Table 1 Meta-analysis of α synuclein/non-amyloid β component precursor allele and genotype distributions in patients with sporadic Parkinson's disease (PD) and controls in Japan

	Allele* frequency						Genotype frequency	
Study	–2	–1	0	1	2	3	Allele 1 (+)	Allele 1 (–)
Present study								
PD (n=165)	0.009		0.518	0.255	0.200	0.018	0.358	0.642
Controls (n=155)	0.013		0.406	0.355	0.210	0.016	0.497	0.503
	χ^2=9.93, df=4, p=0.042, pc=0.21						χ^2=6.3, p=0.012, pc=0.072	
Izumi *et al*[3]								
PD (n=200)		0.003	0.408	0.248	0.330	0.013	0.390	0.610
Controls (n=250)	0.004	0.002	0.390	0.320	0.272	0.012	0.496	0.504
	χ^2=8.37, df=5, p=0.14						χ^2=5.05, p=0.025, pc=0.15	
Combined								
PD (n=365)	0.004	0.001	0.458	0.251	0.271	0.015	0.375	0.625
Controls (n=405)	0.007	0.001	0.396	0.333	0.248	0.014	0.496	0.504
	χ^2=13.9, df=5, p=0.017, pc=0.099						χ^2=11.4, p=0.00073, pc=0.0044 OR 0.61, 95%CI 0.45 to 0.81	

*Nomenclature of the alleles according to Xia *et al*.[2] Alleles 1, 2, and 3 correspond to alleles 3, 2, and 1, respectively, of Krüger *et al*.[4] pc (corrected p value) was obtained by multiply the p value by the number of alleles. CI, confidence interval; OR, odds ratio.

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Meta-analysis of α synuclein/ NACP polymorphism in Parkinson's disease in Japan

α Synuclein is a presynaptic protein highly and broadly expressed in the brain but its normal function is unknown.[1] The protein is also termed non-amyloid β component precursor (NACP) because of its localisation in amyloid plaques of Alzheimer's disease.[1] However, subsequent studies failed to confirm α synuclein as a component of the amyloid plaque.[1] α Synuclein/NACP is now known to be a major component of Lewy bodies in Parkinson's disease (PD).[1] Point mutations of the α synuclein gene found in three independent PD families suggest that α synuclein may participate in the aetiology of sporadic PD.[1] To address this possibility, several groups reported case-control studies using a dinucleotide repeat polymorphism in the promoter region of the gene.[2] The previous Japanese study by Izumi *et al*[3] found a tendency of a lower frequency of allele 1 in Japanese PD patients than in controls.[3] To examine the trend of association, we performed a similar analysis in 165 PD patients and 155 healthy controls in Japan.

The patients with sporadic PD (97 women and 68 men, mean (SD) age 64 (9.6) years, mean age at onset 56 (11) years) had been under treatment at the neurological clinic of Utano National Hospital. The control group was matched for age (mean 63.0 (8.6) years), sex ratio (97 women and 58 men), and birth place (Kyoto and Osaka prefectures) with the PD patients. The controls were selected from the annual health examination at a city clinic. All participants were Japanese. The institutional ethics committees approved the study protocol and informed consent was obtained from each participant. The dinucleotide repeat polymorphism was analysed as reported.[4] We identified five polymerase chain reaction products with different lengths and termed them according to Xia *et al*[2] as follows: 253 bp, allele –2; 257 bp, allele 0; 259 bp, allele 1, 261 bp, allele 2; and 263 bp, allele 3. Statistical analysis was performed by χ^2 test. The corrected p value (pc) was obtained by multiplying the p value by the number of alleles.

As table 1 shows, in our study allele 1 tended to be less frequent in patients with PD than in controls ($p = 0.042$ for allele distribution and $p = 0.012$ for genotype distribution), although the difference was insignificant after correction by the number of alleles ($pc = 0.21$ for allele distribution and $pc = 0.072$ for genotype distribution). This result was similar to the previous Japanese work.[3] To increase the power of the Japanese PD control analysis, we combined our data with those of Izumi *et al*. (table 1). The meta-analysis showed a significantly lower frequency of the allele 1 positive genotype in patients with PD than in controls even after correction ($pc = 0.0044$, odds ratio 0.61, 95%CI 0.45 to 0.81). These results suggest a negative association of allele 1 with PD in Japanese.

As reviewed by Farrer *et al*,[5] results of studies of white populations have varied—some suggested a significant difference between patients with PD and controls and others did not. We did not combine Japanese data with data from white populations because of the difference in allele distribution between them: the frequencies of alleles 0, 1, and 2 in Japanese are 40%, 33%, and 25%, respectively (table 1), while the frequencies of alleles 0, 1, and 2 range from 22–32%, 58–72%, and 3–9%, respectively, in white studies.[5]

The relation between dinucleotide repeat polymorphism and the functional aspects of α synuclein remains unknown. Lee *et al*[6] recently reported that overexpression of α synuclein in human neuroblastoma cell line retards cell death induced by serum withdrawal or hydrogen peroxide. This suggests that the dose of α synuclein may influence neuronal viability. Thus, in Japanese, allele 1 may be associated with high expression or low degradation of α synuclein.

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