RESULTS

Frequencies of neuropathological findings

The frequencies and mean ages at death of the neuropathologically diagnosed subgroups are summarized in Table 2. With the FBB samples, the main neuropathological disorders were cerebrovascular (cerebral infarcts and hemorrhages with or without dementia; 44%), AD (35%) and DLB (12%). Two types of diagnostic changes were noted in 38 cases, and three types were observed in one case (AD pathology, amyloid angiopathy and infarction). Twenty-four patients (9%) were diagnosed with disorders such as cerebral arteriosclerosis, NPH or subdural hemorrhage. Female cases of AD were more frequent than male cases, but no gender bias was noted in other disorders. Percentages of the main neuropathological diagnoses were similar to those of our previous report.[19]

Frequencies of apolipoprotein E alleles and genotypes

Since only 20 (8%) of the FBB samples showed signs of physiological aging alone, we used a population-based non-demented group of elderly subjects (PBC) as a reference control in comparing alleles and genotype frequencies of the APOE gene (Table 3). The genotype distribution of the reference control was similar to that in a previous report.[34] As the population advanced in age, the frequency of the APOE2 allele increased and that of the APOE4 decreased, although the difference between the seventh and the ninth decades was not significant. It was noted that the APOE2 allele frequency in FBB control brain was similar to that of the PBC group.

The FBB samples, as a whole, had a higher frequency of the APOE4 allele compared to the PBC samples ($P < 0.01$) (Table 3). The FBB group was significantly different from the PBC group in both APOE genotype and allele frequencies ($P < 0.01$), and this difference was evident in individuals over 70 years ($P = 0.002$ for the group aged 70–79 years; $P < 0.001$ for that over 80 years) (Table 3). And, the frequencies of APOE2 alleles were not enough, but the APOE2 frequency of FBB group decreased in older age against in that of PBC group. On the other hand, the frequencies of APOE4 in the FBB group were decreased in the same manner as in the PBC group.

Analysis of apolipoprotein E genotypes in the main neurological groups

Distributions of APOE genotypes within the main pathological disorders are summarized in Table 4. The frequencies of APOE genotypes were significantly different in the AD ($P < 0.0001$) and DLB groups ($P < 0.005$), compared to the PBC group. In addition, frequencies in the AD group were significantly different when compared with the physiological aging patients ($P < 0.02$).

Cerebrovascular disorders without CAA showed no association with the APOE genotype. Of six patients with Binswanger's disease, a subtype of vascular dementia, five had the 3/3 subtype and one had 2/4.

Apolipoprotein E analysis of amyloid-β and tangle diseases

Apolipoprotein E genotypes of AD and LNTD are summarized in Table 5. EOAD and LOAD was linked tightly

Table 2 Summary of the main neuropathological subgroup diagnoses*

	Men (%)	Women (%)	Total (%)	Mean ± SD age at death (years)
FBB samples				
AD	36 (30)	54 (41)	90 (35)	83.5 ± 7.62
DLB	14 (11)	17 (13)	31 (12)	80.0 ± 9.46
VD/CI	56 (46)	57 (43)	113 (44)	82.2 ± 7.93
LNTD	2 (2)	2 (2)	4 (2)	95.0 ± 5.72
Control brain	10 (8)	10 (8)	20 (8)	86.8 ± 6.50
Total	122	133	255	82.3 ± 8.49
PBC samples	174	213	387	75.3 ± 5.0†

*Thirty-eight patients had two diagnoses and one had three. Therefore, the total subgroup percentages were over 100%. Each subgroup percentage was determined from the ratio of the number of patients with a specific diagnosis to the total patient number. Twenty-four patients were diagnosed with other neuropathological diseases (not shown). †Age at time blood was drawn. AD, Alzheimer's disease; CI, cerebral infarct; DLB, dementia with Lewy bodies; FBB, Fukushimura Brain Bank; LNTD, limbic neurofibrillary tangle dementia; PBC, population-based control; VD, vascular dementia.

Table 3 Distribution of apolipoprotein E (APOE) genotypes within each Fukushimura Brain Bank (FBB) (upper) and population-based control (PBC) (lower) group*

	Age (years)			
	≤69 (%)	70–79 (%)	80≤ (%)	Total (%)
APOE genotype				
2/2	0	0	0	0
	0	1 (0.3)	0	1 (0.2)
2/3	1 (4.8)	4 (6.2)	4 (2.4)	9 (3.5)
	1 (4.8)	23 (7.6)	8 (12.5)	32 (8.2)
2/4	1 (4.8)	2 (3.1)	1 (0.6)	4 (1.6)
	0	3 (1.0)	0	3 (0.8)
3/3	13 (61.9)	40 (61.5)	117 (69.2)	170 (66.7)
	15 (71.4)	230 (7.2)	48 (75.0)	293 (75.7)
3/4	4 (19.0)	16 (24.6)	42 (24.9)	62 (24.3)
	4 (19.0)	43 (14.3)	8 (12.5)	55 (14.2)
4/4	2 (10.5)	3 (4.6)	5 (3.0)	10 (3.9)
	1 (4.8)	2 (0.7)	0	3 (0.8)
Total	21	65	169	255
	21	302	64	387
APOE allele				
E2	2 (4.8)	6 (4.6)	5 (1.5)	13 (2.5)
	1 (2.4)	28 (4.6)	8 (6.3)	37 (4.8)
E3	31 (73.8)	100 (76.9)	280 (82.8)	411 (80.6)
	35 (83.3)	526 (87.1)	112 (87.4)	673 (87.0)
E4	9 (21.4)	24 (18.5)	53 (15.7)	86 (16.9)
	6 (14.3)	50 (8.3)	8 (6.3)	64 (8.2)

*Percentages are the frequencies of subtypes in each age group.

Table 4 Distribution of apolipoprotein E (APOE) subtypes according to the main neuropathological Fukushimura Brain Bank (FBB) findings compared with those of the population-based control (PBC) group*

	AD	DLB	VD/CI	Control brain	FBB total	PBC
APOE genotype						
2/2	0	0	0	0	0	1 (0.3)
2/3	1 (1)	0	6 (5)	2 (10)	9 (3.5)	32 (8.2)
2/4	1 (1)	0	2 (2)	0	4 (1.6)	3 (0.8)
3/3	44 (49)	20 (65)	85 (75)	14 (70)	170 (66.7)	293 (75.7)
3/4	37 (41)	10 (32)	19 (17)	4 (20)	62 (24.3)	55 (14.2)
4/4	7 (8)	1 (3)	1 (1)	0	10 (3.9)	3 (0.8)
Total	90 (100)	31 (100)	113 (100)	20 (100)	255 (100)	387 (100)
APOE allele						
E2	2 (1)	0	8 (4)	2 (5)	13 (2.5)	37 (4.8)
E3	126 (70)*	50 (81)**	195 (86)	34 (85)	411 (80.6)	673 (87.0)
E4	52 (29)*	12 (19)**	23 (10)	4 (10)	86 (16.9)	64 (8.2)

*AD alleles 3 and 4 compared to aging patients, $P < 0.02$ and PBC, $P < 0.001$. **Dementia with Lewy bodies alleles 3 and 4 compared to PBC, $P < 0.005$. †Percentages represent the frequency of each finding. AD, Alzheimer's disease; CI, cerebral infarct; DLB, dementia with Lewy bodies; VD, vascular dementia.

to the APOE4 allele in comparison with the PBC group ($P < 0.0001$). In addition, compared with our physiological aging samples, eight cases with diffuse and widespread CAA affecting the entire cerebral area showed the highest association (data not shown).

On the other hand, though the number was only four, LNTD, a kind of tauopathy, had no association with APOE4 allele (Table 5).

Apolipoprotein E analysis of dementia with Lewy bodies subtypes

The DLB group did not show as strong an association with APOE genotype as the AD group. A significant difference in the APOE allele frequencies in the DLB group was noted, however, when this group was compared with the PBC group ($P = 0.004$) (Table 4). According to the standardized criteria,[31] 31 DLB

Table 5 Distribution of apolipoprotein E (APOE) subtypes of patients with Aβ and/or NFT deposition diseases compared with FBB normals and PBC†

	LOAD (%)	EOAD (%)	LNTD (%)	PBC (%)
APOE genotype				
2/2	0	0	0	1 (0.3)
2/3	1 (1)	0	0	32 (8.2)
2/4	1 (1)	0	0	3 (0.8)
3/3	38 (50)	6 (43)	3 (75)	293 (75.7)
3/4	31 (82)	6 (43)	1 (25)	55 (14.2)
4/4	5 (6)	2 (14)	0	3 (0.8)
Total	76 (100)	14 (100)	4 (100)	387 (100)
APOE allele				
E2	2 (1)	0	0	37 (4.8)
E3	108 (71)	18 (64)	7 (88)	673 (87.0)
E4	42 (28)*	10 (36)**	1 (12)	64 (8.2)

*All APOE alleles in LOAD patients compared to aging patients, $P < 0.05$ and to Suita controls, $P < 0.001$. **All APOE alleles in EOAD patients compared to aging patients, $P < 0.05$ and to Suita controls, $P < 0.001$. †Percentages were calculated from the frequency of each subtype to the total number of samples of each disease. EOAD, early-onset of Alzheimer's disease; LNTD, limbic neurofibrillary tangle dementia; LOAD, late-onset of Alzheimer's disease; PBC, population-based control.

cases were classified into nine cases with the brain stem, 11 with the limbic and 11 with the neocortical types (Table 1). All DLB cases except for two with the brain stem type had the common form of DLB with AD pathology. The frequency of the APOE4 allele in the neocortical type of DLB was significantly higher than that in the PBC group ($P = 0.039$), and the same tendency was seen in both the brain stem (17%) and limbic (18%) types.

DISCUSSION

Since 1993, it has been known that having the APOE4 allele places an individual at increased risk for LOAD.[2,3] However, its frequency varies according to ethnic background,[35] such as among Caucasians and Japanese.[34] Evans *et al.*[36] reported that the frequency of the APOE4 allele is higher in black populations than among Caucasians, but this higher frequency is not associated with an increased risk of AD. Our results showed that the frequencies of the APOE alleles in the PBC group were similar to those of a Japanese population investigated in a previous study.[34] It seems reasonable to consider the samples used in the present study as representative of the Japanese elderly with respect to the frequencies of APOE genotypes.

It has been noted that the APOE4 allele, which promotes premature atherosclerosis, is significantly less frequent in centenarians than in controls.[37] The APOE2 allele, in contrast, has been positively associated with advancing age.[38] In our reference controls (PBC group), the ratio of the APOE2 allele increased with age and that of the APOE4 allele decreased (Table 3). However, an interesting and deceptively conflicting finding with regard to the APOE4 allele was that the ratio of the APOE4 allele at younger ages was higher than that of older people, even in the PBC group (Table 3). This was because the group of younger subjects might have included normal persons who might eventually develop AD at some future time. The APOE2 allele was seldom found in our FBB samples, and we were unable to detect any particular tendency. Although the number of normal aging FBB samples was limited, the APOE2-positive cases included only patients over 80 years of age. This supports the findings of a previous report.[38] The normal FBB samples showed the same tendency as the PBC with respect to the APOE4 allele. Because 35.2% of FBB samples revealed some form of AD pathology, the frequency of the APOE4 allele in the total FBB group was higher (16.9%) than in the normal group (Table 4). But even in our FBB group of which 35.2% showed AD pathology, the presence of the APOE4 allele might not only represent an AD risk factor, but might also influence longevity, as in the PBC and normal FBB groups (Table 3).

On the other hand, one cannot make comparisons related to the age at death of FBB patients and the age at blood drawing of PBC. The mean ± SD age at death of the patient group (82.3 years ±8.5) was obviously higher than that of the PBC group at blood drawing (75.3 years ±5.0). However, the allele and genotype frequencies of the PBC group could be considered as reference data on Japanese elderly since this group was population-based.

Therefore, allele and genotype frequencies of the patient group or subgroups differing by diagnosis could be compared to those of this non-demented control group.

With respect to dementia, the frequencies of APOE alleles in AD and DLB were significantly different from those of the PBC group (Table 4), and analysis of allele subtype frequencies in both the diseases showed interesting results.

Compared with our 20 control brains and PBC, percentages of the various subtypes in EOAD and

LOAD patients were very different. These differences have already been discussed in previous reports from 1993.[2,3] Among the patients who had CAA, the APOE4 allele tended to have a stronger correlation with CAA than with AD (data not shown) but this will be analyzed in detail at a future time.

The phosphorylated form of tau was more prominent in cases of familial and sporadic AD which were positive for the APOE4 allele and its amounts increased with the gene dose.[39] In an *in vitro* study, the authors reported that isoform-specific interactions between APOE and tau might be important in the regulation of intraneuronal tau metabolism in AD and could alter the rate of formation of paired helical filaments (PHF) and NFT.[40] In our study, we did not analyze correlations between the frequencies of APOE alleles and the quantity of PHF/NFT in AD or LNTD, but we did note that the APOE genotype was not a risk factor for LNTD (Table 5), which is a NFT-only dementia without significant numbers of either diffuse amyloid or neuritic plaques. This would be in agreement with Bancher *et al.* who stated that, although the APOE genotype is not a risk factor for LNTD, LNTD patients would have APOE4 alleles,[11] would be AD. We have only a few autopsied cases with common tauopathies such as PiD, PSP and corticobasal degeneration (CBD). Therefore, we could not statistically examine any correlation between tau phosphorylation and the APOE4 allele. But, according to our results on LNTD and PiD, APOE4 might not influence tau formation.

Dementia with Lewy bodies is the second most frequent neurodegenerative dementia, following AD. Among our FBB samples, 12% had changes characteristic of DLB. As a whole, our DLB group had a high frequency of APOE4 (Table 4) and compared with the PBC, the difference was statistically significant ($P < 0.01$). Using the previously established guidelines,[31] DLB samples were classified into a brain stem type (nine cases), a limbic type (11 cases) and a neocortical type (11 cases) (Table 1). Only the neocortical type showed a statistically significant relationship ($P < 0.05$) with the APOE genotype, but it should be recognized that the single 4/4 neocortical DLB sample would have a strong influence on the result. This case also had CAA changes. In a sample comparison, however, the frequencies of allele 4 in our normal aging group was 10% and in the PBC group, 8.2%, compared to 17% in the brain stem, 18% in the limbic and 23% in the neocortical type of DLB. Each group of DLB had a higher APOE4 allele frequency than the normal groups. In our previous examination of Yokohama City University samples,[8] 39% of those with neocortical DLB had the APOE4 allele. Another Japanese group reported that the frequencies of the APOE4 allele in AD and DLB were similar.[9] In addition, Wakabayashi *et al.* analyzed Lewy body pathology with respect to APOE alleles and concluded that when PD occurs in APOE4-positive individuals, these patients concomitantly develop cortical Lewy body pathology which in a proportion of cases results in limbic (transitional) or neocortical-type Lewy body disease.[10] We also found that the frequency of the APOE4 allele increased going from the brain stem type to the neocortical type. However, all of our limbic and neocortical DLB cases were of the common form. Among our six cases having the brain stem type with a 3/3 genotype, two had the pure form of DLB and four had the common form (Table 1). All three with the APOE-3/4 genotype had the common form. This tendency reflected AD pathology. In the report by Wakabayashi *et al.*[10] samples positive for the APOE4 allele had an increased Lewy body density, and the plaque density was also high. Lewy body disease without concomitant AD pathology (pure form) ($n = 12$) has also been analyzed and the APOE4 allele frequency was found not to be significantly increased.[41] In *in vitro* studies investigating α synuclein as a Lewy body constituent, its interaction with lipid vesicles was highly dependent on their phospholipid composition.[42,43] However, the participation of apolipoprotein in Lewy body formation is not yet clear. Further biochemical analyzes and epidemiological investigations of a sufficient number of pure form DLB samples are needed.

In conclusion, while it is known that the frequencies of APOE alleles in Japan are different from those of Western countries, we found that AD and DLB have a positive correlation with the APOE4 allele. From previous reports, APOE interacts with Aβ and plays a role in SP formation and CAA development. In the present study, APOE4 was confirmed to be a risk factor for AD. As for DLB, we mainly analyzed the common form with AD pathology. Therefore, further data are needed in order to determine whether the APOE4 might also be a risk factor for Lewy body development.

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