢節運動失行よりも観念運動失行が顕著な場合は通常，両上肢に出現する
b. 錐体外路徴候として無動・筋強剛がなくてもジストニー，振戦を示す
(3)認知症は遅れて出現する

(C)非古典型：(1)(2)を満たす
(1)緩徐進行性の神経変性疾患(画像的に他疾患を除外する)
(2)早期には失語，注意障害・異常行動，認知症，尿失禁，偽性球麻痺などの皮質徴候または運動徴候が目立つが，やがて(A)(B)に示した大脳皮質徴候および錐体外路徴候の両者が一側優位性に出現する

“definite CBD”：病理学的にCBDに該当するもの，臨床徴候は問わない
“possible CBD”：資料不足により現状では設けない

リハビリ

廃用性萎縮予防，筋力維持訓練，関節可動域(ROM)の維持訓練，歩行訓練や移動練習，日常生活動作訓練，嚥下訓練などのリハビリテーションが行われる[3]．

生活上の注意

歩行障害，易転倒性に注意する．嚥下障害が著明になると低栄養になって全身衰弱を来し，また，嚥下性肺炎が生じやすくなる．このような場合には，経皮内視鏡胃瘻造設術(PEG)も考慮される[3,7]．

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