Genetic Studies in Human Prion Diseases

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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) in the central nervous system (CNS). The key mechanism in the pathogenesis of prion diseases is the conversion of the cellular prion protein (PrPC) into PrPSc (1). The human prion diseases include kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and familial insomnia (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),...
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→AAG             | Thr→Ala         | 11        |
|           | 188              | AGG→AAG             | Thr→Lys         | 12        |
|           | 196              | GAG→AAG             | Glu→Lys         | 13        |
|           | 200              | GAG→AAG             | Glu→Lys         | 14        |
|           | 203              | GGT→ATT             | Val→Ile         | 13        |
|           | 208              | CSG→CAC             | Arg→His         | 15        |
|           | 210              | GTT→ATT             | Val→Ile         | 16        |
|           | 211              | GAG→AGA             | Glu→Gln         | 13        |
|           | 232              | AGT→AGG             | Met→Arg         | 17        |
|           | 238              | CCA→TCA             | Pro→Ser         | 18        |
| GSS       | 102              | CGG→CTG             | Pro→Leu         | 19        |
|           |                  | CCA→CTA             | Pro→Leu         | 20        |
|           | 105              | CCA→ACA             | Pro→Thr         | 21        |
|           |                  | CCA→TCA             | Pro→Ser         | 22        |
|           | 117              | GOA→GTG             | Ala→Val         | 23        |
|           | 131              | GGA→GTA             | Gly→Val         | 24        |
|           | 145              | TAT→TAG             | Tyr→Stop        | 25        |
|           | 160              | CAA→TAA             | Gin→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              | GAG→CCG             | Glu→Pro         | 28        |
|           | 217              | GAG→CAG             | Gin→Arg         | 27        |
|           | 226              | TAC→TAA             | Tyr→Stop        | 29        |
|           | 227              | CAG→TAG             | Gin→Stop        | 29        |
| FFI       | 117-120M         | GAC→AAC             | Asp→Asn         | 30        |

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

Fig. 1. Mutations in that PRNP gene cause the 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.
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), 188 (GAG→GAC), 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 PRNP1368 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), alpha-1-antichymotrypsin (ACT), a disintegrin and metalloprotease 10 (ADAM10), ribosomal protein SA (RPSA), 14-3-3 eta (YWHAH), 14-3-3 beta (YWHAH), 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, 77-79).

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

| Countries | Control | Sporadic CJD | P value* | References |
|-----------|---------|--------------|----------|------------|
|           | Met/Met | Met/Val | Val/Val | P value* | Met/Met | Met/Val | Val/Val | P value* |           |
| Korea     | 499     | 29      | 1       | 0.001    | 150      | 0      | 0       | 0.001    | 37, 55    |
| Japan     | 164     | 15      | 0       | n.s.     | 552      | 14     | 4       | 0.002    | 43, 56    |
| Netherlands | 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.
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/TM7 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 PrPSc (85). CTSD C224T was associated with an increased risk of the development of sporadic and variant CJD in the British population (86). However, this polymorphism was not associated with 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, rs424577, 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 PrPSc 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 PrPSc and PrPSc (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).

**YWHAA**

YWHAA, the gene encoding 14-3-3 eta, is located on chromosome 2 (109). The 14-3-3-3 protein is detected in the cerebrospinal fluid (CSF) for the diagnosis of sporadic CJD (110). The YWHAH 14-3-3 eta; YWHAH 14-3-3 beta; YWHAH beta site APP cleaving enzyme 1.

**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, c.719T > A, and c.87A > G) in YWHAB were not correlated with

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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/TM7; CALHM1 rs41287502 & rs4918016 | SPRN/A466G (frame shift); STTM2 rs1460163; RARB rs6794719; HECTD2 rs12249864 & 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 rs12249865 & rs7081363; ZBTB38-RASA2 rs268301 | No association | 40, 59, 68, 71, 77-80, 89, 90, 97-99 |

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; UTR, untranslated region; PRNP, prion-like protein gene; UTR, untranslated region; APOE, apolipoprotein E; C224T, C224T; RPSA, ribosomal protein SA; YWHAH, 14-3-3 eta; YWHAH, 14-3-3 beta; RARB, retinoic acid receptor β; STTM2, the SG510 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.
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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