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SHORT COMMUNICATION

Systematic review and meta-analysis of Japanese familial Alzheimer's disease and FTDP-17

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Mutations in *APP*, *PSEN1* and *PSEN2* as the genetic causes of familial Alzheimer's disease (FAD) have been found in various ethnic populations. A substantial number of FAD pedigrees with mutations have been reported in the Japanese population; however, it remains unclear whether the genetic and clinical features of FAD in the Japanese population differ from those in other populations. To address this issue, we conducted a systematic review and meta-analysis of Japanese FAD and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) by literature search. Using this analysis, we identified 39 different *PSEN1* mutations in 140 patients, 5 *APP* mutations in 35 patients and 16 *MAPT* mutations in 84 patients. There was no *PSEN2* mutation among Japanese patients. The age at onset in Japanese FAD patients with *PSEN1* mutations was significantly younger than that in patients with *APP* mutations. Kaplan–Meier analysis revealed that patients with *MAPT* mutations showed a shorter survival than patients with *PSEN1* or *APP* mutations. Patients with mutations in different genes exhibit characteristic clinical presentations, suggesting that mutations in causative genes may modify the clinical presentations. By collecting and cataloging genetic and clinical information on Japanese FAD and FTDP-17, we developed an original database designated as Japanese Familial Alzheimer's Disease Database, which is accessible at http://alzdb.bri.niigata-u.ac.jp/.

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Mutations in *APP*, *PSEN1* and *PSEN2* as the genetic causes of familial Alzheimer's disease (FAD) have been found in various ethnic populations.[1,2] In addition, patients with mutations in *MAPT* associated with frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) have been shown to exhibit Alzheimer's disease (AD)-like phenotypes.[3,4] Although a substantial number of FAD pedigrees have been reported in Japan, it is not yet clear whether the genetic and clinical features of FAD in the Japanese population differ from those in other ethnic populations. To characterize the genetic and clinical features of Japanese FAD and FTDP-17, we here performed a systematic review and meta-analysis, and developed an original database of Japanese FAD and FTDP-17.

To comprehensively review the previously reported Japanese FAD and FTDP-17 cases, we performed a systematic search for publications in PubMed and Ichushi, a bibliographic database of medical literature in Japanese. The terms 'familial Alzheimer', 'familial AD', 'FTDP-17', 'presenilin', '*PSEN1*', '*PSEN2*', '*APP*' and '*MAPT*' were used to search in PubMed, and the equivalent terms in Japanese were used to search in Ichushi. From the literature searches we found 60 English and 29 Japanese articles and/or abstracts that reported on Japanese FAD and FTDP-17 pedigrees bearing the causative mutations (Supplementary Table 1). Using the information obtained by the systematic literature review, we developed an original database for Japanese FAD and FTDP-17 designated as Japanese Familial Alzheimer's Disease database (JFADdb). In the database, each of the mutations in *APP*, *PSEN1/2*, *MAPT* and *GRN* was described in accordance with the reference sequences.[5] Information on age at onset, clinical manifestations, age at death and *APOE* genotype were included in the database (Supplementary Figure 1).

We identified 39 different *PSEN1* mutations in 140 patients, 5 *APP* mutations in 35 patients and 16 *MAPT* mutations in 84 patients (Table 1). Among them, 10 *PSEN1* mutations, 5 *APP* mutations and 11 *MAPT* mutations were not included in the well-known Alzheimer Disease and Frontotemporal Dementia Mutation database (http://www.molgen.ua.ac.be/ADMutations/).[6] No *PSEN2* mutation has been found in Japanese FAD. The frequency of mutated genes in FAD patients in the Japanese population was not significantly different from those in other populations (χ^2, $P=0.99$).[6] Most FAD pedigrees show autosomal dominant inheritance; however, an *APP* ΔE693 mutation was responsible for a recessively inherited FAD.[7] Sporadic occurrences of mutations were observed: five patients with *PSEN1* mutations, one patient with *APP* mutation and two patients with *MAPT* mutations.

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Table 1 Summary of genetic features of Japanese FAD and FTDP-17

Disease	Genes	Number of mutations	Number of pedigrees	Number of patients
FAD	*PSEN1*	39	40	140
	PSEN2	0	0	0
	APP	5[a]	13	35
FTDP-17	*MAPT*	16	29	84
	GRN	2	2	2

Abbreviations: FAD, familial Alzheimer's disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17.
[a]*APP* duplication was included.

In our analysis, the majority of mutations (73%) was observed in a single small pedigree. Considering that novel mutations in FAD tend to be reported rapidly, note that there may be publication bias in the frequency of mutations in the database. Although rare, there were two *GRN* mutations in patients with primary progressive aphasia and frontotemporal lobar degeneration (FTLD).[8] Because the number of *GRN* mutations was too small, the patients with *GRN* mutations were excluded from further meta-analysis.

The ages at onset were 44 ± 8 years (mean $\pm$ s.d.) in patients with *PSEN1* mutations ($n = 87$), 54 ± 9 years in *APP* mutations ($n = 23$) and 45 ± 10 years in *MAPT* mutations ($n = 51$). These ages at onset of FAD in our analysis are consistent with those reported in other ethnic populations.[6,9] The age at onset in patients with *APP* mutations was significantly older than those in patients with *PSEN1* or *MAPT* mutations (Figure 1a). The clinical phenotypes of patients with *MAPT* mutations were classified into three subgroups: FTLD,[10] AD-like[3,4] and progressive supranuclear palsy (PSP) phenotypes.[8] The age at onset in patients with the FTLD or PSP phenotype was significantly younger than that with the AD-like phenotype (Supplementary Figure 2). *APOE* genotypes did not significantly modify the age at onset in patients with causative mutations (Supplementary Figure 3). There was no significant difference in age at death among the patients with mutations in the three genes (Figure 1b). The disease duration from age at onset to death in patients with *MAPT* mutations was significantly shorter than that with *PSEN1* mutations (Figure 1c). The survival of patients after the onset was analyzed by Kaplan–Meier estimation, which revealed that patients with *MAPT* mutations showed a shorter survival than patients with *PSEN1* or *APP* mutations (Supplementary Figure 4).

The clinical diagnosis of AD before the genetic testing was performed in 96% of patients with *PSEN1* mutations and 97% of patients with *APP* mutations (Supplementary Table 2). Notably, only 57% of patients with *MAPT* mutations were clinically diagnosed as having FTLD; 19% and 12% of patients with *MAPT* mutations were clinically diagnosed as having AD and PSP, respectively (Supplementary Table 2). This finding suggests that mutational screening of clinically diagnosed FAD patients should not only include *APP* and *PSEN1/2* mutations but also include *MAPT* mutations.

We next analyzed the frequency of each of the clinical manifestations including psychiatric symptoms, mood disorders, spastic paraparesis, parkinsonism and epilepsy/seizure (Figure 2). As expected, the frequencies of psychiatric symptoms and parkinsonism were significantly higher in patients with *MAPT* mutations. Spastic paraparesis, which is a characteristic symptom of 'variant AD with cotton-wool plaque pathology'[11,12] was observed in 15% of patients with *PSEN1* mutations, whereas none of the patients with *APP* mutations exhibited spastic paraplegia. Epilepsy/seizure was described in 8% of patients with *PSEN1* and 6% of patients with *APP* mutations,

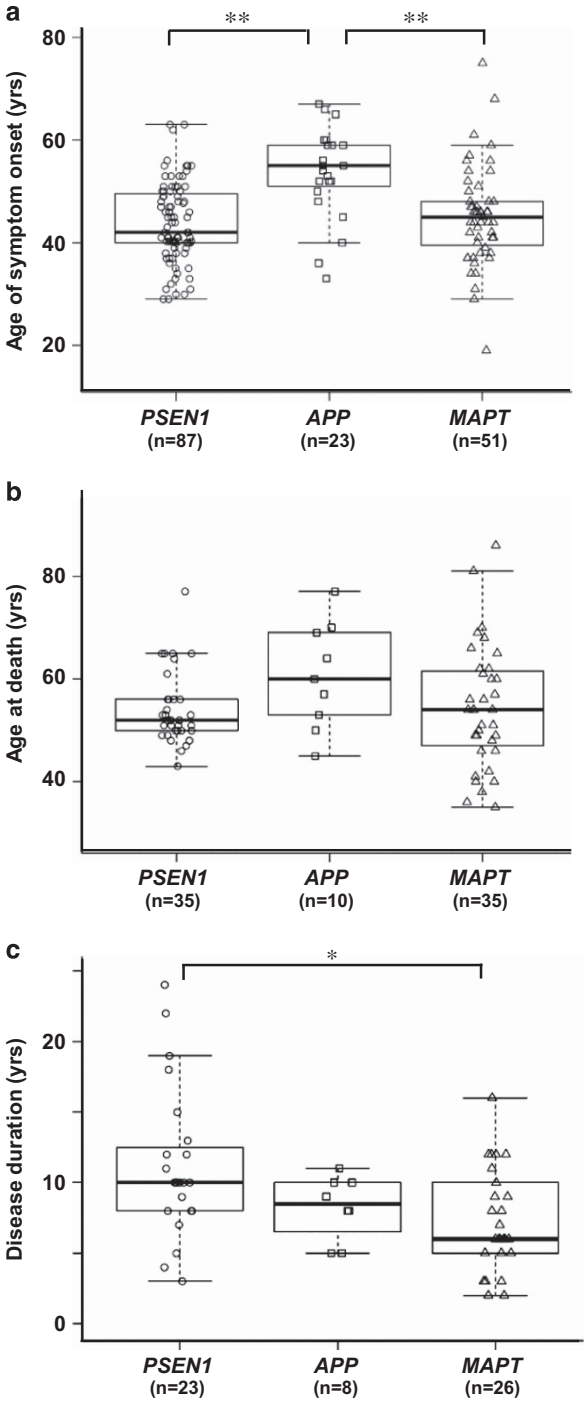

Figure 1 Age at onset and death, and disease duration in Japanese FAD and FTDP-17 patients. (**a**) Age at onset for patients grouped on the basis of *PSEN1*, *APP* and *MAPT* mutations. The horizontal line in the box indicates the median, the lower and upper boundaries of the box represent the lower and upper quartile boundaries, respectively, and whiskers are 1.5 times the interquartile range. Patients with *PSEN1* and *MAPT* mutation showed significantly younger age at onset than patients with *APP* mutations (**$P<0.01$, ANOVA with *post hoc* Tukey's test). (**b**) Age at death of three groups with gene mutations. There was no significant difference in age at death among the groups. (**c**) Disease duration was defined as the period from age at onset to death. The disease courses of patients with *MAPT* mutations (7 ± 4 years, mean $\pm$ s.d.) were significantly shorter than those with *PSEN1* mutations (11 ± 5) (*$P<0.05$, ANOVA with *post hoc* Tukey's test). ANOVA, analysis of variance; FAD, familial Alzheimer's disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17.

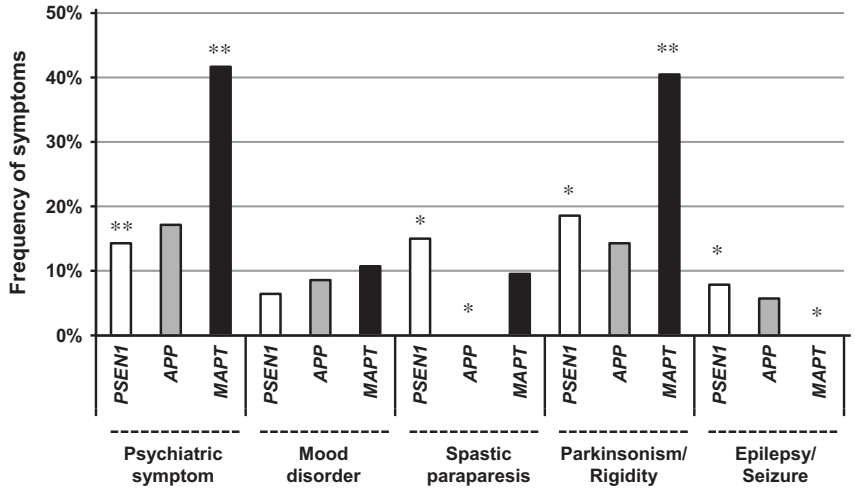

Figure 2 Frequency of each clinical manifestation in patients with Japanese FAD and FTDP-17. We investigated the presence or absence of psychiatric symptoms, mood disorders, spastic paraplegia, parkinsonism and epilepsy/seizure by careful reading of the original papers. We determined the frequency of each of the clinical manifestations by counting the number of patients for whom the presence of the manifestation was described in literature. In case there was no description of the manifestation, the patient was not counted as manifesting the manifestation. The observed frequencies of causative gene mutation were significantly different from the expected frequencies determined by residual analyses for χ^2 statistical analysis ($^*P<0.05$, $^{**}P<0.01$). FAD, familial Alzheimer's disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17.

whereas none of the patients with *MAPT* mutations exhibited epilepsy/seizure. Previous studies showed that the frequency of seizure was relatively high in patients with early onset of AD,[13,14] and low in patients with *MAPT* mutations.[15] These findings suggest that epilepsy/seizure is closely associated with amyloid pathology, and that tauopathy alone may not be sufficient to cause epilepsy. Taken together, mutations in causative genes may modify the clinical presentations in patients with familial dementia.

In summary, we have comprehensively collected, cataloged and systematically meta-analyzed the data from currently available data on Japanese FAD and FTDP-17. We made all the results publicly available on the online database 'JFADdb'. The database may provide information useful for estimating the age at onset and the natural course of disease in future preventive or therapeutic trials of Japanese FAD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Journal of Human Genetics website (http://www.nature.com/jhg)