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Original Article

Association between the prion protein gene polymorphisms and incidence of fatal familial insomnia: a casecontrol study in a Chinese population

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Abstract: This study aimed to explore the association between the prion protein gene (PRNP) polymorphisms and incidence of fatal familial insomnia (FFI) in a Chinese population. Twenty FFI patients were chosen as the case group and forty healthy individuals as the control group. PRNP gene polymorphism sites were screened out, and M129V and E219K were identified as the polymorphic sites. Peripheral blood was extracted from all subjects for PRNP detection and genotyping using polymerase chain reaction restriction fragment length polymorphism. Epidemiological case investigation was conducted in the FFI patients to collect related information. Multivariate logistic regression analysis was employed to screen independent risk factors of FFI and SHEsis online software was used to analyze the haplotypes of M129V and E219K sites of PRNP. Family history, body weight and sleep duration were significantly different in the case group. The M/M, M/V genotypes and M allele at the M129V of PRNP gene could increase the risks of FFI, indicating that carrying 129M/M and 129M/V genotypes were more likely to suffer from FFI than those with 129V/V genotype. The M/M genotype in M129V was significantly correlated with the natural history, disease progression, neurological and pathological changes, loss of weight, electroencephalogram abnormality and sleep time. Multivariate logistic regression analysis indicated that the M/M, M/V genotypes at M129V of PRNP gene, FFI family history, body weight loss and sleep duration < 3 h were all risk factors of FFI. Additionally, VE haplotype might be a potential protective haplotype for FFI (OR = 0.293, 95% CI = 0.093~0.919). These results collectively indicated that the PRNP M129V polymorphisms may be associated with the incidence of FFI.

Keywords: Prion protein gene, polymorphism, fatal familial insomnia, incidence, M129V, E219K, association

Introduction

In 1986, fatal familial insomnia (FFI) was systematically introduced for the first time. So far, nearly 100 cases of this disease have been reported abroad in almost 40 families [1]. However, it's until 2004 that the first account of a Chinese family with FFI was recorded in China [2]. FFI is an autosomal dominant heredopathy and the common clinical characteristics of FFI are like dysautonomia, motor signs and disordered sleep-wake cycle [3, 4]. FFI equally affects both sexes. The mean age at onset of FFI is about 50 years and the disease duration usually varies from 8 to 72 months [5]. It has been reported that FFI is a type of genetic human prion disease or human transmissible spongiform encephalopathies (TSE), which is usually caused by a missense mutation at D178N of prion protein gene (PRNP) polymorphism M129V [6, 7].

PRNP is a kind of endogenous cellular prion protein. It is located on chromosome 20p12.3 in human being and can encode a 253-amino acid protein [8]. PRNP is the main component of prion agents and it can fold into different conformations which are thermodynamically stable [9]. PRNP can usually promote cell proliferation and inhibit apoptosis, and is associated with neurodegenerative disease and TSEs [10-12]. PRNP mutations are correlated with multiple clinical and neuropathological phenotypes, including FFI [13]. In human, the M129V prion protein polymorphism has been associated with neurodegenerative disease develop-

ment and severity [10]. The interaction between pathogenic mutation and polymorphism at the codon 129 can also take an effect in modifying the disease phenotype in familial prion diseases like FFI [14]. E219K is another important factor influencing the incidence of FFI in PRNP gene [15]. And study has indicated that glutamic acid (E)/lysine (K) at codon 219 and methionine (M)/valine (V) at codon 129 are normally occurring polymorphisms of PRNP gene [16]. In spite of some studies on the correlation of PRNP gene polymorphisms with M129V and E219K [17, 18], there is little study on the specific mechanism of PRNP gene polymorphisms on FFI. Therefore, in order to further understand the genetic characteristics, family characteristics and the incidence of FFI, this study targets to explore the association between PRNP gene polymorphisms and FFI on the basis of previous studies, with hope to provide a new sight for a better and early diagnosis of FFI.

Materials and methods

Ethics statement

This study was approved by the Ethics Committee of the First Hospital of Jilin University and in accordance with the standards of the National Research Council. Informed consent was obtained from each patient, or guardians prior to study.

Research subjects

From January 2000 to January 2014, 20 patients diagnosed with FFI in the First Hospital of Jilin University were selected as the case group, including 9 males and 11 females with mean age of 38 (38 ± 10) years. All patients were in line with the FFI diagnostic criteria proposed by Gambetti at. al in 1993 [19], including: (1) patients with autosomal dominant inheritance, with onset of disease occurring in adulthood and duration of 6~32 months; (2) patients with clinical manifestations including insomnia (sleeping pills were unhelpful), memory impairment, autonomic dysfunction, ataxia, myoclonus, pyramidal sign or syndromes; (3) patients with sleep electroencephalogram (EEG) decreased or disappeared; (4) patients with low metabolism firstly appearing at the thalamus examined by 18F positron emission tomography (PET) at disease onset; (5) patients who suffered from atrophy firstly appearing at thalamus. If patients met two or more of the 5 items, they were diagnosed as FFI patients. Pathologic features were as follows: patients already had 6 months of disease duration before hospital admission, having family members with the same disease and in compliance with the characteristics of autosomal dominant inheritance; at the onset of disease, patients slept no more than 4 h every day, and later they showed mental disorder and abnormal sleep behavior at night; in the course of the disease, they received a variety of drug therapies and even neurasthenia treatment, but all were ineffective; in patients' family, some members suffered from the similar symptoms. At the same time, 40 healthy persons were selected as the control group. There was no difference in age and gender ratio between the case and control groups. The clinical information of all the study subjects was available in detail.

Screening of the single nucleotide polymorphism (SNP) of PRNP gene

Based on the genomic data of Chinese Han population in HapMap, this study tried to screen the functional mutation sites of PRNP gene in the way of literature review, and searching for Tag-SNP and FAST SNP. At last, M129V and E219K were identified as the polymorphic sites that were detected in this study.

Case investigation and laboratory examination

Epidemiological case investigation was coducted in the patients confirmed with FFI, including age, gender, family history of disease, autosomes, natural history and disease progression, etc. Venous anticoagulant blood samples were collected from FFI patients and healthy subjects to detect the gene polymorphism of PRNP codons 129 and 219. All patients and healthy people underwent the following pathological examinations: blood, cerebrospinal fluid and electrophysiological examination (by EEG and polysomnography), sleep disorders, vegetative dystonia, movement dysfunction, thalamic atrophy and cortical changes, as well as weight, sleep patterns and sleep time.

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)

Peripheral blood (5 ml) was extracted from all subjects, and then anti-coagulated with ethylenediaminetetraacetic acid (EDTA) and preserved at 4°C. The whole-blood DNA kit was used for extraction of peripheral blood leuko-

Table 1. Baseline characteristics of the subjects between the case and control groups

Item	Case group (n = 20)	Control group (n = 40)	*P*
Age			0.412
< 40	12 (60.0)	18 (45.0)	
≥ 40	8 (40.0)	22 (55.0)	
Gender			0.575
Male	9 (45.0)	14 (35.0)	
Female	11 (55.0)	26 (65.0)	
Family history			< 0.001
Yes	15 (75.0)	0 (00.0)	
No	5 (25.0)	40 (100.0)	
Weight status*			< 0.001
Normal	7 (35.0)	40 (100.0)	
Loss	13 (65.0)	0 (00.0)	
Sleep duration			< 0.001
< 3 h	13 (65.0)	2 (5.0)	
≥ 6 h	7 (35.0)	38 (95.0)	

Notes: *, based on the Chinese criteria for adult body mass index, 18.5 kg/m^2 < body mass index < 24.0 kg/m^2 is normal and 18.5 kg/m^2 refers to weight loss.

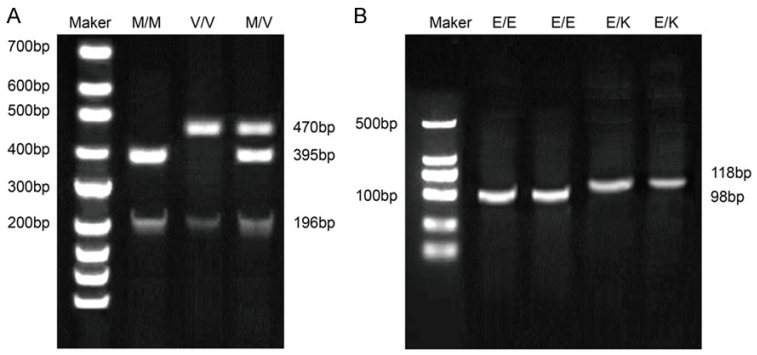

Figure 1. 19E/K heterozygo Enzyme electrophoresis results of M129V and E219K. Notes: Panel A, enzyme electrophoresis map of M129V: at 395 bp, 75 bp, 196 bp, there are bands of M/M genotype; at 470 bp and 196 bp fragments, there are bands of V/V genotype; at 470 bp, 395 bp, 75 bp, 196 bp fragments, there are bands of M/V heterozygotes; the 75 bp is not shown in the electrophoresis due to the small molecular weight; Panel B, enzyme electrophoresis map of E219K: 118 bp fragment is digested into two short fragments, 20 bp and 98 bp; if the 219 residue mutates to Lys, there is no enzyme cutting site but two genotypes 2te and 219E/E homozygote, as shown in the bands.

cyte genomic DNA which was preserved in a refrigerator at -20°C for later use. Primers for polymerase chain reaction (PCR) amplification were synthesized by Shanghai Invitrogen Biotechnology Co, Ltd (Shanghai, China). The forward primer sequence of M129V gene was 5'-GGCAAACCTTGGATGCTGG-3 and the reverse primer sequence was 5'-CCCACTATCAGGAAGATGAGG-3. The forward primer sequence of E-219K gene was 5-TGATACCATTGCTATGCACTCATTC-3 and the reverse primer sequence was 5-GACACCACCACTAAAAGCGCTGCAG-3. The volume of PCR amplification reaction system was 50 μL (10 × PCR buffer 5 μL), containing 4 μL of 2.5 nmol/L dNTPs, forward and reverse primers 1 μL respectively, 0.5 μL of TaqDNA polymerase (Takara Holdings Inc., Kyoto, Japan), 3 μL of template DNA, and 35.5 μL of ddH_2O (adding to 50 μL). Reaction conditions for M129V were a total of 30 cycles of predenaturation for 4 min at 94°C, denatuation for 30 s at 94°C, annealing for 45 s at 58.5°C, and reaction for 1 min at 72°C, and at last extending for 10 min at 72°C as the end of reaction. On the other hand, the reaction conditions for E210K were a total of 30 cycles of pretailed P < 0.05 was considered statistically different.

Results

Baseline characteristics of the subjects between the case and control groups

This study included 20 FFI patients and 40 healthy peple without history of FFI. There were no significant differences in age and gender between the case and control groups (both P > 0.05). However, the two groups showed significant differences in family history, body weight, and sleep duration (all P < 0.05) (**Table 1**).

Enzyme electrophoresis results of M129V and E219K

If Met was the amino acid residue at the 129 site, the PRNP gene had two enzyme cutting

Table 2. M/M, M/V genotypes and M allele at the M129V of PRNP increase the risks of FFI

Genotype/allele	Case group (n = 20)	Control group (n = 40)	RR (95% CI)	*P*
M129V				
V/V	0 (00.0)	10 (25.0)	Ref.	
M/V	4 (20.0)	2 (5.0)	3.000 (0.967~9.304)	0.008
M/M	16 (80.0)	28 (70.0)	1.571 (1.257~1.965)	0.024
M/M + M/V	20 (100.0)	30 (27.5)	1.667 (1.329~2.090)	0.023
Allele V	4 (10.0)	22 (26.3)	Ref.	
Allele M	36 (90.0)	58 (72.5)	1.371 (1.091~1.724)	0.034
E219K				
E/E	16 (80.0)	37 (92.5)	Ref.	
E/K	2 (10.0)	2 (5.0)	1.396 (0.516~3.781)	0.584
K/K	2 (10.0)	1 (2.5)	2.094 (0.418~10.480)	0.239
E/K + K/K	4 (20.0)	3 (7.5)	1.629 (0.680~3.903)	0.208
Allele E	34 (85.0)	76 (95.0)	Ref.	
Allele K	6 (15.0)	4 (5.0)	1.727 (0.800~3.729)	0.082

Note: FFI, fatal familial insomnia; RR, relative risk; CI, confidence interval; PRNP, prion protein gene.

sites, one at the 129 residue site and the other at the 154 residue site, and there were three small DNA fragments, namely, 395 bp, 75 bp, and 196 bp. If Val was the amino acid residue at the 129 site, the PRNP gene had only one enzyme cutting site, the 154 residue site, and DNA was digested into 470 bp and 196 bp fragments. Therefore, the products of enzyme digestion can determine M129V genotypes by electrophoresis as follows: 395 bp, 75 bp, 196 bp were 129M/M genotype, 470 bp and 196 bp fragments were 129V/V wild type homozygotes, and 470 bp, 395 bp, 75 bp, 196 bp fragments were 129M/V heterozygotes; the 75 bp was not shown in the electrophoresis due to the small molecular weight (**Figure 1A**). A product of 118 bp was obtained by PCR amplification of E219K. After introducing a mismatched base into the primer, if the 219 residue was Gul, there was one Bswi I enzyme cutting site and 118 bp fragment was digested into two short fragments, 20 bp and 98 bp; if the 219 residue mutated to Lys, there was no enzyme cutting site and two genotypes 219E/K heterozygote and 219E/E homozygote were obtained (**Figure 1B**).

M/M, M/V genotypes and M allele at the M129V of PRNP increase the risks of FFI

In the case and control groups, when M/M + M/V genotype and V/V genotype were compared, we found that M/M and M/V genotype at the M129V site were related to the occurrence of FFI (M/M vs. V/V: RR = 1.571, 95% CI = 1.257~1.965, P < 0.05; M/V vs. V/V: OR = 3.000, 95% CI = 0.967~9.304, P < 0.05), and that M allele at the M129V site was also associated with the occurrence of FFI (M vs. V: OR = 1.371, 95% CI = 1.091~1.724, P < 0.05). The results indicated that individuals carrying 129M/M and 129M/V genotypes were more susceptible to FFI than individuals carrying 129V/V genotype (both P < 0.05). There was no significant difference in the frequency distribution of E219K genotypes and allele between the case and control groups (both P > 0.05) (**Table 2**). Taken together, M/M, M/V genotypes and M allele at the M129V of PRNP could increase the risks of FFI.

M/M genotype in M129V is correlated with clinicopathological characteristics of FFI patients

Different genotypes of M129V and E219K have different impacts on the clinicopathological characteristics of FFI patients. The M/M genotype at M129V site was significantly correlated with the natural history of disease, the progression of the disease, neurological and pathological changes, the loss of weight, EEG abnormality and sleep time (all P < 0.05), but was not associated with gender, age and sleep mode (all P > 0.05). Besides, neither M/V + V/V genotype at the 129 site nor E219K gene was significantly correlated to clinical pathological features of the patients (all P > 0.05) (**Table 3**).

Table 3. M/M genotype in M129V is correlated with clinicopathological characteristics of FFI patients

Factors	M129V (n = 20)		*P*	E219K (n = 20)		*P*
	M/M	V/V + M/V		E/E + E/K	K/K	
Gender			0.591			1.000
Male	8 (50.0)	1 (25.0)		8 (44.4)	1 (50.0)	
Female	8 (50.0)	3 (75.0)		10 (55.6)	1 (50.0)	
Age			1.000			0.495
< 40	10 (62.5)	2 (50.0)		10 (55.6)	2 (100.0)	
≥ 40	6 (37.5)	2 (50.0)		8 (44.4)	0 (0.0)	
Natural history of disease*			0.014			0.147
Long	12 (75.0)	0 (0.0)		12 (66.7)	0 (0.0)	
Short	4 (25.0)	4 (100.0)		6 (33.3)	2 (100.0)	
Disease progression			0.026			1.000
Rapid	11 (68.8)	0 (0.0)		10 (55.6)	1 (50.0)	
Slow	5 (31.2)	4 (100.0)		8 (44.4)	1 (50.0)	
Neurological changes			0.026			1.000
Dyssomnia + vegetative dystonia	11 (68.8)	0 (0.0)		10 (55.6)	1 (50.0)	
Movement dysfunction	5 (31.2)	4 (100.0)		8 (44.4)	1 (50.0)	
Pathological changes			0.026			1.000
Thalamic atrophy	11 (68.8)	0 (0.0)		10 (55.6)	1 (50.0)	
Cortical changes	5 (31.2)	4 (100.0)		8 (44.4)	1 (50.0)	
Weight loss#			0.007			0.110
Yes	13 (81.3)	0 (0.0)		13 (72.2)	0 (0.0)	
No	3 (18.8)	4 (100.0)		5 (27.8)	2 (100.0)	
EEG abnormality			0.026			0.190
Yes	11 (68.8)	0 (0.0)		11 (61.1)	0 (0.0)	
No	5 (31.3)	4 (100.0)		7 (38.9)	2 (100.0)	
Sleep mode change#			0.549			1.000
Yes	12 (75.0)	2 (50.0)		12 (66.7)	2 (100.0)	
No	4 (25.0)	2 (0.0)		6 (33.3)	0 (0.0)	
Sleep duration			0.007			1.000
< 3 h	13 (81.3)	0 (0.0)		12 (66.7)	1 (50.0)	
≥ 6 h	3 (18.8)	4 (100.0)		6 (33.3)	1 (50.0)	

Note: *, natural history of disease > 14 months is considered long, while natural history of disease ≤ 14 months is considered short; #, weight loss > 5% refers to the appearance of weight loss, while weight loss ≤ 5% refers to normal weight; #, non-rapid eye movement sleep accounting for 75% of the total sleep time and rapid eye movement sleep accounting for 25% refer to no change in sleep mode; FFI, fatal familial insomnia; EEG, electroencephalogram.

FFI family history, body weight loss and sleep time < 3 h are independent risk factors for FFI

Multivariate logistic regression analysis was conducted with FFI as the dependent variable and factors related to the occurrence of FFI, namely, M129V (V/V genotype/M/M + M/V genotype), FFI family history (yes/no), body weight (loss/normal) and sleep time (< 3 h/≥ 6 h) as the independent variables, and the results are shown in **Table 4**. Obviously, the M/M and M/V genotypes can increase the risk of FFI occurrence (OR = 11.849, 95% CI = 1.999~70.218, P = 0.006), and FFI family history, body weight loss and sleep time < 3 h were independent risk factors for FFI (OR = 19.692, 95% CI = 2.259~171.636, P = 0.007; OR = 9.679, 95% CI = 1.366~68.564, P = 0.023; OR = 1.287, 95% CI = 1.022~1.621, P = 0.032).

*VE haplotype is a potential protective haplotype for FF*I

Haplotype analysis was performed to investigate the linkage disequilibrium analysis of M129V and E219K sites of PRNP. The results

Table 4. FFI family history, body weight loss and sleep time < 3 h are independent risk factors for FFI

Variables	B	S.E.	Wald	df	*p*	OR	95% CI
M129V (V/V genotype/M/M + M/V genotype),	2.472	0.908	7.415	1	0.006	11.849	1.999~70.218
FFI family history (yes/no)	2.980	1.105	7.278	1	0.007	19.692	2.259~171.636
Weight status (loss/normal)	2.270	0.999	5.164	1	0.023	9.679	1.366~68.564
Sleep duration (< 3 h/≥ 6 h)	0.252	0.118	4.583	1	0.032	1.287	1.022~1.621

Notes: FFI, fatal familial insomnia; df, degrees of freedom; B, partial regression coefficient; S.E, standard error; OR, odd ratio; CI, confidence interval.

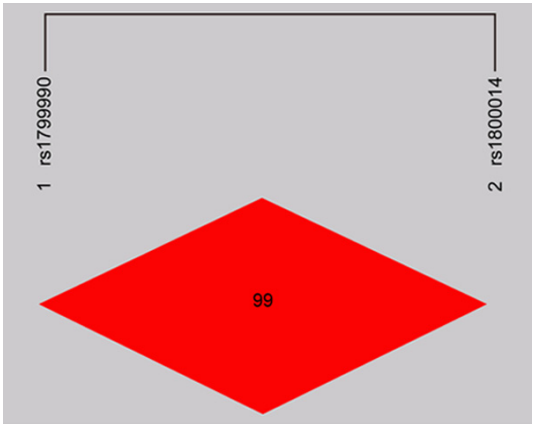

Figure 2. Haplotype analysis shows that there is strong linkage disequilibrium between M129V and E219K sites of PRNP2.

showed that there was a strong linkage disequilibrium, as shown in **Figure 2**, thus haplotype analysis could be performed. SHEsis online software (http://analysis.bio-x.cn/myAnalysis.php) was used to analyze the haplotypes of M129V and E219K sites of PRNP, and to eliminate the genotypes with a frequency of less than 0.03 in each group. As shown in **Table 5**, the differences in VE haplotype between the case group and the control group were statistically significant (P < 0.05), which may be the protective haplotype of FFI (OR = 0.293, 95% CI = 0.093~0.919). There was no significant difference in the haplotypes of ME and MR between the case group and the control group (P > 0.05).

Discussion

FFI remains a rare health problem, which is a type of prion disorders related to the D178N prion protein mutation and determined by the 129M/V polymorphism [20]. FFI is clinically characterized by the loss of sleep, somato-motor abnormalities and oneiric stupor with autonomic or motor hyperactivity [21]. The mean age at onset of FFI patients is nearly 50 years, and patients will eventually die after 7-25 months [5, 22]. Since the FFI was discovered, human beings have devoted much to explore its pathogenesis and therapies, while no effective treatment has been found. Although studies have examined that FFI is closely linked to the clinical and pathological features of PRNP M129V polymorphism [23, 24], there is less specific analysis on the connection of M129V polymorphism and FFI. This paper explored the association between PRNP gene polymophisms and FFI in a Chinese population, which will provide some reference information and theoretical basis for the diagnosis and treatment of the disease.

In this study, it was found that the M/M, M/V genotypes and M allele in the M129V of PRNP gene could increase the risks of FFI, indicating that individuals carrying 129M/M and 129M/V genotypes were more likely to suffer from FFI than those with 129V/V genotype. A previous study reveals that the M129V of PRNP gene has been linked to the development and severity of neurodegenerative disease [10]. Lucia Monari et.al demonstrated that pathogenic mutation interacted with polymorphism at the codon 129 can play important role in modifying the disease phenotype in familial prion diseases like FFI [14]. Prion diseases are caused by misfolding of a normal host-encoded prion protein (PrPC) to pathogenic scrapie prion protein (PrPSc) [10]. The 129M/V polymorphism on the allele determines the molecular basis for the phenotypic heterogeneity [25]. Moreover, M129V can determine PrPSc conformation and alter clinicopathological phenotypes [26]. Therefore, M129V can influence the phenotype of FFI. In addition, Del Bo et al demonstrated that PRNP polymorphisms represent a susceptibility for Alzheimer's disease, with evidence that V + subjects have significantly higher levels of A-plaques than that of MM carriers,

Table 5. VE haplotype is a potential protective haplotype for FFI

Haplotype	Case (freq)	Control (freq)	Chi2	*P*	OR [95% CI]
ME	15 (0.750)	27 (0.675)	0.714	0.398	1.444 [0.614~3.397]
MR	3 (0.150)	2 (0.050)	3.491	0.062	3.353 [0.888~12.655]
VE	2 (0.100)	11 (0.275)	4.812	0.028	0.293 [0.093~0.919]

Notes: FFI, fatal familial insomnia; OR, odd ratio; CI, confidence interval.

which indirectly indicates an impaired anti-oxidant function of PrPc, and the anti-oxidant neuroprotection function of PrPc will become less effective when there is a valine residue at codon 129 [27]. Meanwhile, there was no significant difference in the frequency distribution of E219K genotypes and allele between the case and control groups, and E219K gene had no significant correlation with clinical pathological features of the patients. The clear mechanism behind that remained to be further studied in the future.

Furthermore, in this study, it was also indicated that the sleeping time of FFI patients with M/M, M/V genotypes in M129V was significantly less than those with V/V genotype, suggesting that M/M and M/V genotypes may affect the quality of sleep. Previous studies have indicated that FFI is associated with sleep duration and quality, which is consistent with this result [28, 29]. In addition, the results of logistic regression analysis indicated that the M/M, M/V genotypes in M1 29V of PRNP gene, family history, body weight and sleep duration all were risk factors of FFI. Sun L et al have reported an FFI Chinese case with Met129 genotype exhibiting progressive dementia and a family history of similar symptoms was found [24]. Gemignani et al observed in an FFI individual that the sleep slow oscillation event rate was markedly reduced [30]. Additionally, Rodríguez-Martínez et al suggested that two D178N-129M mutational events independently occurred, preserved and transmitted generation by generation until nowadays [31].

In summary, this study confirmed that PRNP gene polymorphisms are associated with increased risks of FFI. FFI is a rare hereditary prion disease, the clinical characteristics of which are similar with genetic Creutzfeldt-Jakob disease and familiar Creutzfeldt-Jakob disease [32, 33]. Therefore, it is easy to cause missed diagnosis or misdiagnosis, while the detection results of PRNP gene polymorphism are helpful to distinguish between FFI and other diseases. At present, the reported cases have not been treated successfully and the gene therapy has not yet made a breakthrough. Therefore, the earlier detection of PRNP gene polymorphism is made, the more helpful it will be for the diagnosis, treatment and prognosis of the FFI patients. This study can provide a new direction for the treatment of FFI. However, due to the various constraints, there are still some deficiencies in this study, and the mechanism of PRNP in the FFI should be further studied.

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Disclosure of conflict of interest

None.

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