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Editorial

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Creutzfeldt-Jakob Disease Susceptibility: An Approach to Discovering Multiple Candidate Genes for Human Prion Diseases

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Human prion diseases, including Creutzfeldt-Jakob disease (CJD), the most common human prion disease, are fatal neurodegenerative disorders. They are characterized by the accumulation of an abnormal prion protein (PrP^{Sc}), vacuolation, astrocytic gliosis and neuronal cell loss in the brain. CJD is classified as sporadic, infectious, or inherited. Approximately 85% of all human prion diseases are sporadic CJD, which is distributed worldwide and has an incidence rate of about one per million cases per year. The cause of sporadic CJD remains unclear. Additionally, approximately 10-15% of human prion diseases are inherited through germ-line mutations. Less than 1% is acquired by transmission.

Because the prion protein has such a crucial role in prion diseases, it is not surprising that the prion protein gene (*PRNP*) is also extremely important in these diseases. In humans, *PRNP* is located on chromosome 20 and encodes 253 amino acids. A number of mutations in the open reading frame (ORF) of *PRNP* are linked to the inherited forms of human prion diseases [1,2]. For example, polymorphisms at codons 129 and 219 of *PRNP* play an important role in conferring susceptibility or resistance to human prion diseases. In particular, a common single nucleotide polymorphism (SNP) at codon 129 has been shown to be a genetic risk factor for sporadic, iatrogenic or variant CJD in Europeans and Koreans [1,3]. Although data from Japanese patients with sporadic CJD did not confirm these findings, the statistical power of the Japanese data was limited due to small sample size [4]. Additionally, the SNP at codon 219 has been reported to be present in Asian, but not Caucasian, populations [5,6]. Heterozygosity at this SNP is protective against sporadic CJD in East Asians [3,7]. Studies of a correlation between sporadic CJD and several SNPs located outside the *PRNP* ORF, including the *PRNP*1368 SNP, in different populations, showed contradictory results [8-10].

Although the SNP at codon 129 of *PRNP* is a strong genetic factor for sporadic CJD, epidemiological data on the incidence rate of sporadic CJD and genotype frequencies at codon 129 indicate that this SNP is unlikely to be the sole genetic risk factor determining sporadic CJD susceptibility. For example, the frequencies of homozygosity for a codon 129 allele that encodes methionine (Met) are significantly different between British (37%) and Japan (93%) patients [5]; however, the annual mortality rate per million cases of sporadic CJD in the UK (mean 0.83) is similar to that rate in Japan (mean 0.66) [11,12]. In addition, inbred mouse lines that harbor the same *PRNP* amino acid sequence display major differences in prion disease incubation times after being challenged with the same scrapie strains [13]. Furthermore, quantitative trait loci (QTL) studies have identified a small number of non-*PRNP* genetic loci that affect the incubation times of prion diseases [13-15]. These results suggest that genetic factors other than the *PRNP* locus may be involved in prion diseases.

Case-control studies of genes that are structurally similar to *PRNP* or that may be related to prion diseases have been performed in European and East Asian populations to search for candidate genes that affect susceptibility to sporadic CJD. For example, the prion-like protein gene (*PRND*), shadow of prion protein (*SPRN*), cathepsin D (*CTSD*), *HECTD2*, tau, apolipoprotein E (*APOE*), beta site APP cleaving enzyme 1 (*BACE1*), calcium homoeostasis modulator 1-3 (*CALHM 1-3*), alpha1-antichymotrypsin (*ACT*), 14-3-3 eta (*YWHAH*), 14-3-3 beta (*YWHAB*) and ribosomal protein SA (*RPSA*) have been investigated [16-38]. Among these genes, different results have been obtained. Specifically, controversial results with regard to whether *PRND*, *CTSD*, *HECTD2* and *APOE* affect susceptibility to sporadic CJD in European and East Asian populations have been obtained [16-30]; SNPs in *SPRN, BACE1, CALHM 1-3* and *ACT* have been found to be moderately associated with sporadic CJD in only Europeans [31-34]; and SNPs in other genes, including tau, *YWHAH, YWHAB* and *RPSA* have not been found to affect susceptibility to sporadic CJD in Europeans or Koreans [35-38]. Additional investigations, in additional ethnicities, with large sample sizes and high statistical power, will be necessary to further evaluate the association between sporadic CJD and these genes.

Recently, genome-wide association studies (GWAS) have proven to be a powerful technique to identify genetic susceptibility factors for many diseases. In human prion diseases, including sporadic CJD, a total of three GWAS studies in European populations have been published by two groups [39-41]. In these studies, not surprisingly, strong associations of *PRNP* codon 129 with all human prion diseases were confirmed. Additionally, SNPs in the upstream regions of retinoic acid receptor β (*RARB*) and SCG10 protein (*STMN2*) [39] genes, the intronic regions of the myotubularin related protein 7 (*MTMR7*) and neuronal PAS (per-AENT-sim) domain-containing protein 2 gene (*NPAS2*) genes [41], and the *ZBTB38-RASA2* locus and *CHN2* gene [40] were associated with variant CJD. Additionally, the SNP in the *ZBTB38-RASA2* locus was associated with sporadic CJD in Brits but not in Germans [40]. Because SNPs can differ between Asian and European populations [42], GWAS studies in Asian populations need to be performed. Such studies may both confirm GWAS data in European populations and, through the use of Asian-optimized SNP arrays, lead to the discovery of new prion disease-related candidate genes [43]. However, despite the advantages of GWAS tools, such as the genotyping of approximately a million SNPs in a single step, GWAS studies generally exclude rare SNPs, i.e., those with allele frequencies of less than 5%. Hence, case-control studies for rare SNPs that may confer disease susceptibility may continue to identify candidate genes for human prion diseases.

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