RESEARCH ARTICLE

Genetic Influences on Cognitive Decline in Parkinson's Disease

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ABSTRACT: The role of genetic factors in cognitive decline associated with Parkinson's disease (PD) is unclear. We examined whether variations in apolipoprotein E (APOE), microtubule-associated protein tau (MAPT), or catechol-*O*-methytransferase (COMT) genotypes are associated with cognitive decline in PD. We performed a prospective cohort study of 212 patients with a clinical diagnosis of PD. The primary outcome was change in Mattis Dementia Rating Scale version 2 score. Linear mixed-effects models and survival analysis were used to test for associations between genotypes and change in cognitive function over time. The ε4 allele of APOE was associated with more rapid decline (loss of 2.9; 95% confidence interval [CI]: 1.7–4.1) of more points per year; $P < 0.001$) in total score and an increased risk of a $\geq$10 point drop during the follow-up period (hazard ratio, 2.8; 95% CI: 1.4–5.4; $P = 0.003$). MAPT haplotype and COMT genotype were associated with measures of memory and attention, respectively, over the entire follow-up period, but not with the overall rate of cognitive decline. These results confirm and extend previously described genetic associations with cognitive decline in PD and imply that individual genes may exert effects on specific cognitive domains or at different disease stages. Carrying at least one APOE ε4 allele is associated with more rapid cognitive decline in PD, supporting the idea of a component of shared etiology between PD dementia and Alzheimer's disease. Clinically, these results suggest that genotyping can provide information about the risk of future cognitive decline for PD patients. © 2012 *Movement* Disorder Society

Key Words: genetics; Parkinson's disease; cognitive symptoms; apolipoprotein E; microtubule-associated protein tau

Cognitive impairment is common in PD and is associated with increased morbidity and mortality.[1] Estimates of dementia prevalence in PD vary, depending on the population studied,[2] but increase with disease duration. Mild cognitive deficits may be indentified in approximately 20% of newly diagnosed patients,[3] and dementia occurs in up to 80% of patients over the course of the disease.[4,5]

The rate and intensity with which cognitive problems develop vary substantially among individuals.[6] Clinical characteristics that are measured at time of diagnosis, including older age, sex, poor semantic fluency, or inability to copy intersecting pentagons, have been associated with increased rates of cognitive decline and conversion to dementia.[7,8] Biologic markers associated

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with cognitive decline, including genetic polymorphisms and analytes measurable in CSF or blood,[9,10] may provide additional information on risk and help in the understanding of the biological basis for clinical heterogeneity.

Some genes previously associated with cognitive impairment in PD (e.g., α-synuclein[11] and catechol-O-methyltransferase [*COMT*][12]) implicate dopaminergic systems in the pathophysiology of cognitive impairment in PD. Other genes, such as apoliporotein E (*APOE*) and microtubule-associated protein tau (*MAPT*), are of particular interest because of their known association with dementia in other neurodegenerative diseases, such as Alzheimer's disease (AD) and atypical parkinsonian syndromes, including progressive supranuclear palsy and corticobasal degeneration.[13,14]

Studies investigating the association of individual genes with cognitive function in PD have yielded conflicting results and have been limited by small samples or cross-sectional designs.[15–18] Analysis of one small prospective cohort did not suggest a relationship between *APOE* genotype and cognitive decline in PD.[19] Only one cohort of more than 100 PD patients has been described with a prospective assessment of cognitive abilities and an examination of multiple genotypes. In this cohort of recently diagnosed PD patients, cognitive decline was strongly associated with *MAPT* haplotype, but not *APOE* genotype.[8,20–22] Additionally, *COMT* genotype was associated with poor performance on frontally based tasks, perhaps through an interaction with dopaminergic tone or medications, but not with a significantly increased risk of dementia.[12,21,23] In the present study, we sought to determine the association of *APOE*, *MAPT*, and *COMT* genotype with cognitive performance in PD, as measured by mean annual change in Dementia Rating Scale-2 (DRS-2) score and risk of experiencing at least a 10-point decline in DRS-2 score.

Patients and Methods

Subjects

Patients 60 years of age or older having a diagnosis of PD based on UK Brain Bank criteria[24] and with a range of cognitive function were recruited to the University of Pennsylvania Udall Center of Excellence in Parkinson's Disease Research (Philadelphia, PA). No subjects met criteria for dementia with Lewy bodies.[25] A total of 212 subjects who were assessed for the genotypes of interest and had at least one annual follow-up visit were included in this analysis.

Standard Protocol Approvals, Registrations and Consents

The study was approved by the University of Pennsylvania Institutional Review Board. Informed consent was obtained before any study procedure.

Assessments

Clinical and neuropsychological assessments were administered by trained research staff. Demographic and general clinical information were collected in PD-DOC (http://www.pd-doc.org) recommended format. Evaluations were completed between August 2006 and March 2011.

Genotyping

DNA was extracted from peripheral blood, following the manufacturer's protocols (FlexiGene; QIAGEN, Valencia, CA, or QuickGene DNA whole blood kit L; AutoGen, Inc., Holliston, MA). Genotyping was performed using real-time allelic discrimination with Applied Biosystems (ABI; Foster City, CA) TaqMan probes. The following single-nucleotide polymorphisms were genotyped with the corresponding ABI assay by design: *MAPT* (rs1052553, C_7563736_10), COMT p.V158M (rs4680, C_25746809_50), and *APOE* (rs7412, C_904973_10 and rs429358, C_3084793_20). Genotyping was performed on an ABI 7500 real-time instrument using standard conditions. Data were analyzed using ABI 7500 software v2.0.1.

Neuropsychological Assessment

Cognitive function was assessed with the Mattis Dementia Rating Scale (version 2, DRS-2).[26] The DRS-2 is a well-characterized measure of general cognitive ability. It gives a total score and subscores for specific cognitive domains, including memory, attention, initiation/perseveration, construction, and conceptualization. A total of 144 points are possible, with higher scores indicating better cognitive function. The DRS-2 has been validated for use in PD.[27]

Motor Examination

Clinical assessments of motor function, including H & Y stage[28] and UPDRS-III,[29] were performed by trained examiners. Motor assessments were conducted while patients were taking their normal schedule of dopaminergic and other medications.

Statistical Analysis

Descriptive statistics for demographic, clinical, and neuropsychological variables were calculated. Based on previous reports of genotype-phenotype associations,[12,20,30] the cohort was dichotomized based on the following genotypes: (1) *APOE*: ε4 carrier versus not; (2) *APOE*: ε2 carrier versus not; (3) *MAPT* genotype: H1/H1 versus other; and (4) *COMT*: Met/Met versus other. Between-group differences in baseline demographic, clinical, and neuropsychological variables were assessed using *t* tests, chi-squared tests, or Wilcoxon-Mann-Whitney's tests, as appropriate (Table 1).

TABLE 1. Baseline Cohort Demographic and Disease Characteristics as a Function of Genotype

		APOE						*MAPT*			*COMT*		
Characteristics	Cohort	ε2$^+$ (N = 25)	ε2$^-$ (N = 187)	P*	ε4$^+$ (N = 57)	ε4- (N = 155)	*P* Value*	H1/H1 (N = 148)	H1/H2 H2/H2 (N = 64)	*P* Value*	Met/Met (N = 56)	Val/Met Val/Val (N = 156)	*P* Value*
Age	71 (7.4)	69 (6.3)	72 (7.8)	0.08	71 (7.7)	71 (6.7)	0.72	71 (7.3)	71 (7.5)	0.98	70 (6.6)	72 (7.6)	0.25
Sex (% male)	68	64	68	0.65	76	65	0.14	67	70	0.75	71	67	0.61
Race (% white)	96	100	95	0.74	93	97	0.60	97	95	0.63	98	95	0.52
Education (years)	16 (2.4)	16 (2.4)	16 (2.4)	0.95	16 (2.5)	16 (2.4)	0.76	16 (2.4)	16 (2.3)	0.26	16 (2.3)	16 (2.5)	0.40
Duration (years)	6.7 (5.2)	6.9 (5.1)	6.7 (5.2)	0.83	7.2 (4.3)	6.5 (5.4)	0.35	6.9 (5.1)	6.1 (5.9)	0.70	5.5 (5.9)	7.0 (5.5)	0.06
UPDRS-III	23 (11)	19 (9.0)	23 (11)	0.07	27 (12)	21 (10)	0.01	23 (12)	23 (10)	0.93	24 (11)	22 (11)	0.15
H &Ymedian (IQR)	2 (2.0–2.5)	2 (2.0–2.5)	2 (2.0–2.5)	0.19	2.5 (2–3)	2 (2.0–2.5)	0.02	2 (2.0–2.5)	2 (2.0–2.5)	0.63	2 (2.0–2.5)	2 (2-2.5)	0.93
DRS-2 score	134 (9.4)	136 (5.4)	134 (10)	0.55	131 (13)	135 (7.4)	0.24	134 (8)	133 (12)	0.87	135 (6.4)	134 (10)	0.57
Annual visits median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.33	3 (2–4)	3 (2–4)	0.14	3 (2–4)	3 (2–4)	0.86	3 (2–4)	3 (2–4)	0.50

*P value was from *t* test or Wilcoxon-Mann-Whitney's test for continuous variables and from the chi-square test for categorical variables.Abbreviation: IQR, interquartile range.

Linear mixed-effects models[31] were used to test for associations between different genotypes and changes in cognitive function over time, as measured by the DRS-2 and its subscales. Linear mixed-effects models account for within-subject correlations over time and accommodate both variable length of follow-up for different subjects and variation in the interval between assessments. In our analysis, the intercept and regression coefficients for the follow-up time were treated as random effects, such that each individual would have a unique intercept and regression coefficient for the follow-up time. Population mean coefficients for the follow-up time were then obtained by averaging the subject-specific regression coefficients for follow-up time. The population mean regression coefficient for the follow-up time estimates the annual change in DRS-2 score over time and accounts for differences in baseline DRS-2 scores. The interaction term "time × genotype" represents the effect of a given genotype on DRS-2 change over time and can be interpreted as the between-group difference in annual DRS-2 decline.

We used Cox's proportional hazards regression model to examine factors associated with the risk of a 10-point drop from baseline DRS-2 score. A 10-point drop was chosen because it represents an unequivocal, clinically significant change in DRS score. Using robust norms for a 70 year old, a change from a score of 145 to 135 is a drop from the 98th to approximately the 25th percentile and a change from a score of 135 to 125 is a drop from the 25th to the 1st percentile.[32] Failure time was measured from baseline assessment until reaching a 10-point drop in DRS-2 score. We used a stepwise model-selection procedure to decide the final model from the following baseline covariates: sex, *APOE*4 genotype (ε4 carrier), *MAPT* haplotype, *COMT* genotype, age, education, baseline DRS-2 score, disease duration, H & Y, and UPDRS-III. Cox's regression analysis was performed using SAS software (*version 9.2*; SAS Institute Inc., Cary, NC). All other analyses were carried out using PASW (*version 18.0*; SPSS, Inc., Chicago, IL). All statistical tests were two-sided. Statistical significance was set at the 0.05 level.

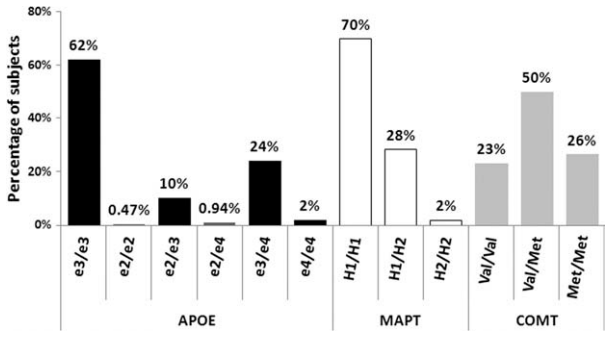

FIG. 1. Distribution of genotypes in cohort. Data are expressed as the percentage of subjects (total, N = 212) with the given genotype.

Results

Of the subjects in this analysis, 65 (31%) had a total of two evaluations (i.e., 1 year of follow-up), 60 (28%) had three evaluations, 78 (37%) had four evaluations and 9 (4%) had five evaluations. The annualized rate of decline in DRS-2 score in the entire cohort was 1.3 ± 0.43 (standard error of the mean) points. Baseline demographic and disease characteristics of the cohort are described in Table 1.

Frequency of variants at each of the loci of interest is summarized in Figure 1A. Comparison of demographic and disease characteristics between genotype groups is shown in Table 1. These characteristics were similar between groups, with the exception of higher UPDRS and H & Y in *APOE* ε4 carriers (Table 1).

TABLE 2. Relationship Between Genotype and Annual Change in DRS-2 Score

	Estimated Association With Annual Change in DRS-2	95% CI	*P* Value
APOE ε4[+a]	−2.9	(−4.0, −1.5)	<0.001
ε2[+a]	0.94	(−0.64, 2.5)	0.24
MAPT H1/H1[b]	−0.63	(−1.8, 0.55)	0.29
COMT Met/Met[c]	0.1	(−1.1, 1.8)	0.87

Data are shown as regression coefficients (β) from mixed-effects models with associated 95% CIs. Coefficients represent the difference in annual rate of change of the DRS-2 for between the genotype/haplotype of interest and the comparison group indicated. For example, a coefficient of −2.9 for *APOE* ε4 indicates that DRS-2 scores for ε4 carriers declined 2.9 points faster each year than for all other genotypes. Estimates of rate of change are adjusted for age, sex, disease duration, H & Y, and baseline DRS-2 score.
[a]Relative to all other *APOE* genotypes.
[b]Relative to all other *MAPT* haplotypes.
[c]Relative to all other *COMT* genotypes.

TABLE 3. Association Between APOE ε4 and Annual Change in DRS-2 Domain Subscores

DRS-2 Domain	Estimated *APOE* ε4-Associated Annual Change	95% CI	*P* Value
Initiation	−1.1	(−1.7, −0.48)	<0.001
Attention	−0.1	(−0.43, 0.22)	0.53
Construction	−0.21	(−0.58, −0.35)	0.006
Conceptualization	−0.7	(−1.1, −0.26)	0.002
Memory	−0.84	(−1.3, 0.41)	<0.001

Data are shown as regression coefficients (β) from mixed-effects models with associated 95% CI. Coefficients represent the difference in annual rate of change of the DRS-2 subscale scores between *APOE* ε4 carriers and all other genotypes. Estimates of rate of change are adjusted for age, sex, disease duration, H & Y, and baseline DRS-2 score. Maximum scores on each subscale are: Initiation, 37 points; Attention, 37 points; Construction, 6 points; Conceptualization, 39 points; Memory, 25 points.

Association of Genetic Variants With Cognitive Status

There were no significant differences in baseline DRS-2 scores among genotype groups for *APOE*, *MAPT*, or *COMT* (Table 1). Linear mixed-effects models were used to examine the association of genotype with cognitive decline, estimated by the magnitude of the "gene × time" interaction term. The presence of the *APOE* ε4allele was associated with a significantly higher annual rate of decline in DRS-2 score, compared with all other *APOE* genotypes (Table 2). Furthermore, *APOE* ε4 carrier status was associated with higher risk of a 10-point decline in DRS-2 score during the follow-up period, adjusting for age, sex, education, disease severity and duration, and baseline DRS-2 score (adjusted hazard ratio [HR], 2.8; 95% confidence interval [CI]: 1.4–5.4; $P = 0.003$; Fig. 2). A total of 37 subjects experienced a ≥10-point decline during follow-up. *APOE* ε2, *MAPT* H1/H1genotype, and *COMT* Met/Met genotypes were not associated with change in DRS-2 score over time (Table 2).

Effect of *APOE* genotype on cognitive decline was not domain specific, because the ε4 allele was associated with more rapid decline in DRS-2 subscales measuring initiation, construction, conceptualization, and memory (Table 3). *COMT* Met/Met genotype was associated with higher attention subscale scores over the entire study period (0.38 ± 0.13 points; $P = 0.03$), but not with changes in attention score over time ($P = 0.17$). *MAPT* H1/H1 genotype was associated with lower scores in memory subscale over the entire study period (0.47 ± 0.23 points; $P = 0.04$), but not with changes in memory score over time ($P = 0.49$). There were no other significant associations between *MAPT* or *COMT* and DRS-2 subscale scores (data not shown).

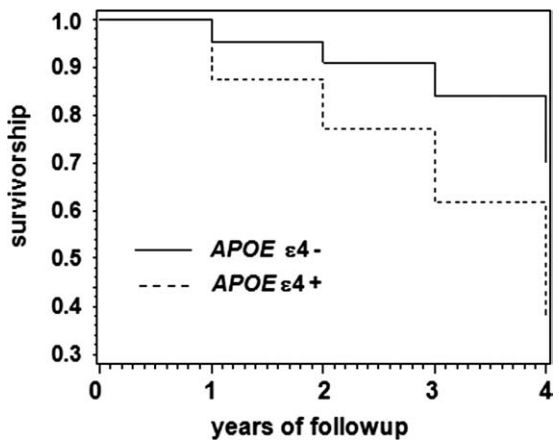

FIG. 2. *APOE* ε4 carriers are at increased risk for clinically significant decline in cognitive function in PD. Survivorship plot derived from Cox's proportional hazards regression model comparing the risk of a ≥10-point drop from baseline DRS-2 score between *APOE* ε4 carriers (ε4[+], blue) and noncarriers (ε4[−], red). HR = 2.8; 95% CI: 1.4 to 5.4.

Discussion and Conclusion

We found that DRS-2 scores declined nearly 3 points per year faster among *APOE* ε4 carriers with PD (Table 2). It seems likely that this disparity should be clinically significant, because, if ongoing, it might be expected to result in a 10- to 15-point differential over 5 years. The difference between baseline DRS-2 score in our cohort and a commonly used cutoff for dementia (<124)[33] was approximately 10 points. Indeed, *APOE* ε4 carrier status was associated with a 2.8-fold increased risk of a ≥10 point decline in DRS-2 score during follow-up (Fig. 2). These results indicate that the more rapid decline in mean DRS-2 scores among *APOE* ε4 carriers was not driven by large changes in only a few individuals. Also, carrier status was associated with increased risk for earlier onset of clinically significant cognitive decline. More rapid cognitive decline among *APOE* ε4 carriers was observed across multiple cognitive domains, arguing for a diffuse, rather than focal, degenerative process.

Notably, however, *APOE* ε4 was not associated with changes on the DRS-2 attention subscale (Table 3). We did observe an association between *COMT* genotype and performance on a measure of attention, as has been described by others, and is thought to reflect modulation of a frontostriatal network.[12,21,23] However, *COMT* genotype did not influence overall rates of DRS-2 score decline, consistent with the hypothesis that these deficits represent a distinct cognitive phenotype that does not herald dementia.[21] In contrast, *MAPT* H1/H1 genotype was associated with worse performance only on the memory subscale of the DRS-2, perhaps suggesting a temporal lobe-predominant effect, as observed in AD. The idea that individual genetic factors could influence distinct cognitive domains is intriguing and warrants further investigation.

Our findings add to a growing body of evidence on the association of *APOE* with cognitive decline in PD. The ε2 allele has been associated with increased incidence of PD[34] and a potentially protective effect in dementia,[13] but we did not observe an association between the ε2 allele and cognitive decline. In cross-sectional analyses, the *APOE* ε4 allele has been associated with higher risk of dementia in several studies,[17,35,36] whereas others have failed to find an effect.[15,16,18,22]

A meta-analysis summarizing some of these studies and examining 458 pooled PD cases (163 with dementia and 295 without) supported an association between *APOE* ε4 and cognitive decline.[30] A more recent study updating this analysis (1,145 PD cases and 501 PD dementia [PDD] cases) found an overrepresentation of ε4 carriers among PDD cases (odds ratio [OR], 1.74; 95% CI: 1.36–2.23), but raised concerns that small samples, heterogeneity of ORs, and publication bias may have confounded the finding.[22] Together, these reports support an association between *APOE* and PDD, but suggest that the effect size may be small. Furthermore, they highlight many of the difficulties in trying to study longitudinal change with cross-sectional studies. In one community-based longitudinal study of 107 newly diagnosed PD patients from Cambridge, UK, followed for an average of 5 years, *APOE* genotype was not associated with rate of cognitive decline in PD.[22]

That some studies should fail to find any effect of *APOE* genotype on cognitive status is surprising, given the influence of this gene on cognitive decline in AD and in the general population.[37,38] One possibility is that PD patients are somehow ''protected'' from the effects of *APOE* variation, though it is unclear through what mechanism this might occur. Another explanation is that these studies failed to detect an effect as a result of lack of power or other factors. For example, in the longitudinal cohort described above,[22] detection of an association between cognitive decline and *APOE* genotype may have been obscured by smaller sample size and the use of Folstein's Mini–Mental State Examination (MMSE), a relatively insensitive measure of cognitive function in PD,[39] as the primary outcome measure.

We did not find a significant association between *MAPT* haplotype and rates of cognitive decline. The *MAPT* H1variant has been associated with a higher risk of PD and cognitive decline, and a specific subhaplotype (H1p) has recently been implicated.[20,40] However, several other studies failed to demonstrate a relationship between MAPT variants and dementia in PD.[16,41] In the same longitudinal cohort from Cambridge, UK, described above,[22] there was a faster rate of decline in MMSE scores among indivuduals with the *MAPT* H1 variant.[20] All subjects developing dementia during the initial 3-year follow-up (11 of 109) carried the H1/H1 genotype,[20] and the increased risk persisted after 5 years.[21]

One key distinction between the present study and that of the Cambridge cohort is that we enrolled subjects primarily in the middle of the course of PD, whereas the other cohort was enrolled near the time of diagnosis. One explanation for the discrepancy in our findings is that different genetic mechanisms may subserve early- versus late-onset cognitive decline in PD. These previous studies demonstrated an association between *MAPT* haplotype and cognitive decline within the first 5 years of diagnosis. Conversely, we found an association between *APOE* genotype and cognitive decline that occurs later in the course of PD.

Our findings cannot definitively establish whether the association we observed between *APOE* and cognitive decline is specific to PD or simply the previously described effect of *APOE* genotype on cognitive function that may be observed in otherwise healthy older individuals.[38] However, several lines of evidence support overlap in the pathology of PDD and AD. AD pathology is often observed in postmortem PDD brains, and abnormalities in aβ and Tau protein are possible biomarkers of cognitive change in PD.[10,42] Disruption of *APOE* ameliorates aβ accumulation and neurodegeneration in a mouse model of PD,[43] thus this overlap may reflect interaction of APOE with distinct neural substrates to produce the specific pattern of changes observed in PDD, rather than superimposed, unrelated accumulation of AD pathology. In this study, we did not find that *APOE* ε4 carriers had disproportionate memory impairments, compared to other domains, as would be expected if the effect of *APOE* genotype was simply a result of coexisting AD pathology. Combined with our report of depressed aβ, but not elevated CSF tau, in PD patients,[10] this finding suggests that the accelerated cognitive decline observed in *APOE* carriers is not simply the result of an increased risk of coexisting AD, but rather a disease-specific effect of *APOE* gene status on cognition in PD.

The prospective design and size of the longitudinal cohort are strengths of the present study. However,

these results should be interpreted in the context of several limitations. Education level in this cohort was high (mean, 16 years), but observed DRS-2 scores were consistent with those in previously reported PD cohorts, and education was not a significant covariate in any of our mixed-effects models or survival analysis. The majority of patients were followed for a relatively short period, and the number of subjects with more than 2 years of follow-up was modest, compared with the size of the entire cohort. However, use of mixed-effects models accounts for variability in length of follow-up. The cohort was not incident, and disease duration at enrollment varied widely, complicating an unbiased assessment of the time to onset of cognitive decline; however, adjustment for disease duration and other clinical characteristics in mixed effects models did not affect the associations observed. It should be noted that though mixed-effects models account, in part, for variations in length of follow-up and disease duration, associations between genetic factors and longitudinal change or effects at a particular disease stage could have been underestimated.

Aging is a risk factor for countless human diseases, but appears to play a particularly important role in cognitive decline observed in neurodegenerative disorders and the general population. The previously described strong association between *MAPT* and cognitive decline in the Cambridge cohort was highly age dependent,[20,21] although we did not observe significant effects for gene-age interaction terms in our mixed effects models (not shown). Thus, the importance of aging in PD-associated cognitive decline may depend on particular genetic factors. Ultimately, cognitive changes over time in any given PD patient may reflect multiple, potentially overlapping, pathologic processes superimposed onto ''normal'' aging or specific gene-age interactions. Although the present study was not powered to do so, investigating potential gene-gene interactions and their effect on cognitive status in PD may be of particular interest. Because the effect size for any one factor may be relatively modest, future studies of larger prospective cohorts examining multiple candidate loci, perhaps in combination with other biologic markers, may be necessary to fully elucidate the predictive value and etiologic roles of these genes in neurodegenerative dementias, including PDD. ■

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