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The prion gene is associated with human long-term memory

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Human cognitive processes are highly variable across individuals and are influenced by both genetic and environmental factors. Although genetic variations affect short-term memory in humans, it is unknown whether genetic variability has also an impact on long-term memory. Because prion-like conformational changes may be involved in the induction of long-lasting synaptic plasticity, we examined the impact of single-nucleotide polymorphisms (SNPs) of the prion protein gene (*PRNP*) on long-term memory in healthy young humans. SNPs in the genomic region of *PRNP* were associated with better long-term memory performance in two independent populations with different educational background. Among the examined *PRNP* SNPs, the common Met129Val polymorphism yielded the highest effect size. Twenty-four hours after a word list-learning task, carriers of either the 129^{MM} or the 129^{MV} genotype recalled 17% more information than 129^{VV} carriers, but short-term memory was unaffected. These results suggest a role for the prion protein in the formation of long-term memory in humans.

INTRODUCTION

Human memory is a heritable and polygenic behavioral trait. Converging evidence from twin studies suggests that ~50% of the interindividual variability in memory capacity is attributable to genetic factors (1,2). However, very little is known about the identity of the underlying genes and whether different parts of this cognitive ability, such as short-term and long-term memory, share common genetic factors or are genetically distinct. Recently, naturally occurring and functionally relevant genetic variations (single-nucleotide polymorphisms, SNPs) in the genes encoding the serotonin 2a receptor (*HTR2A*) and the brain-derived neurotrophic factor (*BDNF*) were found to influence medial temporal lobe (MTL)-dependent short-term memory capacity in healthy human subjects (3,4).

In contrast to short-term memory, long-term memory (i.e. the ability to retain information for several hours, days and even years) depends on *de novo* protein synthesis and on long-term changes in the molecular components of the neuronal synapse (5). However, little is known about the cell biology and molecular mechanisms that initiate and maintain these structural changes. Recent experiments in yeast and *Aplysia* suggest that a prion-like protein switch might help to maintain long-term synaptic changes required for the formation of long-term memory. Specifically, it has been shown that a neuronal isoform of the cytoplasmic polyadenylation element binding protein (CPEB) regulates local protein synthesis and stabilizes synapse-specific long-term facilitation in *Aplysia* (6). In addition, *Aplysia* CPEB has prion-like properties when expressed in yeast and it is the self-perpetuating prion-like form of CPEB that has the capacity to activate translationally dormant mRNA (7). These studies led to the radically new notion that prion-like conformational changes may be a key event for the maintenance of structural synaptic changes underlying long-term memory. If the conversion of proteins into a self-perpetuating state represents a mechanism for long-term memory storage, genes encoding proteins with prion-like properties are excellent candidates for association with human long-term memory capacity.

In humans, the only protein with well-characterized prion properties is the prion protein PrP, encoded by the *PRNP* gene on the short arm of chromosome 20. *PRNP* is polymorphic with intronic, 5′- and 3′-UTR SNPs as well as a

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common methionine/valine polymorphism at codon 129 (M129V), which modulates the folding behavior of the protein (8,9) and controls susceptibility to prion diseases (10). Human genetic variation is often organized into population-specific haplotype blocks, i.e. areas of the genome with substantial correlations among neighboring alleles (11). In populations of Caucasian origin, genetic variability of *PRNP* is represented by a haplotype block spanning ~25 kb including the M129V SNP (www.celera.com). On the basis of the recent experimental observations related to the mechanisms of long-term memory formation (6,7), we hypothesized that human genetic variability of *PRNP* might be related to long-term memory and, therefore, investigated the influence of polymorphic sites within *PRNP* on memory capacity in 354 healthy young subjects (Table 1).

RESULTS

Influence of *PRNP* SNPs on human long-term memory

All investigated SNPs in the genomic region of *PRNP* ($n = 3$) were significantly associated with long-term memory performance (free recall 24 h after learning; logistic regression analysis) (Fig. 1), whereas none was associated with short-term memory (free recall immediately or 5 min after learning). The M129V polymorphism displayed the highest level of significance ($P = 0.001$, Fig. 1 and Table 2). To improve the estimation of the type I statistical error, we performed permutation analysis and used Monte Carlo simulations in addition to the logistic regression analysis. The association remained significant both after 50 000 permutations and Monte Carlo simulations (100 000 random samplings; $P = 0.006$ for both methods). Although the three *PRNP* SNPs were tightly linked [For multi-locus linkage disequilibrium (LD) $P \leq 0.00001$], extended haplotype analysis did not increase the significance. In addition, the 5′-UTR SNPs failed to show any association with long-term memory performance when statistically controlled for the effect of the M129V polymorphism. Conversely, the significant effect of the M129V polymorphism was not affected when controlled for the 5′-UTR SNPs. Therefore, we conclude that the M129V polymorphism accounted fully for the association of the *PRNP* region with long-term memory. The significant effect of the M129V polymorphism on long-term memory performance was present in both the academic group ($n = 240$; $P = 0.006$) and the non-academic group ($n = 114$; $P = 0.05$; Table 2). Analysis of covariance showed that subjects homozygous or heterozygous for the 129^{M} variant exhibited 17% better memory performance in the 24 h recall than valine homozygotes (Fig. 2, Tables 3 and 4). Importantly, values for 24 h recall performance in each of the genotype strata were normally distributed ($P > 0.1$). Forward and backward logistic regression analyses in the entire sample revealed that, besides the M129V polymorphism, 5 min delayed recall performance and gender significantly influenced long-term memory performance (Table 2). Exclusion of these covariates from the regression model did not influence the effect of the M129V polymorphism on long-term memory. Importantly, immediate and 5 min delayed recall were not affected by the M129V polymorphism (Table 3), indicating that the genotype-dependent differences in 24 h recall are unlikely to be caused by confounding factors such as motivation or attention.

Exclusion of nearby genomic loci

Next, we investigated whether the observed association of the M129V SNP with long-term memory was due to linkage disequilibrium with a nearby genetic variation. In the 3′ flanking region of *PRNP*, we analyzed the T174M substitution of the *PRND* gene, which is located 25 kb 3′ to the M129V SNP and encodes the PrP homologue doppel (Fig. 1). Twenty five kilobases 5′ to the M129V SNP we analyzed SNP rs1029273 which has been previously shown to confer susceptibility for sporadic Creutzfeldt-Jakob disease (CJD) independently of the M129V polymorphism (12). Consistent with existing data in the populations of Caucasian origin (www.celera.com), the three *PRNP* SNPs and the 5′-flanking SNP rs1029273 were part of a haplotype block in our study population (multi-allelic $D' = 0.82$, $P < 0.000001$) with the *PRNP* SNPs exerting the highest LD values. The T174M SNP of *PRND* was not part of the haplotype ($D' = 0.05$, $P = 0.4$). Of note, none of the examined SNPs deviated from Hardy-Weinberg equilibrium ($P \geq 0.2$). Neither T174M nor rs102973 showed significant association with long-term memory performance (Fig. 1 and Table 3). Therefore, we conclude that the codon 129 polymorphism fully accounts for the association between the *PRNP* locus and long-term memory.

Exclusion of non-random genetic heterogeneity

Association studies in outbred populations such as the present one may be prone to false-positivity because non-random genetic heterogeneity within the study sample (i.e. population structure) can lead to spurious associations between a candidate marker and a phenotype (13). Therefore, we calculated the structure of genetic heterogeneity in our study population by genotyping each subject for 318 SNPs located in both genic and non-genic regions and distributed over all autosomes. Structured association analysis (14) revealed a low allele-frequency divergence in our population (Kullback-Leibler distance = 0.23). The individual genetic background values were normally distributed ($P = 0.6$, Fig. 3). Ten subjects were identified as outliers (i.e. beyond the 25 or 75% limits of the normal distribution curve). Importantly, our findings remained unchanged after exclusion of these subjects from the statistical analyses. In addition, we included each subject's genetic background value as a covariate in each analysis. Again, the results remained unchanged. Therefore, we conclude that the significant association of the M129V SNP with long-term memory is independent of the observed genetic heterogeneity levels of our population.

DISCUSSION

The present study shows that *PRNP* is genetically associated with human long-term memory performance. SNP-mapping within the *PRNP* locus and extended haplotype analysis revealed that the observed association is caused by the M129V SNP of *PRNP*. Other possibilities such as adjacent

Table 1. Demographic and behavioral data of the study population

	Entire sample, $n = 354$	Students, $n = 240$	Trainees, $n = 114$	Females, $n = 244$	Males, $n = 110$
Gender (females)	244 (69%)	169 (70%)	75 (66%)	—	—
Education (students)	240 (68%)	—	—	169 (69%)	71 (65%)
Age (years ± SE)	23 ± 0.2	23 ± 0.3	22 ± 0.2	23 ± 0.2	23 ± 0.5
Immediate free recall (words ± SE)	24.0 ± 0.2	24.4 ± 0.2[a]	23.2 ± 0.4[a]	24.1 ± 0.2	23.8 ± 0.3
5 min free recall (words ± SE)	8.8 ± 0.2	9.2 ± 0.2[b]	7.9 ± 0.3[b]	9.2 ± 0.2[c]	7.9 ± 0.3[c]
24 h free recall (words ± SE)	7.6 ± 0.2	8.0 ± 0.2[d]	6.8 ± 0.3[d]	8.0 ± 0.2[b]	6.6 ± 0.3[b]
129^{MM} genotype (n, %)	159 (45)	111 (46)	48 (42)	110 (45)	49 (45)
129^{MV} genotype (n, %)	151 (43)	103 (43)	48 (42)	109 (45)	42 (38)
129^{VV} genotype (n, %)	44 (12)	26 (11)	18 (16)	25 (10)	19 (17)

Values with common superscripts are significantly different.
[a]$P = 0.004$.
[b]$P < 0.001$.
[c]$P = 0.001$.
[d]$P = 0.002$.

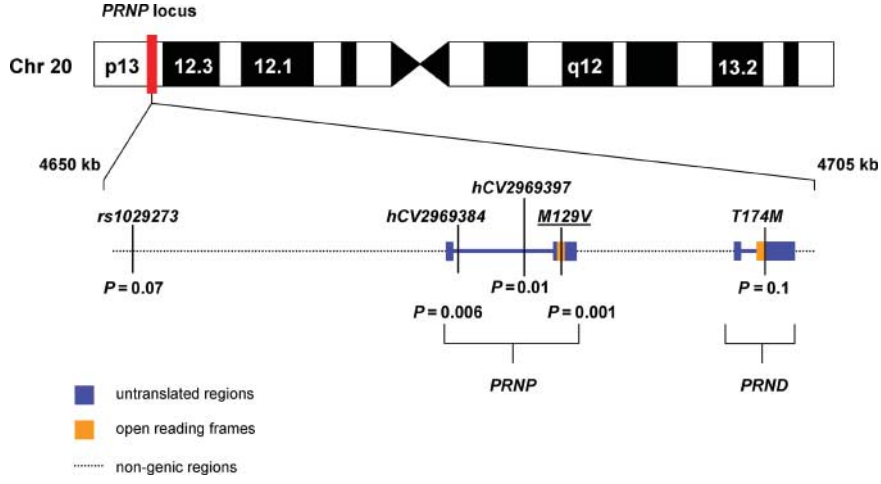

Figure 1 Genomic structure and association findings of the chromosomal region harboring the prion protein gene. *PRNP* and *PRND* (encoding prion protein and Doppel, respectively) are located on the short arm of chromosome 20 between 4660 and 4700 kb (NCBI Map Viewer, http://www.ncbi.nlm.nih.gov/mapview/). SNPs hCV2969384 and hCV2969397 (Celera database: http://myscience.appliedbiosystems.com/navigation/mysciMain.jsp) are G to C and A to G transitions, respectively, and are located within *PRNP*. SNP rs1029273 (dbSNP: http://www.ncbi.nlm.nih.gov/SNP/index.html) is a T to C transition ~25 kb 5′ to *PRNP*. The methionine to valine substitution at codon 129 of *PRNP* (M129V) is caused by a common A to G transition (rs1799990); the threonine to methionine substitution at codon 174 of *PRND* (T174M) is caused by a common C to T transition (rs2245220). All *PRNP* SNPs were significantly ($P \leq 0.01$) associated with long-term memory performance, with M129V (underlined) yielding the most significant result. T174M and rs1029273 failed to reach significant levels of association. Significances were obtained by forward and backward logistic regression analyses controlled for age, gender, education and 5 min free-recall performance. Long-term memory performance (median split) served as the dependent binary variable.

genomic loci, population structure and sampling bias were excluded. Although mechanistical explanations of genetic association findings are rather speculative and must be, therefore, treated with caution, our results do raise the question of the nature of the observed association.

In vitro experiments suggest that the 129^{M} allele results in a higher propensity of the prion protein to form beta-sheet-rich oligomers (9). Recently, transgenic mice expressing human PrP with methionine 129, but not valine 129, presented with a variant CJD-related phenotype (15). These findings indicate that the 129^{M} allele may facilitate self-perpetuating conformational changes of the human prion protein. Interestingly, our results demonstrate a beneficial effect of the 129^{M} allele on long-term memory in healthy young subjects and therefore support the hypothesis that a prion-based mechanism is involved in the formation of long-term memory.

Is the association of the *PRNP* locus with human long-term memory related to the susceptibility for prion diseases? In humans, but not in any other mammalian species (16), *PRNP* displays the common methionine/valine polymorphism at codon 129. Approximately 40% of our population was heterozygous for this polymorphism, which is in line with reports in middle European populations (17). However, 129^{MM} and 129^{VV} homozygotes are heavily over-represented in sporadic CJD and iatrogenic CJD (10). In addition, all victims of variant CJD, which is thought to result from infection with bovine prions, were found to be 129^{MM} homozygotes (18). Therefore, 129^{MV} heterozygosity appears to be protective against prion infection (10,19). We observed that the methionine allele correlated dominantly with better long-term memory, because we were unable to discern any difference between the 129^{MM} and the 129^{MV} subgroups. Therefore, the

Table 2. Variables significantly associated with long-term memory performance

Variable	Significance (P)	Odds ratio	95% CI
Entire sample, $n = 354$			
129^{M} allele	0.001	4.6	1.8–11.7
hCV2969397	0.01	4.5	1.2–16.1
hCV2969384	0.006	3.9	1.5–10.5
5 min recall performance	10^{-15}	1.9	1.6–2.2
Female gender	0.018	2.1	1.1–3.9
Students, $n = 240$			
129^{M} allele	0.006	4.8	1.6–14.4
hCV2969384	0.009	4.7	1.5–14.9
5 min recall performance	10^{-14}	1.9	1.6–2.2
Trainees, $n = 114$			
129^{M} allele	0.05	5.3	1.04–28.2
5 min recall performance	6×10^{-7}	1.9	1.5–2.4

Significances, odds ratios and 95% confidence intervals (CI) of odds ratios were obtained by forward and backward logistic regression analysis. Long-term memory performance (median split) served as the dependent binary variable.

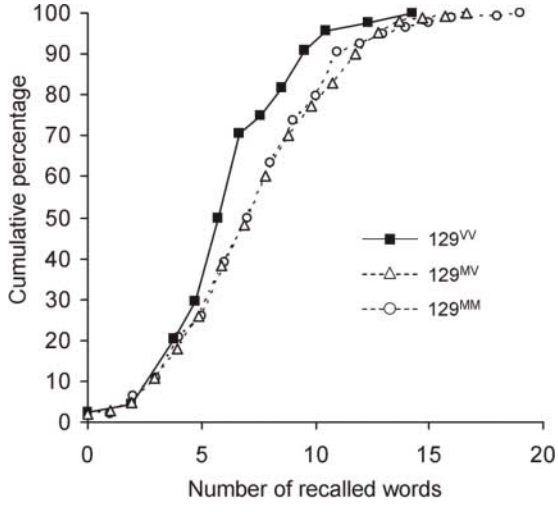

Figure 2 Better long-term memory performance in 129^{MM} and 129^{MV} carriers. The figure shows the cumulative percentage of study subjects with increasing long-term memory performance (number of freely recalled words 24 h after presentation of a word list). The curves of 129^{MM} carriers ($n = 159$) and of 129^{MV} carriers ($n = 151$) are essentially identical. 129^{VV} carriers ($n = 44$) have significantly ($P = 0.001$) lower long-term memory performance than 129^{MM} and 129^{MV} carriers, as indicated by the left shift of the corresponding curve.

association of the *PRNP* locus with human long-term memory seems to be unrelated to the susceptibility for prion diseases.

Although prions were originally described as transmissible pathogens (20), the induction of a self-perpetuating conformational change within populations of cellular proteins does not always need to be deleterious (21). For example, the *Podospora anserina* prion, Het-S, may confer a selection advantage to its host (22). Also, the Sup35 translational termination factor may act as a useful evolutionary buffer for infected yeast (23). Finally, the CPEB protein which is involved in the maintenance of long-term synaptic changes (6) has been shown to possess prion-like properties when expressed in yeast (7). One might therefore speculate that the impact of PrP variants on long-term memory in healthy humans is related to physiologically occurring conformational changes (24).

Table 3. Influence of *PRNP* and adjacent polymorphisms on distinct memory phases

Polymorphism	Immediate recall	5 min recall	24 h recall
T174M			
C/C, $n = 92$	24.2 ± 0.5	8.7 ± 0.4	7.3 ± 0.3
C/T, $n = 171$	23.5 ± 0.3	8.2 ± 0.3	7.4 ± 0.2
T/T, $n = 85$	23.5 ± 0.5	8.3 ± 0.4	7.5 ± 0.3
M129V			
129^{MM}, $n = 159$	23.7 ± 0.3	8.2 ± 0.3	7.6 ± 0.2^{a}
129^{MV}, $n = 151$	23.6 ± 0.3	8.4 ± 0.3	7.6 ± 0.2^{b}
129^{VV}, $n = 44$	24.4 ± 0.5	8.9 ± 0.5	$6.5 \pm 0.3^{a,b}$
hCV2969397			
A/A, $n = 192$	24.1 ± 0.3	8.2 ± 0.3	7.6 ± 0.2^{b}
A/G, $n = 134$	23.2 ± 0.3	8.4 ± 0.3	7.4 ± 0.2^{c}
G/G, $n = 23$	24.2 ± 0.8	9.7 ± 0.8	$6.0 \pm 0.5^{b,c}$
hCV2969384			
G/G, $n = 171$	24.0 ± 0.3	8.0 ± 0.3	7.5 ± 0.2
G/C, $n = 143$	23.6 ± 0.3	8.7 ± 0.3	7.6 ± 0.2
C/C, $n = 39$	23.8 ± 0.7	8.5 ± 0.6	7.0 ± 0.4
rs1029273			
T/T, $n = 118$	23.5 ± 0.4	8.6 ± 0.3	7.3 ± 0.2
T/C, $n = 159$	23.7 ± 0.3	8.3 ± 0.3	7.5 ± 0.2
C/C, $n = 62$	23.7 ± 0.5	8.5 ± 0.5	7.7 ± 0.3

Means with common superscripts are significantly different. Significances were obtained by multiple analysis of covariance controlled for gender, education (both binomial, categorical variables), age and 5 min recall (both continuous variables). Data (number of recalled words) are means $\pm$ SE.
[a]$P = 0.004$.
[b]$P = 0.006$.
[c]$P = 0.01$.

Taken together, the human prion protein is genetically associated with long-term memory. Further evaluation of the biological consequences of the M129V polymorphism in neurons will help elucidate the molecular mechanisms underlying this association.

MATERIALS AND METHODS

Study subjects and memory testing

Memory testing and genotyping were done in a total of 354 healthy young Swiss subjects [244 females, 110 males; mean age 23 ± 0.2 (standard error)]. This population consisted of two independently recruited and tested groups of 240 university students and 114 non-academic employees/trainees (Table 1). After complete description of the study to the subjects, written informed consent was obtained. The ethics committee of the Canton of Zurich, Switzerland approved the study protocol.

Memory capacity was tested during two consecutive days. On the first day, subjects viewed six series of five semantically unrelated nouns presented at a rate of one word per second with the instruction to learn the words for immediate free recall after each series. In addition, subjects underwent an

Table 4. Influence of *PRNP* and adjacent polymorphisms on long-term memory (24 h free recall of words) in the entire sample and the two subsamples

Polymorphism	Entire sample, $n = 354$	Students, $n = 240$	Trainees, $n = 114$
T174M			
C/C	7.3 ± 0.3	8.0 ± 0.3	6.5 ± 0.5
C/T	7.4 ± 0.2	8.0 ± 0.2	6.8 ± 0.3
T/T	7.5 ± 0.3	7.8 ± 0.3	7.1 ± 0.5
M129V			
129^{MM}	7.6 ± 0.2^{a}	8.1 ± 0.2^{b}	6.9 ± 0.3^{c}
129^{MV}	7.6 ± 0.2^{d}	8.1 ± 0.2^{e}	7.0 ± 0.2^{b}
129^{VV}	$6.5 \pm 0.3^{a,d}$	$7.1 \pm 0.4^{b,e}$	$5.6 \pm 0.3^{b,c}$
hCV2969397			
A/A	7.6 ± 0.2^{d}	8.0 ± 0.2	6.8 ± 0.3^{e}
A/G	7.4 ± 0.2^{f}	7.8 ± 0.2	6.9 ± 0.3^{b}
G/G	$6.0 \pm 0.5^{d,f}$	7.6 ± 0.5	$4.8 \pm 0.9^{e,b}$
hCV2969384			
G/G	7.5 ± 0.2	8.0 ± 0.2	6.8 ± 0.4
G/C	7.6 ± 0.2	8.2 ± 0.2^{g}	6.8 ± 0.3
C/C	7.0 ± 0.4	7.1 ± 0.4^{g}	6.4 ± 0.7
rs1029273			
T/T	7.3 ± 0.2	7.7 ± 0.2	6.7 ± 0.4
T/C	7.5 ± 0.2	8.1 ± 0.2	6.7 ± 0.3
C/C	7.7 ± 0.3	8.1 ± 0.3	7.1 ± 0.5

Means with common superscripts are significantly different. Significances were obtained by multiple analysis of covariance controlled for gender, education (both binomial, categorical variables), age and 5 min recall (both continuous variables). Data (number of recalled words) are means $\pm$ SE.
[a]$P = 0.004$.
[b]$P = 0.03$.
[c]$P = 0.05$.
[d]$P = 0.006$.
[e]$P = 0.04$.
[f]$P = 0.01$.
[g]$P = 0.02$.

unexpected delayed free-recall test of the learned words after 5 min and again after 24 h. Both delayed recall tests reflect episodic memory (25). In contrast to the 5 min recall, the 24 h recall additionally requires long-term synaptic changes (5). To control for type I statistical error and for effects of educational level on memory, we recruited two independent populations of either university students (academic group) or non-academic employees/trainees (non-academic group).

Blood collection and genotyping

We collected 18 ml blood (2×9 Monovette® tubes with EDTA; Sarstedt, Germany) from each donor by venous puncture. Genomic DNA was extracted using the QIAamp DNA blood maxi kit (Qiagen). Genotyping of *PRNP* SNPs was done by the Amplifluor™ method with following primers. For the M129V SNP primers, 5′-GAA GGT GAC CAA GTT CAT GCT CAT GGC ACT TCC CAG CAT-3′ (A allele), 5′-GAA GGT CGG AGT CAA CGG ATT GCT CAT GGC ACT TCC CAG CAC-3′ (G allele) and 5′-TGG GGG GCC TTG GCG GCT A-3′ (common) were used. Primers for SNP hCV2969397 were 5′-GAA GGT GAC CAA GTT CAT GCT TAG TAA TAA ACA GGT ATT GAC CAT TAC CA-3′ (T allele), 5′-GAA GGT CGG AGT CAA CGG ATT GTA ATA AAC AGG TAT TGA CCA TTA CCG-3′ (C allele) and 5′-GTC CTC TGG CAT ATT TCA AGA TAT CCT AT-3′ (common). Primers for SNP hCV2969384 were 5′-GAA GGT GAC CAA GTT CAT GCT CCC ACC CTC TGT TCT CCA GG-3′ (C allele), 5′-GAA GGT CGG AGT CAA CGG ATT CCC ACC CTC TGT TCT CCA GC-3′ (G allele) and 5′-GCA GAC CTG CAG CTC CTC TCT-3′ (common). The T174M SNP of *PRND* and rs1029273 were genotyped by Pyrosequencing™ on a PSQ™96 machine. Primers for T174M were 5′-ATT GCG AGT TTT GGT TGG AG-3′ (forward), 5′-GTC ACT TGC CAG GAT TTG CT-3′ (reverse, 5′ biotinylated) and 5′-GGC TTT GAT CTG GCT C-3′ (sequencing primer). Primers for rs1029273 were 5′-AAC CAG AAA CAT GGG GTG TT-3′ (forward), 5′-CCT GGC TTT TAC AAA GAA CCT C-3′ (reverse, 5′ biotinylated) and 5′-GGT GTT AAA TCA ATT ACA GG-3′(sequencing primer). To analyze the genetic structure of our population, we used 318 SNPs located in both genic and non-genic regions and distributed over all autosomes. Please contact the authors for the detailed list of examined SNPs.

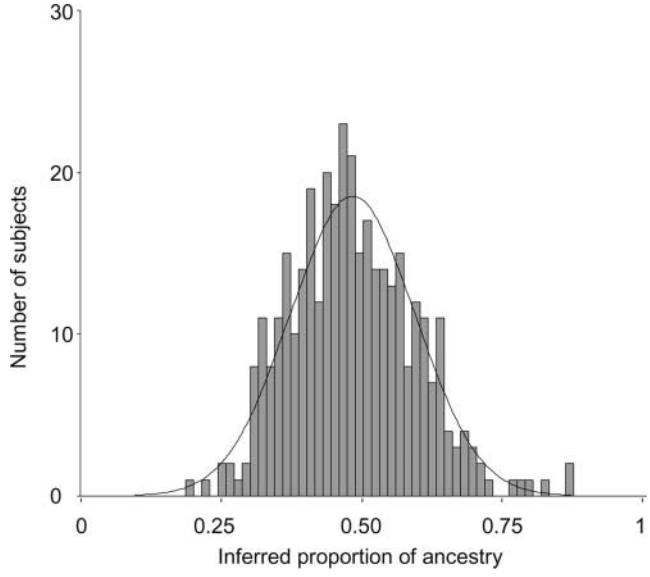

Figure 3 Genetic structure of the study population: estimates of the ancestry of study subjects under the *a priori* assumption of $K=2$ discrete subpopulations. The histograms show the number of individuals with distinct proportions of ancestry in subpopulation 1. Using 318 unlinked SNPs, structured association analysis revealed low allele-frequency divergence among populations (Kullback-Leibler distance = 0.23). The superimposed curve indicates normal distribution of the data ($P = 0.6$, Kolmogorov-Smirnov test). Ten subjects were identified as outliers (i.e. outside the 25 or 75% limits of the normal distribution curve). Identical results were obtained under the *a priori* assumption of $3 \leq K \leq 6$ discrete subpopulations.

Statistics

Analysis of linkage disequilibrium and haplotype reconstruction was done with PowerMarker version 3.22 (www.powermarker.net). Forward and backward logistic regression analyses and multifactorial analyses of covariance were done for the simultaneous assessment of the influence of age, gender, education, and *PRNP* and *PRND* genotype effect on

immediate, 5 min and 24 h delayed free-recall performance. To improve estimation of the type I statistical error, we performed permutation analysis (50 000 permutations) and used Monte Carlo simulations (100 000 random samplings) in addition to the logistic regression analysis. All tests were two-tailed.

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Conflict of Interest statement. None declared.

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