($n=566$; glutamic acid homozygotes: 0.86, heterozygotes: 0.14, lysine homozygotes: 0; E allele: 0.93, K allele: 0.07) (Kitamoto *et al.*, 1994; Ohkubo *et al.*, 2003) ($P<0.001$). The frequencies of the K allele (0.013) and heterozygous genotype (0.016) at codon 219 in genetic prion diseases were also significantly lower than in the general Japanese population (both $P<0.001$), while in dura mater graft-associated Creutzfeldt–Jakob disease, the frequencies of the K allele (0.02) and heterozygosity (0.04) were not significantly different from the general population.

Sporadic Creutzfeldt–Jakob disease

The very high frequency of PSWCs in sporadic Creutzfeldt–Jakob disease (97%), compared with the data of western countries (Collins *et al.*, 2006), is related to the application of the diagnostic criteria by Masters *et al.* (1979) and the low autopsy rate in Japan. Regarding the subtypes according to Parchi's classification (Parchi *et al.*, 1999), the MM1 type was the most common (25/44, 56.8%), characterized by typical Creutzfeldt–Jakob disease features: rapid clinical course, positive PSWCs and CSF 14-3-3 protein and typical MRI findings (Table 4). Among atypical cases other than the MM1 type, the proportion of the MM2 type was relatively high (10/44, 22.7%) compared with Europe, the USA (12/300, 4.0%) (Parchi *et al.*, 1999) and Germany (12/243, 4.9%) (Heinemann *et al.*, 2007). MM2 type cases included cortical (50%), thalamic (40%) and combined (cortical and thalamic) forms (10%). Our results were influenced by the bias that atypical cases might have been more selectively autopsied to confirm the diagnosis; however, the relatively high proportion of the MM2 type in Japanese patients with sporadic Creutzfeldt–Jakob disease reflected the high proportion of the methionine homozygote genotype in the Japanese population.

Clinical characteristics of each sporadic Creutzfeldt–Jakob disease subtype (MM1, MM2-cortical, MM2-thalamic, MV2 and VV2) were almost the same as in previous reports (Parchi *et al.*, 1999; Collins *et al.*, 2006), except for the higher frequency of extrapyramidal signs (72%) in the MM1 type [7% in a previous report (Parchi *et al.*, 1999)] and the lower frequency of pyramidal signs (0%) in MM2-cortical subtype [83% in previous reports (Parchi *et al.*, 1999; Krasnianski *et al.*, 2006)]. The deficiency of pyramidal or other neurological signs in the MM2-cortical subtype would lead to difficulties in the clinical diagnosis of MM2-type sporadic Creutzfeldt–Jakob disease on the basis of the current sporadic Creutzfeldt–Jakob disease criteria, although cortical hyperintensities on MRI suggest the diagnosis (Hamaguchi *et al.*, 2005). In this study, the age at onset of the MM2-thalamic subtype was younger with a longer duration than the MM1 type, and neither PSWCs on EEG nor hyperintensities on MRI were identified in the MM2-thalamic subtype.

Dura mater graft-associated Creutzfeldt–Jakob disease

Worldwide, the majority of patients with dura mater graft–associated Creutzfeldt–Jakob disease have been reported from Japan (Belay *et al.*, 2005; Brown *et al.*, 2006; Noguchi-Shinohara *et al.*, 2007; Nakamura *et al.*, 2008; Yamada *et al.*, 2009). In Japan, all dura mater graft-associated Creutzfeldt–Jakob disease cases in which the origin of the dural grafts could be identified were recipients of Lyodura®, as previously reported (Yamada *et al.*, 2009). In Japan, the import of Lyodura® was approved in 1973 and then prohibited in 1997. The mean incubation period of dura mater graft-associated Creutzfeldt–Jakob disease (11.8 years) was shorter than human growth hormone-associated Creutzfeldt–Jakob disease (20.5 years) (Belay *et al.*, 2005). The longest incubation period of dura mater graft-associated Creutzfeldt–Jakob disease was 30 years, and the year when the patient received implantation (1975) was also the earliest among previous reports (Nakamura *et al.*, 2008; Yamada *et al.*, 2009). Regarding the medical conditions in which patients received the implantation of cadaveric dura mater grafts, non-life-threatening conditions such as hemifacial spasm and trigeminal pain were relatively common, because recipients with lethal conditions might have died before dura mater graft-associated Creutzfeldt–Jakob disease developed. Clinical duration (from onset to akinetic mutism or death) of dura mater graft-associated Creutzfeldt–Jakob disease was longer than that of sporadic Creutzfeldt–Jakob disease, and positive rates of PSWCs on EEG and hyperintensities on MRI were lower than those of sporadic Creutzfeldt–Jakob disease (Table 3). These findings can be explained by the fact that dura mater graft-associated Creutzfeldt–Jakob disease presented with two distinct clinicopathological subtypes, i.e. 'plaque' and 'non-plaque' types: in contrast to the non-plaque type with classic Creutzfeldt–Jakob disease features, the plaque type shows relatively slow progression and no or late occurrence of PSWCs on EEG (Noguchi-Shinohara *et al.*, 2007; Yamada *et al.*, 2009). When patients with negative PSWCs and dura mater graft-associated Creutzfeldt–Jakob disease were combined with those with plaque-type dura mater graft-associated Creutzfeldt–Jakob disease, and patients with positive PSWCs and dura mater graft-associated Creutzfeldt–Jakob disease with those with non-plaque type dura mater graft-associated Creutzfeldt–Jakob disease, one-third of patients with dura mater graft-associated Creutzfeldt–Jakob disease could have 'plaque type' (data not shown), which was almost the same as in previous reports (Noguchi-Shinohara *et al.*, 2007; Yamada *et al.*, 2009).

Genetic prion diseases

As shown in Table 6, the proportion of *PrP* mutations was quite different from those of EUROCJD, the European Creutzfeldt–Jakob Disease Surveillance Network (Kovacs *et al.*, 2005). The V180I mutation was the most common in Japan but is very rare in Europe (only one case in France). Conversely, the most common mutation in Europe was E200K, which was the third most common in Japan. Additionally, the V210I mutation was the second most common mutation in Europe but was not identified in Japan.

In China, the following 10 genetic prion diseases cases have been reported; three D178N-129M cases and one case each of S97N, G114V, T188K, F198V, E200K, R208C and M232R (Shi *et al.*, 2008; Zheng *et al.*, 2009); in Korea, three genetic prion disease cases (D178N-129M, E200K and M232R) have been identified (Choi *et al.*, 2009). The V180I mutation was not

identified in China or Korea but, conversely, S97N, G114V, T188K, F198V and R208C mutations were not identified in Japan or Korea. Despite the similar ethnic background of East Asia, the distribution of genetic prion diseases in Japan might be different from China and Korea; however, the number of patients reported from China and Korea (Shi *et al.*, 2008; Choi *et al.*, 2009) is too small to reach a conclusion, requiring a larger study in the future.

V180I and M232R mutations were common in Japan but rare in European countries. Interestingly, patients with V180I or M232R mutations had no or rare family histories; therefore, they would have been misdiagnosed with sporadic Creutzfeldt–Jakob disease if genetic analysis had not been performed. Previous reports also showed no family history in cases of V180I or M232R mutations (Bratosiewicz *et al.*, 2001; Jin *et al.*, 2004; Shiga *et al.*, 2007; Zheng *et al.*, 2008; Choi *et al.*, 2009). These findings suggest that V180I and M232R might be polymorphisms, but not pathogenic mutations. Compared with the genotypes of *PrP* in the general Japanese population ($n=466$; isoleucine allele at codon 180:0; arginine at codon 232:0) (Ohkubo *et al.*, 2003), both V180I and M232R mutations had significantly higher proportions of overall prion disease with *PrP* ($n=881$) (both $P<0.001$), indicating that V180I and M232R are not simple polymorphisms, but are disease related.

Age at disease onset of patients with the V180I mutation was older than that of sporadic Creutzfeldt–Jakob disease ($P<0.001$), and patients with the V180I mutation had a longer clinical duration ($P<0.001$) and lower rate of positive PSWCs on EEG ($P<0.001$) than those with sporadic Creutzfeldt–Jakob disease (Tables 3 and 7). Similar findings were reported by Jin *et al.* (2004), who mentioned that MRI findings in V180I revealed characteristic hyperintensities in medial regions, posterior to the parieto-occipital sulci in occipital lobes on T_2-weighted, fluid-attenuated inversion recovery, and diffusion weighted images. The following characteristics of V180I cases appeared to be similar to the MM2-cortical type: longer duration, hyperintensities on MRI and a lower rate of PSWCs; therefore, genetic analysis for *PrP* is necessary for a differential diagnosis.

The M232R mutation was the fourth most common in Japan, but is rare worldwide. Outside Japan, only three cases (Polish, Chinese and Korean) have been identified (Bratosiewicz *et al.*, 2001; Zheng *et al.*, 2008; Choi *et al.*, 2009). As the M232R mutation has been identified mainly in Asian countries, this mutation may be particular to an Asian ethnic background. M232R cases included two clinical subtypes, slow and rapid, as reported previously (Shiga *et al.*, 2007). The proportion of the slow type was higher (39%) than reported earlier (25%) (Shiga *et al.*, 2007). While rapid-type patients with the M232R mutation present with clinical and laboratory findings, similar to MM1 type sporadic Creutzfeldt–Jakob disease, patients with the slow-type M232R mutation have atypical features similar to MM2-cortical type sporadic Creutzfeldt–Jakob disease. Further, M232R cases with a much longer clinical duration may be misdiagnosed as other neurodegenerative diseases if genetic examination of *PrP* is not performed.

In conclusion, the incidence rate of prion diseases was similar to that of western countries, but dura mater graft-associated Creutzfeldt–Jakob disease was frequent in Japan. Genetic differences, such as codon 129 and 219 polymorphisms and mutations in *PrP*, show some differences in the phenotypes of prion diseases between Japan and western countries.

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