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Genetic Studies in Human Prion Diseases

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Human prion diseases are fatal neurodegenerative disorders that are characterized by spongiform changes, astrogliosis, and the accumulation of an abnormal prion protein (PrP^{Sc}). Approximately 10%-15% of human prion diseases are familial variants that are caused by pathogenic mutations in the prion protein gene (*PRNP*). Point mutations or the insertions of one or more copies of a 24 bp repeat are associated with familial human prion diseases including familial Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia. These mutations vary significantly in frequency between countries. Here, we compare the frequency of *PRNP* mutations between European countries and East Asians. Associations between single nucleotide polymorphisms (SNPs) of several candidate genes including *PRNP* and CJD have been reported. The SNP of *PRNP* at codon 129 has been shown to be associated with sporadic, iatrogenic, and variant CJD. The SNPs of several genes other than *PRNP* have been showed contradictory results. Case-control studies and genome-wide association studies have also been performed to identify candidate genes correlated with variant and/or sporadic CJD. This review provides a general overview of the genetic mutations and polymorphisms that have been analyzed in association with human prion diseases to date.

Keywords: Creutzfeldt-Jakob Disease; Genome-Wide Association Study; Prion Diseases; Mutation; Prion Protein Gene; Polymorphism, Single Nucleotide

INTRODUCTION

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are fatal neurodegenerative disorders that affect humans and animals. These diseases are characterized by spongiform changes, astrogliosis, and the accumulation of an abnormal prion protein (PrP^{Sc}) in the central nervous system (CNS). The key mechanism in the pathogenesis of prion diseases is the conversion of the cellular prion protein (PrP^{C}) into PrP^{Sc} (1). The human prion diseases include kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI) (2). The majority of human prion diseases are sporadic (85%). Approximately 10%-15% of human prion diseases are inherited, i.e., caused by mutations in the prion protein gene (*PRNP*), and less than 1% are acquired (3, 4).

PRNP is located on chromosome 20p12 in humans. The human *PRNP* gene contains two exons, and the 253 amino acid prion protein (PrP) is encoded by the larger second exon (5). PrP is an N-linked glycosylated protein that is posttranslationally processed to remove a 22 amino acid signal peptide and is attached to the cell membrane by a glycosylphosphatidylinositol (GPI) anchor. The N-terminal domain of human PrP comprises a five octapeptide repeat, and the C-terminal domain contains two N-glycosylation sites and an intermolecular disulfide bond (6).

To date, more than 30 mutations of *PRNP* have been found in the open reading frame (ORF) of this gene (3, 6-30). These mutations are the only cause of familial prion diseases, which include familial CJD, GSS, and FFI (31-33). In addition to these mutations, many polymorphisms have also been observed in the ORF of *PRNP* (3, 34). In particular, single nucleotide polymorphisms (SNPs) at codons 129 or 219 of *PRNP* represent susceptibility factors for human prion diseases (35-37). Candidate gene studies and genome-wide association studies (GWAS) have been conducted to identify genetic susceptibility factors for human prion diseases (38-40).

In this review, we summarize the genetics of familial human prion diseases and current studies of the genetic factors in sporadic human prion diseases.

PRNP MUTATIONS

Genetic CJD

Familial CJD is caused by inherited autosomal dominant point mutations and insertion/deletion mutations of octapeptide repeats (OPRI/OPRD) (41). Among these mutations, many have been identified in patients without a family history of prion disease, known as genetic CJD. Genetic CJD accounts for 5%-15% of all CJD cases. Genetic CJD may be caused by point mutations at codons 114 (GGT→GTT), 178 (GAC→AAC), 180 (GTC→ATC),

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183 (ACA→ACG), 188 (ACG→AAG), 196 (GAG→AAG), 200 (GAG→AAG), 203 (GTT→ATT), 208 (CGC→CAC), 210 (GTT→ATT), 211 (GAG→CAG), 232 (ATG→AGG), or 238 (CCA→TCA), or by insertional mutations of 1, 2, 3, 4, 5, 6, or 7 octapeptide repeat segments (Table1 and Fig. 1) (2, 3, 7-18).

Table 1. *PRNP* pathogenic point mutations

Phenotype	Mutations (codon)	DNA sequence change	Amino acid change	Reference
gCJD	114	GGT→GTT	Gly→Val	8
	178-129V	GAC→AAC	Asp→Asn	9
	180	GTC→ATC	Val→Ile	10
	183	ACA→ACG	Thr→Ala	11
	188	ACG→AAG	Thr→Lys	12
	196	GAG→AAG	Glu→Lys	13
	200	GAG→AAG	Glu→Lys	14
	203	GTT→ATT	Val→Ile	13
	208	CGC→CAC	Arg→His	15
	210	GTT→ATT	Val→Ile	16
	211	GAG→CAG	Glu→Gln	13
	232	ATG→AGG	Met→Arg	17
	238	CCA→TCA	Pro→Ser	18
GSS	102	CCG→CTG	Pro→Leu	19
		CCA→CTA	Pro→Leu	20
	105	CCA→ACA	Pro→Thr	21
		CCA→TCA	Pro→Ser	22
	117	GCA→GTG	Ala→Val	23
	131	GGA→GTA	Gly→Val	24
	145	TAT→TAG	Tyr→Stop	25
	160	CAA→TAA	Gln→Stop	12
	187	CAC→CGC	His→Arg	26
	198	TTC→TCC	Phe→Ser	27
	202	GAC→AAC	Asp→Asn	28
	211	GAG→GAC	Glu→Gln	13
	212	CAG→CCG	Gln→Pro	28
	217	CAG→CGG	Gln→Arg	27
	226	TAC→TAA	Tyr→Stop	29
	227	CAG→TAG	Gln→Stop	29
FFI	178-129M	GAC→AAC	Asp→Asn	30

gCJD, genetic Creutzfeldt-Jakob disease; GSS, Gerstmann-Sträussler-Scheinker syndrome; FFI, fatal familial insomnia.

The distribution and frequency of *PRNP* mutations in genetic CJD differ between Europeans and East Asians (Table 2). The most common *PRNP* mutation in European genetic CJD patients is in the codon 200, followed by mutations in codons 210 and 178, whereas the most common mutation in Japanese CJD patients is in codon 180, followed by mutations in codon 200 and 232 (42, 43). In particular, the *PRNP* mutation at codon 210 is prevalent in European countries but rare in East Asian populations. Conversely, that mutation in codon 232 has been observed in Japanese patients but not European patients. The frequency of mutations in codons 180 ($P < 0.001$), 200 ($P < 0.001$), 210 ($P < 0.001$), and 232 ($P < 0.001$) are significantly different between Europeans and East Asians. However, the frequencies of point mutations in codons 171, 178, 188, 196, 203, 208, and 211 were not significantly different between Europeans and Asians. Several mutations in the ORF of *PRNP* have been found in genetic CJD patients in Korea. Five mutations in codon 180, three in codon 200, two in codon 203, and two in codon 232 have been identified (44-49). The frequency of genetic CJD in Korea is very similar to that in Japan.

The onset of genetic CJD typically occurs between 30 and 55 yr of age with progressive confusion and memory impairment, ataxia, and myoclonus. The duration of genetic CJD ranges from a few months to several years (50). The mean age at disease onset and the mean duration in genetic CJD was linked to methionine (Met) or valine (Val) at codon 129 in the mutated allele. PrP^{Sc} type, histological changes, and clinical features of genetic CJD patients with most mutations in cis with Met at codon 129 were overall very similar to those of the sporadic CJD MM1 phenotype.

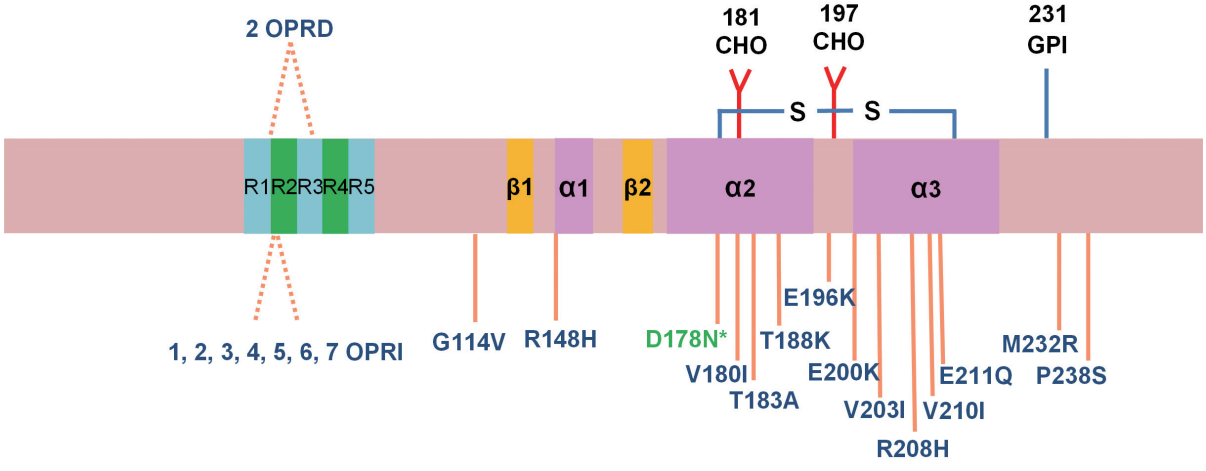

Fig. 1. Mutations in that *PRNP* gene the cause genetic Creutzfeldt-Jakob disease (CJD) or FFI in humans. D178N* is associated with familial CJD or fatal familial insomnia (FFI), depending on the allele present at codon 129 (Met, M = FFI, Val, V = familial CJD). The single-letter designations for the amino acids are as follows: D = aspartic acid, E = glutamic acid, G = glycine, H = histidine, I = isoleucine, K = lysine, M = methionine, N = asparagine, P = proline, Q = glutamine, R = arginine, S = serine, T = threonine, and V = valine. OPRI and OPRD indicate octapeptide repeat insertion and octapeptide repeat deletion, respectively. CHO, Asn-linked glycosylation sites; GPI, glycosylphosphatidylinositol.

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Table 2. The distribution of genetic prion diseases in East Asians and European countries

Diseases	Mutations	Europeans (42)				East Asians (43-48)		*P* value*
		Italy (n = 115)	France (n = 84)	Germany (n = 68)	Total (n = 267)	Japan (n = 216)	Korea (n = 15)	
gCJD	Insertion	3	5	0	8	3	0	n.s.
	171	0	1	0	1	0	0	n.s.
	178-129V	0	8	0	8	1	0	n.s.
	180	0	1	0	1	89	5	< 0.001
	188	0	0	2	2	0	0	n.s.
	196	0	1	3	4	0	0	n.s.
	200	35	46	15	96	37	3	< 0.001
	203	1	3	0	4	2	2	n.s.
	208	1	0	1	2	1	0	n.s.
	210	50	6	9	65	0	0	< 0.001
	211	1	2	1	4	0	0	n.s.
	232	0	0	0	0	33	2	< 0.001
GSS	102	8	3	3	14	39	2	< 0.001
	105	0	0	0	0	5	0	0.018
	117	0	2	5	7	0	0	0.019
FFI	178-129M	10	6	17	33	3	1	< 0.001

*The differences of frequencies of *PRNP* mutations between Europeans and East Asians were measured by the chi-square-test or Fisher's exact test. gCJD, genetic Creutzfeldt-Jakob disease; GSS, Gerstmann-Sträussler-Scheinker syndrome; FFI, fatal familial insomnia; n.s., not significant.

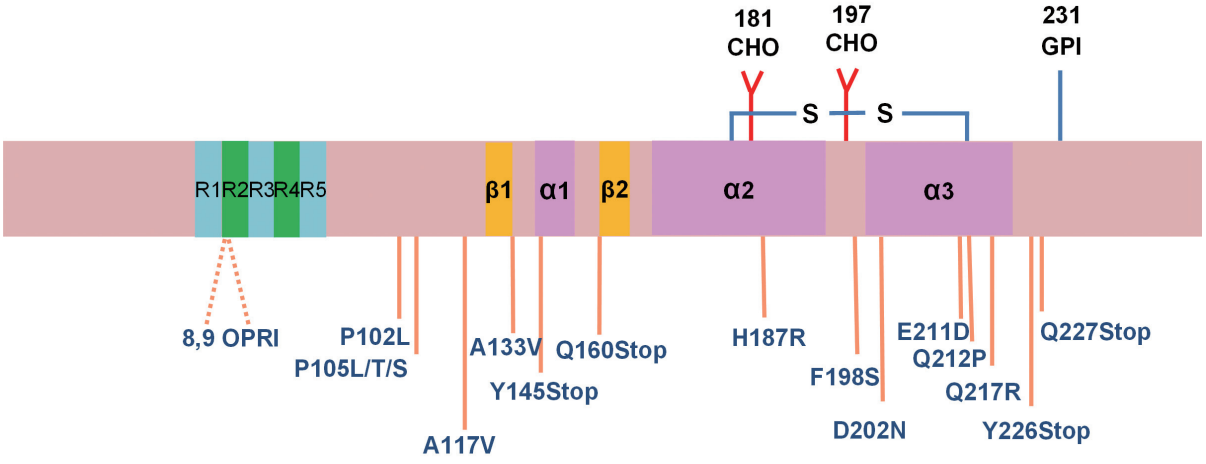

Fig. 2. Mutations in the *PRNP* gene that cause Gerstmann-Sträussler-Scheinker syndrome (GSS). The single-letter designations for the amino acids are as follows: A = alanine, D = aspartic acid, E = glutamic acid, F = phenylalanine, H = histidine, L = leucine, N = asparagine, P = proline, Q = glutamine, R = arginine, S = serine, T = threonine, V = valine, and Y = tyrosine. OPRI indicates the octapeptide repeat insertion. The stop indicates a stop codon. CHO, Asn-linked glycosylation sites; GPI, glycosylphosphatidylinositol.

GSS

GSS has been associated with point mutations at codons 102 (CCG→CTG), 105 (CCA→CTA, ACA, TCA), 117 (GCA→GTG), 131 (GGA→GTA), 145 (TAT→TAG), 160 (CAA→TAA), 187 (CAC→CGC), 198 (TTC→TCC), 202 (GAC→AAC), 211 (GAG→GAC), 212 (CAG→CCG), 217 (CAG→CGG), 226 (TAC→TAA), and 227 (CAG→TAG), and insertional mutations of 8 and 9 octapeptide repeat segments (Table 1 and Fig. 2) (2, 3, 7, 19-29).

The distribution and frequency of *PRNP* mutations in GSS were also clearly distinct between Europeans and East Asians (Table 2). The most common *PRNP* mutation in GSS patients in European countries and East Asia is in codon 102. The *PRNP* mutation at codon 105 is observed in East Asian, but not European populations. In contrast, the mutation in codon 117 is found in European, but not East Asian populations (42, 43). There were significant differences in the frequencies of three mutations (codon 102, $P < 0.001$; codon 105, $P = 0.018$; codon 117, $P = 0.019$) between European and East Asian GSS patients. In Korea, a mutation at codon 102 of *PRNP* has been reported in two GSS patients (44, 51).

The onset of GSS mainly occurs between 40 to 60 yr of age. The clinical symptoms of GSS include cerebellar dysfunction, gait disturbance, dementia, and mild dysarthria. All GSS cases exhibit PrP plaque deposits (50). The hallmark of GSS is the extensive PrP-amyloid deposits with minimal spongiform change. In addition, neurofibrillary tangles have been detected in the GSS patients with *PRNP* mutations at codon 105, 145, and 217 (52-54).

FFI

FFI is caused by a mutation at codon 178 (GAC→AAC) of *PRNP* in combination with a polymorphism that generates a Met at

codon 129 (Table 1 and Fig. 1) (2, 3, 7, 34). The frequency of the *PRNP* mutation at codon 178 in conjunction with M129 is more prevalent in European than East Asian countries ($P < 0.001$) (Table 2) (42, 43). In Korea, a mutation at codon 178 accompanied by M129 has been reported in one FFI patient (46).

FFI typically presents between 20 and 72 yr of age, with an average age of onset of approximately 50 yr. The duration of FFI ranges from 6 months to 33 months with an average of 18.4 months. The major clinical symptom of FFI is insomnia (50). Ataxia, dysarthria, myoclonus, dysphagia and pyramidal signs can also be observed.

PRNP POLYMORPHISMS

In addition to the mutations described above, many polymorphisms have been observed in the ORF of *PRNP*. *PRNP* polymorphisms are observed at codons 129 (ATG→GTG), 142 (GGC →AGC), 171 (AAC→AGC), 188 (ACG→AAG), and 219 (GAG→AAG), and the deletion of 1 octapeptide repeat segments is also considered a polymorphism (2, 3, 55).

Codon 129 SNP

The *PRNP* codon 129 SNP introduces an amino acid substitution of Val for Met. The SNP at codon 129 of *PRNP* has been considered a genetic risk factor for human prion diseases (34, 37). This SNP was strongly associated with sporadic CJD in Korean, Japanese, Dutch, British, Spanish, French and German populations (Table 3) (37, 38, 43, 55-62). Heterozygosity at codon 129 is protective against sporadic, iatrogenic or variant CJD in Europeans and East Asians (35, 37, 38, 58-65). In particular, all cases of variant CJD are homozygous for Met at this SNP (65). The frequency of Met homozygosity at codon 129 of *PRNP* is considerably different between Europeans (32%-45%) and East Asians (92%-94%) normal populations (Table 3).

Codon 219 SNP

The *PRNP* codon 219 SNP introduces an amino acid substitution of lysine (Lys) for glutamic acid (Glu) (36). The SNP at codon 219 has been reported in Asian but not Caucasian populations (36, 37, 43, 55, 66). This SNP was linked to the development of sporadic CJD in the Korean and Japanese populations (36, 37).

Other *PRNP* polymorphisms

The deletion of the *PRNP* octapeptide repeat was not associated with sporadic CJD in the British population (67). Several SNPs outside the coding region of *PRNP* have also been investigated. The *PRNP*1368 polymorphism was associated with sporadic CJD in the British and German populations (68, 69). However, this finding could not be confirmed in the Korean population (70). Case-control studies in a Dutch population have shown contradictory results (71, 72). The *PRNP* -101, 310 and 385 SNPs showed a significant association with an increased risk of developing sporadic CJD after adjusting for the *PRNP* codon 129 genotype (73-75).

POLYMORPHISMS IN OTHER CANDIDATE GENES

Previous association studies of several genes other than *PRNP* have been performed in Europeans and East Asians (Table 4). For example, the prion-like protein gene (*PRND*), shadow of PrP (*SPRN*), cathepsin D (*CTSD*), HECTD2, tau protein gene (*MAPT*), apolipoprotein E (*APOE*), alpha1-antichymotrypsin (*ACT*), a disintegrin and metalloprotease 10 (*ADAM10*), ribosomal protein SA (*RPSA*), 14-3-3 eta (*YWHAH*), 14-3-3 beta (*YWHAB*), beta site APP cleaving enzyme 1 (*BACE1*), and calcium homeostasis modulator 1-3 (*CALHM1-3*) have all been investigated for relationships with human prion diseases.

PRND

PRND, the gene encoding the downstream prion-like protein (doppel or Dpl), is located downstream of human *PRNP* (76). Two SNPs in *PRND*, T26M and/or P56L, were not associated with sporadic CJD (68, 71, 77, 78). The T174M polymorphism has been inconsistently linked with sporadic CJD (68, 71, 77-

Table 3. Genotype distribution of *PRNP* codon 129 SNP in various populations between sporadic CJD patients and controls

Countries	Genotype frequency, No.							*P* value†	References
	Control				Sporadic CJD				
	Met/Met	Met/Val	Val/Val	*P* value*	Met/Met	Met/ Val	Val/ Val		
Korea	499	29	1	-	150	0	0	0.001	37, 55
Japan	164	15	0	n.s.	552	14	4	0.002	43, 56
Netherland	435	440	90	< 0.001	98	32	10	< 0.001	57, 58
UK	294	324	81	< 0.001	307	98	101	< 0.001	38
Spain	129	165	41	< 0.001	112	36	27	< 0.001	59
France	38	45	9	< 0.001	260	57	75	< 0.001	60, 61
Germany	15	27	4	< 0.001	39	6	5	< 0.001	62

*Based on the comparison of frequencies between Korea and other countries in the controls by the chi-square-test or Fisher's exact test; †Based on the comparison of frequencies between the controls and sporadic CJD patients of the same nationality by the chi-square-test or Fisher's exact test. CJD, Creutzfeldt-Jakob disease; Met, Methionine; Val, Valine; n.s., not significant.

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Table 4. The association results of SNPs of other genes excepting *PRNP* between sporadic or variant CJD and controls

Results	Sporadic CJD	Variant CJD	References
Association	*PRND* 3′ UTR +28; *SPRN* T7M; *CALHM1 rs41287502 & rs4918016*	*SPRN* A46G (frame shift); *STMN2 rs1460163*; *RARB rs6794719*; *HECTD2 rs12249854* & *rs7081363*; *CTSD* C224T; *MTMR7 rs4921542*; *NPAS2 rs7565981*; *ZBTB38-RASA2 rs295301*; *CHN2 rs1016726*	38-40, 59, 81, 83, 86, 89, 118
Controversial results	*PRND* T174M; *APOE*; *HECTD2 rs12249854* & *rs7081363*; *ZBTB38-RASA2 rs295301*		40, 59, 68, 71, 77-80, 89, 90, 97-99
No association	*PRND* T26M & P56L; *ADAM10 rs972801*; *ACT* signal peptide; *MAPT* (6 SNPs); *RPSA* (4 SNPs); *YWHAH* 753G/A; *CALHM3* (2 SNPs); *YWHAB* (6 SNPs); *STMN2 rs1460163*; *RARB rs6794719*; *CTSD* C224T; *BACE1 rs638405*; *CALHM1 rs2986016 & rs2986017*; *MTMR7 rs4921542*; *NPAS2 rs7565981*; *CHN2 rs1016726*		38-40, 68, 71, 77, 78, 87, 88, 94, 102, 105, 108, 111, 114, 116, 118-120

CJD, Creutzfeldt-Jakob disease; *PRND*, prion-like protein gene; UTR, untranslated region; *SPRN*, shadow of PrP; *CALHM1-3*, calcium homeostasis modulator 1-3; *APOE*, apolipoprotein E; *ADAM10*, a disintegrin and metalloprotease 10; *ACT*, alpha1-antichymotrypsin; *MAPT*, tau protein gene; *RPSA*, ribosomal protein SA; *YWHAH*, 14-3-3 eta; *YWHAB*, 14-3-3 beta; *RARB*, retinoic acid receptor β; *STMN2*, the SCG10 protein; *CTSD*, cathepsin D; *MTMR7*, myotubularin-related protein 7 gene; *NPAS2*, neuronal PAS (per-ARNT-sim) domain-containing protein 2 gene; *BACE1*, beta site APP cleaving enzyme 1.

80). An association between sporadic CJD and a polymorphism in the 3′ untranslated region (UTR) +28 position of *PRND* has been reported in the Korean population (81).

SPRN

SPRN encodes the shadow of PrP (Shadoo or Sho), which exhibits homology to PrP (82). The *SPRN* T7M SNP was linked to the development of sporadic and variant CJD in the British population (83).

CTSD

CTSD, the gene encoding cathepsin D, is located on chromosome 11 (84). Cathepsin D co-localizes with PrP^{Sc} (85). *CTSD* C224T was associated with an increased risk of the development of variant CJD in the British population (86). However, this polymorphism was not associated with an increased risk of sporadic CJD in Korean or European populations (87, 88).

HECTD2

HECTD2, an E3 ubiquitin ligase, is located on chromosome 10. SNPs in *HECTD2* have been associated with variant and sporadic CJD in the British population (89). However, the -247G > A and +16066T > A polymorphisms were not associated with genetic susceptibility to sporadic CJD in a Korean population (90).

MAPT

MAPT is located on chromosome 17 (91) and plays a key role in the pathogenesis of several neurodegenerative disorders (92, 93). Six analyzed SNPs (rs212559, rs242557, rs3785883, rs2471738, H1/H2, and rs7521) in *MAPT* were not related to sporadic CJD development in the European population (94).

APOE

APOE is located on chromosome 19, and the *APOE* ε4 allele is a major risk factor for Alzheimer's disease (AD) (95, 96). Studies of the relationship between the *APOE* ε4 allele and the risk of sporadic CJD have produced divergent findings (59, 97-100).

ACT

ACT is located on chromosome 14 and is one of the factors that may enhance amyloid formation (101). The signal peptide polymorphism in *ACT* was determined to be unlikely confer genetic susceptibility to sporadic CJD in the Italian population (102).

ADAM10

ADAM10 is located on chromosome 15 (103) and is involved in the cleavage of PrP^{C} in cells (104). The rs972801 SNP in *ADAM10* was not associated with sporadic CJD in a French population (105).

RPSA

Ribosomal protein SA (*RPSA*), also known as 37 kDa laminin receptor precursor (LRP)/67 kDa laminin receptor (LR), is located on chromosome 3. LRP/LR acts as a receptor for PrP^{C} and PrP^{Sc} (106, 107). Four *RPSA* SNPs (5′ UTR-8T > C, 134-32C > T, 519G > A, and 793+58C > T) were not linked to sporadic CJD susceptibility (108).

YWHAH

YWHAH, the gene encoding 14-3-3 eta, is located on chromosome 22 (109). The 14-3-3 protein is detected in the cerebrospinal fluid (CSF) for the diagnosis of sporadic CJD (110). The *YWHAH* 753 G/A SNP was not associated with sporadic CJD in a Korean population (111).

YWHAB

YWHAB, the gene encoding 14-3-3 beta, is located on chromosome 20 (112). The 14-3-3 beta protein interacts with PrP (113). Six SNPs (c.60A > C, c.685-120G > A, c.685-89G > A, 92G > A, c.185T > A, and c.377A > C) in *YWHAB* were not correlated with

sporadic CJD in a Korean population (114).

BACE1

BACE1 is located on chromosome 11 and encodes the β-secretase enzyme (115). The *BACE1* rs638405 SNP was associated with an increased risk of sporadic CJD in a Spanish population, mainly in *PRNP* M129M homozygous subjects (116).

CALHM1-3

The *CALHM1* gene, which encodes a calcium homeostasis regulator, is located on chromosome 10 and controls cytosolic calcium levels (117). Two SNPs (rs41287502 and rs4918016) were associated with sporadic CJD in a Spanish population. However, two SNPs (rs2986016 and rs2986017) in *CALHM1* and two SNPs (rs2986035 and rs3014199) in *CALHM3* were not found to be associated with sporadic CJD in the Spanish population (118).

GENOME-WIDE ASSOCIATION STUDIES (GWAS)

Recent GWAS have been performed to identify genetic susceptibility factors for human prion diseases, including kuru, variant CJD and sporadic CJD (119). The rs6794719 and rs1460163 SNPs in the region upstream of *RARB*, which encodes retinoic acid receptor β and *STMN2*, which encodes the SCG10 protein, were strongly associated with kuru and variant CJD in a British population (38). These two SNPs in *RARB* and *STMN2* were not associated with sporadic CJD in a Korean population (120). In addition, rs4921542, in the intronic region of the myotubularin-related protein 7 gene (*MTMR7*), and rs7565981, in the neuronal PAS (per-ARNT-sim) domain-containing protein 2 gene (*NPAS2*), were associated with variant CJD in the British and French populations but not sporadic CJD in three countries (39). Finally, SNPs at the *ZBTB38-RASA2* locus were correlated with sporadic CJD in a British population but not a German population. A SNP in the *CHN2* gene was associated with variant CJD but not sporadic CJD in a British population (40).

CONCLUSION

The human prion diseases are fatal neurodegenerative disorders characterized by the accumulation of PrP^{Sc}. Sporadic and genetic forms of human prion diseases are occurring worldwide. There is no doubt that mutations and polymorphisms in the *PRNP* play an important role in determining prion disease susceptibility. In this review, we have summarized that the proportion of *PRNP* mutations was quite significantly different between Europeans and East Asians and *PRNP* polymorphisms such as codons 129 and 219 were associated with sporadic CJD in the Europeans and East Asians. Nevertheless, the SNPs of other genes, including *PRND, CTSD, HECTD2,* and *APOE* have been showed contradictory results. Because GWAS studies have been reported in only the Europeans, these studies in the East Asians will be necessary to confirm and identify candidate genes for human prion diseases. In the future, the identification of new candidate gene in human prion diseases will contribute to understand numerous questions and potential therapeutic targets in prion diseases.

DISCLOSURE

The authors declare no conflict of interest.

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