Prion Protein *(PRNP)* Genotypes in Frontotemporal Lobar Degeneration Syndromes

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The common polymorphism of the human prion protein gene *(PRNP)* at codon 129 is known to be a strong susceptibility or modifying factor for all forms of human prion disease.[1] A number of nonprion diseases have also been proposed to associate with *PRNP* polymorphisms. Li and colleagues[2] report a strong association of this polymorphism with language syndromes in frontotemporal lobar degeneration (FTLD): codon 129 heterozygosity was present in 14 of 16 (88%) nonfluent, 5 of 5 (100%) fluent, and 14 of 18 (78%) logopenic aphasia cases, compared with a frequency of about 50% in the general UK population.

We looked at the genotypic distribution for codon 129 and single nucleotide polymorphism (SNP)-1368 (an upstream polymorphism of *PRNP* associated with sporadic Creutzfeldt–Jakob disease[3]) in 66 patients with a clinical diagnosis in the FTLD spectrum. Based on a retrospective clinical analysis by two experienced neurologists, cases were classified according to current consensus criteria as behavioral or frontal variant FTLD, progressive nonfluent aphasia, progressive fluent aphasia/semantic dementia,[4] frontotemporal dementia with motor neuron disease, or corticobasal degeneration syndrome (Table). Cases with known genetic mutations were excluded. Codon 129 and SNP-1368 genotypes were determined by allelic discrimination using an SDS7000 (Applied Biosystems, Foster City, CA) instrument. Pearson's χ^2 and odds ratio were calculated with SPSS (SPSS, Chicago, IL).

We found no significant associations between genotype or allele frequency at codon 129 or SNP-1368 for the FTLD group as a whole or for individual FTLD syndromes (see the Table). The codon 129 heterozygous–homozygous genotype odds ratio for FTLD was 0.67 (95% confidence interval, 0.40–1.13). These data do not support an association between *PRNP* genotype and FTLD diagnosed by consensus clinical criteria. Possible bases for discrepancy between different series include relatively small sample sizes for uncommon diseases, inclusion of clinically atypical codon 129 heterozygous cases of prion disease, or regional variation in other unidentified genetic or epigenetic factors. These considerations underscore the need for multicenter prospective analyses and pathological correlation with clinical and genotypic data.

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Table. Genotype Table of PRNP Codon 129 and Upstream of PRNP Single Nucleotide Polymorphism 1368 in 66 Patients with Frontotemporal Lobar Degeneration and a Large Sample Representative of the Healthy UK Population

	Codon 129 Genotype, % (n)[a]			SNP-1368 Genotype, % (n)[b]		
Group (n)	MM	MV	VV	CC	CT	TT
fvFTLD (29)	52 (15)	38 (11)	10 (3)	28 (8)	48 (14)	24 (7)
PNFA (5)	40 (2)	60 (3)	0	0	60 (3)	40 (2)
SD (19)	63 (12)	21 (4)	16 (3)	21 (4)	53 (10)	26 (5)
FTD-MND (6)	50 (3)	33 (2)	17 (1)	0	50 (3)	50 (3)
CBD (7)	29 (2)	71 (5)	0	0	71 (5)	29 (2)
All (66)	52 (34)	38 (25)	11 (7)	18 (12)	53 (35)	29 (19)
UK control subjects (566)	42 (238)	48 (270)	10 (58)	18 (101)	49 (277)	33 (188)

[a]All versus UK control χ^2, $p = 0.29$ (2df).

[b]All versus UK control χ^2, $p = 0.76$ (2df).

SNP = single nucleotide polymorphism; fvFTLD = frontal variant frontotemporal lobar degeneration; PNFA = progressive nonfluent aphasia; SD = semantic dementia; FTD-MND = frontotemporal dementia with motor neuron disease; CBD = corticobasal degeneration syndrome.

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