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SHORT COMMUNICATION

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Polymorphisms of the prion protein gene (PRNP) in a Korean population

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Abstract Human prion protein gene (PRNP) has been considered to be involved in the susceptibility of humans to prion diseases. Polymorphisms of methionine (Met)/valine (Val) at codon 129 and of glutamic acid (Glu)/lysine (Lys) at codon 219 are thought to play an important role in susceptibility to sporadic, iatrogenic and variant Creutzfeldt–Jakob disease (CJD). Although the genotype distribution of polymorphisms in PRNP open reading frame (ORF) has been reported in many European populations, among Asian groups, it has been reported only in the Japanese population. We examined the PRNP polymorphisms in 529 healthy Koreans. We observed that genotype frequencies at codon 129 was 94.33% Met/Met, 5.48% Met/Val, and 0.19% Val/Val with an allele frequency of 0.971:0.029 Met:Val, and that genotype frequencies at codon 219 was 92.06% Glu/Glu, 7.94% Glu/Lys, and 0% Lys/Lys with an allele frequency of 0.96:0.04 Glu:Lys. The frequencies of the Glu/Glu genotype ($\chi^2 = 10.075$, $P = 0.0015$) and of the Glu allele ($\chi^2 = 9.486$, $P = 0.0021$) at codon 219 were significantly higher in the Korean population than the Japanese population. In addition, the genotype frequency of heterozygotes (12.7%) at codons 129 or/and 219 was significantly lower in Koreans than in people from Great Britain ($\chi^2 = 89.52$, $P < 0.0001$). The deletion rate of one octarepeat (R2 deletion) was 0.38%, with 99.62% undeleted homozygotes and 0% deleted homozygote. To our knowledge, the R2 octarepeat deletion has never been found in people from countries other than Korea. The data of PRNP polymorphism at codon 219 suggest that Koreans may be more sensitive to sporadic CJD than the Japanese population.

Keywords Prion protein gene · Polymorphism · Creutzfeldt–Jakob disease · Single nucleotide polymorphism · Deletion · Korean

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Introduction

Human prion protein contains 253 amino acids encoded by the prion protein gene (PRNP), which is located on chromosome 20 in humans. PRNP is considered to play an important role in conferring susceptibility to prion disease. The human prion diseases are neurodegenerative disorders characterized by the accumulation of an abnormal protease-resistant isoform of the prion protein, PrP^{Sc} (Prusiner 1991). A number of point and insertion mutations of PRNP have been linked to familial Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker disease (GSS), and fatal familial insomnia (FFI) (Doh-ura et al. 1989; Hsiao et al. 1989; Goldfarb et al. 1991). Moreover, polymorphisms of PRNP appear to be able to influence expression of prion disease in sporadic and iatrogenic CJD (Collinge et al. 1991; Palmer et al. 1991; Shibuya et al. 1998).

In humans, four polymorphisms that cause the substitution of amino acids have been identified in the PRNP. Three are located at codons 129, 171, and 219.

The fourth is the deletion of one octarepeat (24 bp). The polymorphism at codon 129 results in an amino acid substitution (Met/Val) (Owen et al. 1990). In two studies, genotype frequencies for the codon 129 polymorphism were analyzed in Caucasians and in British population and showed 37–45% Met/Met, 40–51% Met/Val, and 8–15% Val/Val (Salvatore et al. 1994; Zimmermann et al. 1999). In contrast, genotype frequencies for this polymorphism in Japanese populations are considerably different from those seen in many Europeans (Doh-ura et al. 1991). Homozygosity of Met and Val at codon 129 of PRNP causes a predisposition to sporadic and iatrogenic CJD in the United Kingdom (Collinge et al. 1991; Desly et al. 1994; Palmer et al. 1991). This is not consistent with data in Japanese patients with sporadic CJD (Doh-ura et al. 1991). All cases of variant CJD are homozygous for methionine at codon 129 (Collinge et al. 1996). The polymorphism at codon 219 results in an amino acid substitution (Glu/Lys). Codon $219^{Glu/Lys}$ heterozygous polymorphism has been reported to occur in 79 of 566 healthy Japanese, with an allele frequency of 7% but not in Caucasians (Furukawa et al. 1995; Petraroli and Pocchiari 1996; Ohkubo et al. 2003). The Lys allele appears to protect against CJD by binding to protein X. This binding appears to prevent PrP^{C} from being converted into PrP^{Sc} (Kaneko et al. 1997). Recently, the polymorphism of codon 219 was reported to influence the clinicopathological features of GSS with a codon 102 mutation (Furukawa et al. 1995), and heterozygosity of this codon was also reported to serve as a protecting factor against sporadic CJD (Shibuya et al. 1998). The polymorphism at codon 171 results in an amino acid substitution (Asn/Ser) (Laplanche et al. 1990). This polymorphism has been found in Caucasians, and it is not known to influence the pathogenesis of prion disease (Kaneko et al. 1997). Another polymorphism is the deletion of a single octarepeat. This polymorphism has been found in Caucasians with a frequency of 2.5% (Laplanche et al. 1990). Although polymorphisms of PRNP have been studied in many countries including the United Kingdom and Japan, polymorphisms of PRNP in the Korean population remain unknown. The purpose of this study was to investigate genotype frequencies of PRNP polymorphisms in 529 healthy Koreans.

Materials and methods

Blood samples

Blood samples were collected from a random selection of the Korean population. Donors were 529 healthy volunteers. The study was approved by the Ethical Committee of Chunchon Sacred Heart Hospital, and all volunteers gave informed consent. All blood samples were frozen at −70°C prior to analysis.

Polymerase chain reaction (PCR)

Genomic DNA was extracted from 200 µl blood using the QIAamp DNA blood mini kit (Qiagen, USA) following the supplier's instructions. PCR was performed with T-1 (GATGCTGGTTCTCTTTGTGG) and T-2 (CCCACTATCAGGAAGATGAG) primers. The PCR reagents contained 50 pmol of each primer, 5 µl of 10×Taq DNA polymerase buffer, 1.5 mM $MgCl_2$, 0.2 mM of each dNTP mixture, and 2.5 units of Taq DNA polymerase (Promega, USA). The PCR conditions were 94°C for 5 min to denature; 30 cycles of 94°C for 1 min, 56°C for 1 min, and 72°C for 2 min; and 1 cycle of 72°C for 10 min to extend the reaction using Perkin–Elmer Cetus DNA thermal cycler (Perkin–Elmer, USA).

Restriction fragment-length polymorphism (RFLP)

Restriction cleavage sites were searched using Webcutter, ver. 2.0 (Carolina Biological Supply Co., USA). PCR mixtures were purified with Gel extraction kits (Qiagen, USA). A 20-µl aliquot of purified PCR mixture was digested at 37°C for 1 h with 5 units of *Nsp*I (MBI, USA). Restriction products were separated on a 1.5% agarose gel and visualized with ethidium bromide staining under UV light.

Nucleotide sequencing analysis

Purification of PCR products for sequencing was done using a PCR purification kit (Qiagen, USA). DNA sequencing was carried out on an ABI 377 automatic sequencer using a *Taq* dideoxy terminator cycle sequencing kit (ABI, USA). The following sequencing primers were used: T-1 (GATGCTGGTTCTC TTTGTGG), S-13 (AAGCCTGGAG GATGGAACAC), K-6 (ACACATCTGCTCAA CCACGC), T-2 (CCCACTATCAGGAAGATGAG). Nucleic acid sequences were assembled and edited using a combination of the ABI 377 DNA Sequencer Data Analysis program and Sequence Navigator software.

Statistical analysis

Statistical analysis was performed using SAS 8.0 software (SAS Institute, Inc., USA). Differences in genotype frequencies between healthy Koreans and people from other countries were analyzed by χ^2 tests.

Results

Frequencies for the codon 129 polymorphism in the healthy Japanese population are considerably different from those in Europeans (Doh-ura et al. 1991; Erginel-

Unaltuna et al. 2001; Salvatore et al. 1994; Zimmermann et al. 1999). In order to investigate polymorphism of PRNP at codon 129, we sequenced the ORF of PRNP (700 bp) amplified from 529 healthy Koreans (Fig. 1a). Codon 129 genotypes were also confirmed using restriction endonuclease *Nsp*I (Fig. 1b). Of the 529 normal samples, 499 (94.33%) were homozygous for Met, one (0.19%) homozygous for Val, and 29 (5.48%) heterozygous at codon 129 with allele frequency of 0.971:0.029 Met:Val (Table 1). The Val homozygote was found in Korean; it has not been found in Japan. The frequency of Met allele was significantly higher in a normal Korean population than that reported in the United Kingdom ($\chi^2 = 232.531$, $P < 0.001$) (Palmer et al. 1991). However, there was no difference in the frequency of Met allele between Korean and Japanese populations ($\chi^2 = 0.5785$, $P = 0.4469$) (Doh-ura et al. 1991; Ohkubo et al. 2003).

Codon $219^{Glu/Lys}$ heterozygous polymorphism has been reported to occur in 79 of 566 healthy Japanese people, with a Lys allele frequency of 7%; this polymorphism was not seen in Caucasians (Furukawa et al. 1995; Petraroli and Pocchiari 1996; Ohkubo et al. 2003). Recently, it has been suggested that Glu/Lys heterozygote at codon 219 serves as a protecting factor against sporadic CJD (Shibuya et al. 1998). We also found the codon 219 polymorphism in normal Koreans (Fig. 1c). Genotype frequencies at codon 219 in the normal Korean population were 487 (92.06%) Glu/Glu and 42 (7.94%) Glu/Lys. Allele frequency of Glu:Lys was 0.96:0.04 (Table 1). Lys/Lys homozygosity was not found in Koreans, nor was it present in Japanese. Significant differences in genotype ($\chi^2 = 10.075$, $P = 0.0015$) and allele ($\chi^2 = 9.4861$, $P = 0.0021$) frequencies at codon 219 were observed between the Korean and Japanese populations (Furukawa et al. 1995; Ohkubo et al. 2003). The results with codon 219 suggest that Koreans are at higher risk of developing sporadic CJD than the Japanese population and that codon 219 polymorphism is found in eastern Asians but not in Europeans.

The deletion of a single octarepeat (24 bp) has been found in six (2.5% deleted allele frequency) of 120 Caucasians (Laplanche et al. 1990), two (1% deleted allele frequency) of 100 Turkish people (Erginel-Unaltuna et al. 2001), and two (0.39% deleted allele frequency) of 255 northern European individuals (Palmer et al. 1993). We identified two individuals (0.38% deleted allele frequency) with a deleted octarepeat (Table 1). We found no individuals with a deleted homozygote. Of four northern European and Turkish people with octarepeat deletion, one case was a deletion between R2 and R3 and the other between R3 and R4. However, each of the two Korean individuals had the R2 deletion (Fig. 1d,e). This is the first report of R2 deletion in normal populations and the first electropherograms showing a deletion of a single octarepeat. Three polymorphisms at codon 117, 124, and 161 do not result in amino acid substitutions. We also looked for the presence of polymorphisms of PRNP at codons 171 (Asp/Ser), 117(Ala/Ala), 124 (Gly/Gly), and 161 (Val/Val). None of the 529 healthy Koreans exhibited any of these polymorphisms (data not shown). Based on these three polymorphisms, six different genotypes for the PRNP were detected in the normal Korean population. The frequency of $^{M}129^{M}/^{Q}219^{Q}/^{+}Octa^{+}$ genotype was 86.7% (Table 2). The frequencies of heterozygotes (12.7%) at codon 129 or/and 219 were significantly lower in Koreans than in people from the United Kingdom ($\chi^2 = 89.52$, $P < 0.0001$).

Discussion

We report that the genotype frequencies of PRNP at codon 129 in a sample of the normal Korean population (94.33% Met/Met, 5.48% Met/Val, and 0.19% Val/Val) do not differ significantly from those previously reported for the Japanese population (93% Met/Met, 7% Met/Val, and 0% Val/Val) (Doh-ura et al. 1991; Ohkubo et al. 2003) (Table 1). The genotype frequencies differ markedly from those observed in British (37% Met/Met, 51% Met/Val, and 12% Val/Val) (Collinge et al. 1991), Italian (45% Met/Met, 40% Met/Val, and 15% Val/Val) (Salvatore et al. 1994), French (41% Met/Met, 49% Met/Val, and 9% Val/Val) (Laplanche et al. 1994), Turkish (57% Met/Met, 34% Met/Val, and 9% Val/Val) (Erginel-Unaltuna et al. 2001), and American (41% Met/Met, 51% Met/Val, and 8% Val/Val) populations. The previous study of the Japanese population failed to reveal an association between Met homozygosity and sporadic CJD (Doh-ura et al. 1991). Nevertheless, homozygosity at codon 129 in the European populations appears to be important in conferring susceptibility to sporadic CJD (Palmer et al. 1991). The different result may be a function of the fact that there is a very high frequency of Met/Met genotypes in the Japanese population, and many CJD patients would need to be assessed to establish significance. The genotype analysis of Korean CJD patients combined with those of eastern Asian patients may provide sufficient numbers to establish a relationship.

There was a significant difference in the frequencies of genotype ($\chi^2 = 10.075$, $P = 0.0015$) and allele ($\chi^2 = 9.486$, $P = 0.0021$) at codon 219 between the Korean and Japanese populations (Table 1) (Furukawa et al. 1995; Ohkubo et al. 2003). Absence of this polymorphism in Europeans suggests that the Glu/Lys heterozygote at codon 219 may pertain only to eastern Asians. In a study of codon 129 polymorphism in the United Kingdom, 9% of people with sporadic CJD have the Met/Val heterozygote (Palmer et al. 1991). This suggests that the codon 129 Met/Val heterozygous polymorphism cannot completely prevent the development of sporadic CJD. In the polymorphism at codon 219, Glu/Lys heterozygosity found in the general Japanese population was not observed in 85 sporadic Japanese CJD (Shibuya et al. 1998). This suggests that the codon 219 Glu/Lys heterozygous polymorphism serves as a protecting factor against sporadic CJD.

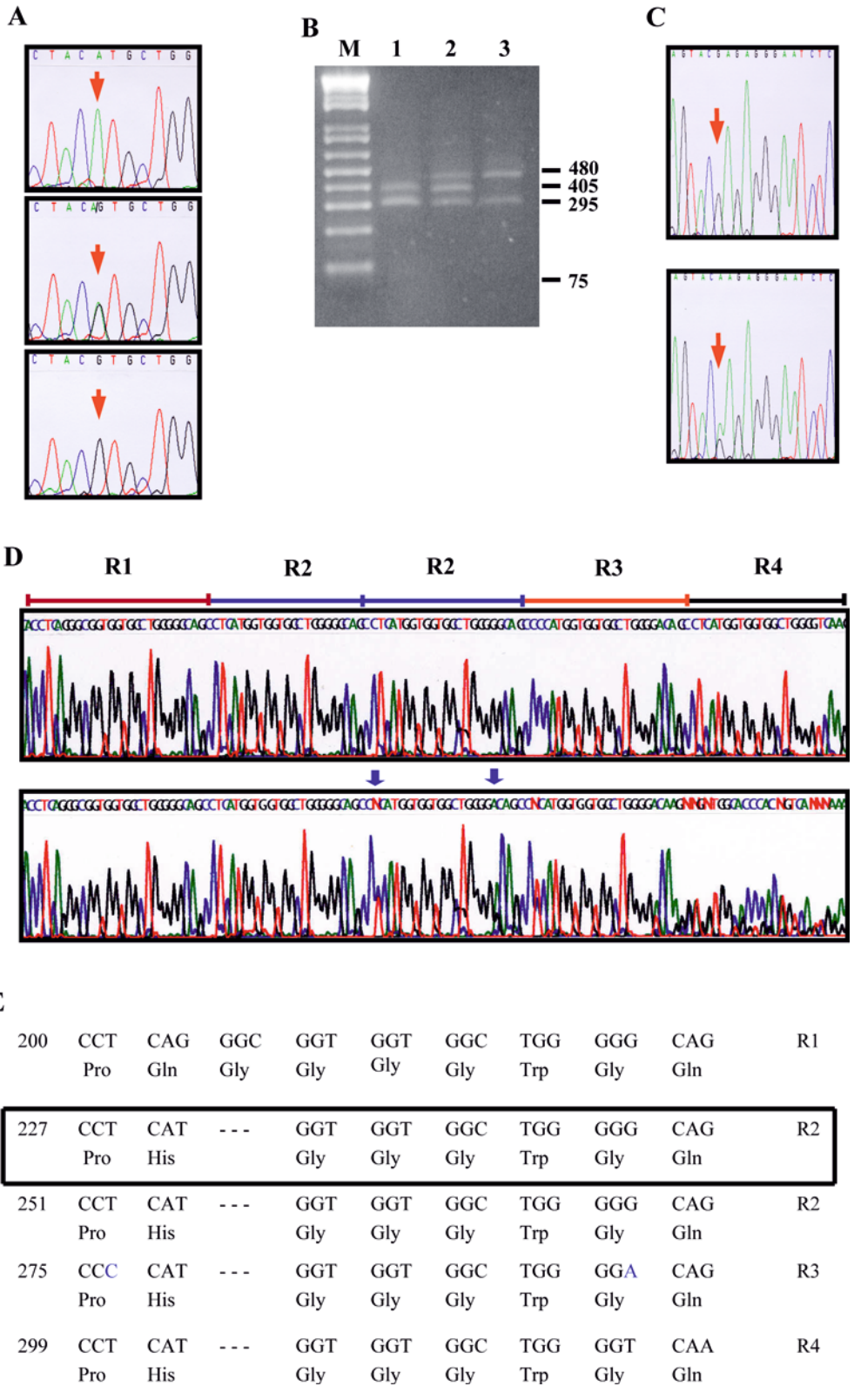

Fig. 1a–e Polymorphisms at codons 129, 219, and octarepeat region in a sample of the Korean population. **a** Electropherograms showing the three genotypes at polymorphic codon 129 of healthy Koreans. *Upper portion*: Met/Met, *middle portion*: Met/Val, *lower portion*: Val/Val. **b** Restriction analysis of PrP open reading frame (ORF) digested with *Nsp*I. *Nsp*I cuts codon 129 when it encodes Met/Met: 100-bp ladder DNA marker, *lane 1*: Met/Met, *lane 2*: Met/Val, *lane 3*: Val/Val. **c** Electropherograms showing the two genotypes at polymorphic codon 219 of healthy Koreans. *Upper portion*: Glu/Glu, *lower portion*: Glu/Lys. **d** Electropherograms showing the polymorphism at the octapeptide repeat region. Deletion of a single octapeptide repeat (24 bp) was found in two of 529 healthy Koreans. *Upper portion*: no deletion/no deletion, *lower portion*: an octapeptide repeat deletion/no deletion. *Blue arrows* indicate overlapped nucleotides between R2 and R3. **e** Deletion R2 of the repeat region of the prion protein gene (PRNP). The *dark box* represents the deletion found in both cases with the R2 deletion. The abbreviated name for each repeat is shown on the *right*

The prion protein contains a region of five octapeptides named R1, R2, R3, and R4. Insertional mutations in PRNP are associated with familial CJD and described to consist of one, two, four, five, six, seven, eight, and nine extra octapeptide repeats between codons 51 and 91 (Capellari et al. 1997). However, octapeptide deletions in PRNP are not associated with CJD. This polymorphism was exclusively reported in Europeans. These deletions are probably generated by unequal crossover between normal alleles. Deletions found in normal Europeans are

Table 1 Genotype and allele frequencies of polymorphisms at codon 129, 219, and octapeptide repeat regions in samples of normal British, Japanese, Turkish, northern European, and Korean populations

Polymorphism	Populations	Total, *n*	Genotype frequency, *n* (%)			Allele frequency	
			Met/met	Met/val	Val/val	Met	Val
Codon 129	British[a]	106	39 (36.79)	54 (50.94)	13 (12.27)	0.623	0.377
	Japanese[b,c]	645	600 (93.0)	45 (7.0)	0 (0)	0.965	0.035
	Korean	529	499 (94.33)	29 (5.48)	1 (0.19)	0.971	0.029
Polymorphism	Populations	Total, *n*	Genotype frequency, *n* (%)			Allele frequency	
			Glu/glu	Glu/lys	Lys/lys	Glu	Lys
Codon 219	Caucasian[d]	100	100 (100)	0 (0)	0 (0)	1.0	0
	Japanese[c,e]	566	487 (86.0)	79 (14.0)	0 (0)	0.93	0.07
	Korean	529	487 (92.06)	42 (7.94)	0 (0)	0.96	0.04
Polymorphism	Populations	Total, *n*	Genotype frequency, *n* (%)			Allele frequency	
			5/5	5/4[f]	4/4	5	4
Octapeptide repeat region	North European[g]	255	253 (99.2)	2 (0.8)	0 (0)	0.996	0.004
	Turkish[h]	100	98 (98.0)	2 (2.0)	0 (0)	0.99	0.01
	Korean	529	527 (99.62)	2 (0.38)	0 (0)	0.998	0.002

[a]Palmer et al. 1991.
[b]Doh-ura et al. 1991.
[c]Ohkubo et al. 2003.
[d]Petraroli and Pocchiari 1996.
[e]Furukawa et al. 1995.
[f]Five indicates no deletion of octarepeat (24 bp) and four indicates a deletion of octarepeat.
[g]Palmer et al. 1993.
[h]Erginel-Unaltuna et al. 2001.

Table 2 Genotype distribution for codon 129, 219, and the octa-repeat region of prion protein gene (PRNP) in 529 healthy Koreans

Genotypes	Healthy Koreans, $n = 529$ (%)
$^{M}129^{M}/^{Q}219^{Q}/^{+}Octa^{+}$ [a]	459 (86.7)
$^{M}129^{M}/^{Q}219^{K}/^{+}Octa^{+}$	38 (7.2)
$^{M}129^{V}/^{Q}219^{Q}/^{+}Octa^{+}$	25 (4.7)
$^{M}129^{V}/^{Q}219^{K}/^{+}Octa^{+}$	4 (0.8)
$^{M}129^{M}/^{Q}219^{Q}/^{+}Octa^{-}$	2 (0.4)
$^{V}129^{V}/^{Q}219^{Q}/^{+}Octa^{+}$	1 (0.2)

[a] $Octa^{+}$ indicates no deletion of octarepeat (24 bp) and $Octa^{-}$ indicactes a deletion of octarepeat.

usually the R2–R3 deletion or the R3–R4 deletion (Erginel-Unaltuna et al. 2001; Palmer et al. 1993). However, in the current study, a single R2 deletion was found in two normal Koreans (Table 1). The previous data reported polymorphisms of PRNP at codons 171 (Asp/Ser), 117(Ala/Ala), 124 (Gly/Gly), and 161 (Val/Val) (Fink et al. 1994). These polymorphisms were not found in the sample of the Korean population that was tested. This discrepancy between Europeans and eastern Asians may be related to ethnic background.

In conclusion, PRNP polymorphism data in European populations have been reported in many studies, whereas PRNP polymorphism in Asians has been reported only in the Japanese population. Our data will help to determine genotype frequencies of the PRNP polymorphisms in eastern Asians. Furthermore, the study of PRNP polymorphisms in Korean sporadic CJD patients in the future will help to evaluate the correlation between the homozygotes (codons 129 and 219) of PRNP and susceptibility to sporadic CJD.

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