COMT genotype and cognitive function

An 8-year longitudinal study in white and black elders

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ABSTRACT

Objective: Catechol-O-methyltransferase (COMT), an enzyme that catalyzes the degradation of dopamine, is necessary for cognitive function. Few studies have examined the prospective association between COMT (Val¹⁵⁸Met) genotype and cognition in older adults.

Methods: We assessed a biracial cohort of 2,858 elderly subjects without dementia who were followed for 8 years. The Modified Mini-Mental State Examination (3MS) and Digit Symbol Substitution Test (DSST) were administered at baseline and years 3, 5, and 8. COMT by race, gender, and APOE status interactions were examined.

Results: Stratified by race and adjusted for covariates, repeated-measures mixed-effects models showed no association between COMT genotype and baseline cognitive function in black or white subjects. In white subjects, COMT was associated with change in 3MS (Met/Met: −2.3 [0.60], Met/Val: −1.7 [0.40], and Val/Val: −1.2 [0.50]) and DSST (Met/Met: −5.60 [1.00], Met/Val: −4.80 [0.70], Val/Val: −4.00 [0.90]). In black subjects, COMT was associated with change in the DSST (Met/Met: −4.10 [2.1], Met/Val: −4.80 [0.90], Val/Val −2.60 [1.00]).

Conclusion: These findings suggest that the Val allele has a protective impact on cognitive decline in late life. *Neurology*® 2010;74:1296-1302

GLOSSARY

3MS = Modified Mini-Mental State Examination; **BMI** = body mass index; **CES-D** = Center for Epidemiologic Studies-Depression Scale; **COMT** = catechol-O-methyltransferase; **DSST** = Digit Symbol Substitution Test; **Health ABC** = Health Aging and Body Composition; **PFC** = prefrontal cortex.

Aging is commonly associated with decline in cognitive function, with the largest decline noted in prefrontal cortex (PFC)-dependent executive functioning.¹ Recent studies have reported that age-related loss of dopaminergic function correlates with cognitive impairment.² Indeed, dopamine is necessary for PFC function and an imbalance of dopamine may produce deficits in PFC-dependent tasks, namely tasks of executive function.³

Catechol-O-methyltransferase (COMT) catalyzes the degradation of catecholamines and the methylation of catechol estrogens.⁴ Due to its role in dopamine degradation, the *COMT* gene has received attention as a genetic contributor to variations in cognitive function. The gene that codes for COMT contains a functional common Val¹⁵⁸Met polymorphism, with the Val allele exhibiting a threefold to fourfold increase in enzyme activity compared to the Met allele.⁵ Several cross-sectional studies show that the Val/Val genotype is associated with less efficient cognitive processing and poorer performance on cognitive tests compared to the Met/

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Met genotype.^{6,7} Furthermore, carriers of the Val/Val genotype exhibit PFC alterations on various physiologic measures during task performance.⁷⁻⁹

To date, very few longitudinal studies exist and the majority of studies assessing the relationship between COMT and cognitive function have focused on clinical populations and young non-racially diverse adults. The goal of this investigation was to evaluate the association between COMT genotype and performance on tests of cognitive function over an 8-year period in a biracial cohort of elderly men and women. We tested a race-by-COMT interaction on cognitive function. Also, given past suggestions of sex effects¹⁰ and the reported synergistic association between COMT and *APOE* in Alzheimer disease,¹¹ we tested sex- and *APOE*-by-COMT interactions on cognitive function.

METHODS Study population. The present study involves a subgroup of participants from the Health Aging and Body Composition (Health ABC) study, which consisted of 3,075 community-dwelling black and white men and women aged 70 to 79 without dementia upon recruitment in 1997. To identify potential participants, a random sample of white and black Medicare-eligible elders within designated zip code areas surrounding the Memphis, TN, and Pittsburgh, PA, field centers were contacted. Eligibility requirements included no difficulty with activities of daily living, walking a quarter of a mile, or climbing 10 steps without resting. Participants also had to be free of life-threatening cancer diagnoses and did not plan to move out of the study area within 3 years. Details can be found elsewhere.¹²

Among the 3,075 participants recruited, 2,858 participants were randomly genotyped for the *COMT* gene, of which 2,840 participants had cognitive measures.

Standard protocol approvals, registrations, and patient consents. All eligible participants signed a written informed consent, approved by the institutional review boards at the clinical sites and the coordinating center (University of California, San Francisco).

Measurements. Baseline factors. Baseline demographic factors included age, race (white, black), sex, and self-reported education level (< or ≥ high school). Baseline health characteristics included self-rated health (good, very good, or excellent vs fair or poor), current smoking status, and self-report of drinking any alcoholic drinks per week. Depressive symptoms were assessed with the 20-item Center for Epidemiologic Studies–Depression Scale (CES-D¹³), with a score above 15 categorized as having high depressive symptoms. Body mass index (BMI: kg/m²) was calculated from direct height and weight measurements. Hypertension was defined by self-report of a diagnosis, use of antihypertensive medications, or measured systolic blood pressure exceeding 140 mm Hg or diastolic blood pressure exceeding 90 mm Hg. Diabetes was defined by self-report of diabetes diagno-

sis, use of diabetes drug, or fasting plasma glucose >126 mg/dL or 2-hour postchallenge glucose >200 mg/dL. History of myocardial infarction, stroke, or TIA was determined from self-report of physician diagnoses. Finally, *APOE* genotype was determined using standard single nucleotide polymorphism analyses.

Cognitive tests. The Modified Mini-Mental State Examination (3MS) was administered at years 1 (baseline), 3, 5, and 8. The 3MS is an expanded, and more sensitive, version^{14,15} of Folstein's Mini-Mental State Examination, with possible scores ranging from 0 to 100. It is a measure of global cognitive performance with components for orientation, concentration, language, praxis, and immediate and delayed memory.¹⁶

The Digit Symbol Substitution Test (DSST) was administered at years 1, 5, and 8. The DSST measures response speed, sustained attention, visual spatial skills, and set shifting, all of which reflect executive cognitive function.^{17,18} The test is reported to distinguish mild dementia from healthy aging.¹⁹ The DSST score is calculated as the total number of items correctly coded in 90 seconds, with a higher score indicating better cognitive function.¹⁸

COMT genotyping. Genomic DNA was extracted from EDTA anticoagulated whole blood by standard methods (Gentra Systems, Minneapolis, MN), and PCR-based COMT genotyping was carried out using flanking primers COMTF: 5_-CACATCACCATCGAGATCAACA-3_ and COMTR: 5_GATGACCCTGGT GATAGTGG-3_, as described elsewhere.²⁰ The 210-bp fragment flanking the Val¹⁵⁸Met polymorphism (dbSNP, rs4680) was digested with 1.5 units of *Nla*III, and the fragments resolved on 1% agarose gel. Genotypes were scored by comparison to sequence-verified control samples run on the same gel. For quality control, a 5% sample of blind duplicates was included, with complete concordance for genotypes. Hardy-Weinberg equilibrium for genotype distribution was assessed.

Statistical analysis. Following categorization of Met/Met, Met/Val, and Val/Val genotype, the association between COMT and baseline factors was determined using χ^2 for categorical variables and analysis of variance or Kruskal-Wallis test for continuous variables. Variables that differed between COMT genotype groups ($p < 0.01$) were considered covariates for subsequent analyses.

Because genotype frequency and cognitive function differed by race, stratified analyses were conducted. Repeated-measures mixed-effects models were conducted to determine if COMT was associated with baseline and rate of change over 8 years (i.e., slope) on the 3MS and DSST. Models included random intercepts and slopes for change in cognitive score over years. Specifically, COMT genotype and covariates (in adjusted model) were entered as fixed effect predictors and participants were specified as a random effects factor. A variable indicating time between first and subsequent visit was created and entered into the model to specify that the slopes over time are associated with an individual and are also random. Tests were considered statistically significant at $p < 0.05$.

As sex and *APOE* may moderate the association between genotype and cognitive function, tests of interaction were assessed for both baseline and change (i.e., slope) in cognitive score over years. Significant interactions ($p < 0.10$) would result in subsequent stratified analyses.

As African Americans in the United States are known to be an admixture population, with ancestry from both Africans and Europeans, an additional adjustment was made for admixture

Table 1 Characteristics across COMT genotype group in white elders

	COMT (rs4680) genotype			p Value ^a
	Met/Met (n = 426)	Met/Val (n = 853)	Val/Val (n = 400)	
Age, y, mean (SD)	73.7 (2.9)	73.7 (2.8)	74.0 (2.8)	0.010
Female, %	47.7	50.1	43.3	<0.001
Education < high school, %	12.7	12.0	11.8	0.60
BMI, mean (SD)	26.6 (3.8)	26.4 (4.3)	26.8 (4.2)	<0.001
CES-D ≥16, %	4.0	5.7	3.8	0.001
APOE ε4 carrier, %	24.9	24.4	21.9	0.045
History of MI, %	12.2	11.9	11.1	0.49
Stroke/TIA, %	7.3	6.9	9.9	<0.001
Hypertension, %	60.1	55.0	55.8	<0.001
Diabetes, %	20.4	19.4	18.4	0.29
Self-rated health fair/poor, %	7.5	8.9	7.3	0.040
Any alcoholic drinks/week, %	50.9	61.0	60.7	<0.001
Current smoker, %	5.2	7.8	5.0	<0.001

Abbreviations: BMI = body mass index; CES-D = Center for Epidemiologic Studies–Depression Scale; COMT = catechol-O-methyltransferase; MI = myocardial infarction.

^ap Value by analysis of variance for continuous variables and χ^2 test for categorical variables.

effects.^{21,22} Admixture was approximated using STRUCTURE,²³ which incorporates both genome-wide and local (SNP-based) estimates of the percent genetic contribution of European or African reference genotypes from HapMap2.

RESULTS **Genotype frequency.** Of the 2,858 participants, 1,679 were white and 1,179 were black. The genotype distribution was 25% Met/Met, 51% Met/Val, and 24% Val/Val in white participants and 10% Met/Met, 44% Met/Val, and 46% Val/Val in black

participants. Although genotype distribution was consistent with Hardy-Weinberg equilibrium in both white and black subjects ($\chi^2 = 0.45$, $p = 0.50$ and $\chi^2 = 0.15$, $p = 0.70$), analyses showed that genotype frequency differed by race ($\chi^2 = 195.61$, $p < 0.001$).

Baseline characteristics by COMT genotype. Among all participants, baseline characteristics including age, sex, BMI, stroke/TIA, self-rated health, and current smoking status differed across genotype group. Among white subjects, genotype differences were also found for depression score, hypertension, APOE ε4 status, and alcoholic drinks/week. Among black subjects, genotype differences were also found for diabetes (tables 1 and 2).

Association between COMT genotype and cognitive scores stratified by race. **3MS.** Adjusted models revealed a significant association between COMT genotype and change in performance on the 3MS over 8 years in white but not black elders. No association was found for baseline performance in either white or black elders (see table 3). Adjusting for admixture effects did not change the results.

DSST. Adjusted models revealed a significant association between COMT genotype and change in performance on the DSST over 8 years in both white and black elders. No association was found for baseline performance in either white or black elders (table 4). Adjusting for admixture effects did not change the results.

No consistent COMT-by-APOE and COMT-by-sex interactions on cognitive function were observed in black or white participants ($p > 0.10$).

DISCUSSION The COMT genotype has recently been evaluated for its role in influencing cognitive function. To date, few studies have prospectively investigated the association between COMT and trajectory of cognitive decline over time. In addition, we assess this relationship in a diverse cohort of older adults. Overall, we found that COMT genotype is associated with change in cognitive function over 8 years in both white and black elders, with more consistent findings in a task that taps into executive cognitive function compared to a task that assesses global cognitive function.

Although we observed a pattern of baseline cognitive performance being slightly lower among Val/Val carriers compared to Met carriers, no clear association was found between COMT genotype and baseline cognitive function on either the 3MS or the DSST. However, we found that COMT genotype is associated with change in cognitive function over 8 years. Specifically, we found that black and white

Table 2 Characteristics across COMT genotype group in black elders

	COMT (rs4680) genotype			p Value ^a
	Met/Met (n = 118)	Met/Val (n = 519)	Val/Val (n = 542)	
Age, y, mean (SD)	73.3 (2.9)	73.3 (2.9)	73.6 (2.9)	0.010
Female, %	55.9	59.0	56.1	0.08
Education < high school, %	44.4	42.4	43.9	0.44
BMI, mean (SD)	29.1 (6.2)	28.4 (5.2)	28.9 (5.2)	<0.001
CES-D ≥16, %	4.4	4.7	4.1	0.61
APOE ε4 carrier, %	35.7	36.3	35.7	0.87
History of MI, %	10.4	12.6	11.4	0.25
Stroke/TIA, %	9.6	6.9	9.3	0.002
Hypertension, %	73.7	73.6	73.1	0.89
Diabetes, %	34.5	28.8	31.3	0.014
Self-rated health fair/poor, %	25.4	25.1	29.1	0.003
Any alcoholic drinks/week, %	36.4	38.3	38.2	0.68
Current smoker, %	22.2	15.2	15.4	<0.001

Abbreviations: BMI = body mass index; CES-D = Center for Epidemiologic Studies–Depression Scale; COMT = catechol-O-methyltransferase; MI = myocardial infarction.

^ap Value by analysis of variance for continuous variables and χ^2 test for categorical variables.

Table 3 Mean (SE) 3MS scores by COMT genotype in white and black elders

	COMT (rs4680) genotype, adjusted scores, mean (SE) ^a			
	Met/Met	Met/Val	Val/Val	p Value ^b
White elders				
Baseline	93.7 (0.3)	93.9 (0.2)	93.7 (0.3)	0.50
Change (slope)	-2.3 (0.6)	-1.7 (0.4)	-1.2 (0.5)	<0.01
Black elders				
Baseline	86.2 (0.9)	87.7 (0.4)	86.8 (0.5)	0.56
Change (slope)	-3.2 (1.6)	-3.6 (0.8)	-3.5 (0.9)	0.49

Abbreviations: 3MS = Modified Mini-Mental State Examination; COMT = catechol-O-methyltransferase.

^aIn white subjects, adjusted for age, sex, body mass index, depression, APOE ε4, hypertension, stroke, self-rated health, alcohol use, and smoking. In black subjects, adjusted for age, sex, body mass index, stroke, diabetes, self-rated health, and smoking.

^bp Value for trend for the fixed effect of COMT genotype in a repeated-measures mixed-effects regression model.

participants with the Val/Val genotype displayed less decline on the DSST compared to carriers of the Met allele. We also found that Val/Val carriers displayed less decline over years on the 3MS, but this finding was limited to white participants only. These associations were independent from the effects of age, sex, APOE ε4 status, and health factors, including cardiovascular factors. Also, given the statistical model that was employed, these findings are independent of baseline cognitive function.

Overall, our findings somewhat contrast previous studies that report the Val/Val genotype as having a detrimental effect on cognitive function.^{24,25} In 2 studies^{24,26} that assessed the association between COMT and cognitive function in a group of men without dementia, aged 35–85, Met/Met carriers performed better than Val carriers (Val/Val + Met/Val combined as one group) on baseline tests of episodic and semantic memory,²⁴ as well as on tests of

executive function and visuospatial abilities.²⁶ Interestingly, the genotype association with visuospatial ability was limited to middle-aged participants and was not found in older adults 50–85 years of age, suggesting that there may be age differences in the association between COMT and cognitive function. In assessing change in cognitive function over time, this group reported Val/Val carriers to exhibit greater decline on executive function compared to Met/Met and Met/Val carriers. However, participants were included as young as 35 years of age in this analysis, which may explain why our findings differ. Of note, those aged 50–60 years with the Met/Met genotype displayed greater decline on an episodic memory task over 5 years compared to those with the Val allele, which is similar to our findings.²⁴

In a recent study²⁵ in which the influence of COMT genotype was investigated among elders with a mean age of 65, Met/Met performed better than Val/Val carriers on processing speed. However, no association was found for 4-year change in cognitive function. One potential explanation is that reliable decline in cognitive function in healthy adults may only be realized by the age of 74.²⁷ Another recent 10-year prospective study of older adults between the ages of 67 and 86 found no association between COMT and cognitive function.²⁸ However, this analysis was based on a very small sample size (n = 53) and may not have had sufficient power to detect a difference. Thus, it is possible that the present findings differ from previous studies due to age of the cohort.

Although the Val/Val genotype group displayed the lowest level of decline on the DSST in both black and white participants, the overall relationship between COMT and cognitive function was not linear for both races. In white subjects, a common linear function was observed, with Val/Val carriers showing the least amount of decline, followed by Met/Val carriers, with Met/Met carriers displaying the greatest amount of decline over 8 years. This linear pattern was not observed among black participants, with Met/Val carriers displaying the greatest amount of decline on the DSST over years. Additional studies are needed to assess whether this nonlinear pattern among black elders is valid, or whether it is attributed to the relatively small number of black participants in the Met/Met group. Given the relatively large amount of variability in the Met/Met group, we believe that the latter explains this pattern. Indeed, combining the Met/Met and the Met/Val group diminishes the amount of variability in cognitive scores and increases power in this subgroup.

While the Val/Val genotype has been shown to have detrimental effects on younger populations, the

Table 4 Mean (SE) DSST scores by COMT genotype in white and black elders

	COMT (rs4680) genotype, adjusted scores, mean (SE) ^a			
	Met/Met	Met/Val	Val/Val	p Value ^b
White elders				
Baseline	40.7 (0.6)	41.2 (0.3)	40.4 (0.5)	0.74
Change (slope)	-5.6 (1.0)	-4.8 (0.7)	-4.0 (0.9)	0.05
Black elders				
Baseline	27.9 (1.5)	28.2 (0.5)	26.2 (0.6)	0.14
Change (slope)	-4.1 (2.1)	-4.8 (0.9)	-2.6 (1.0)	0.03

Abbreviations: COMT = catechol-O-methyltransferase; DSST = Digit Symbol Substitution Test.

^aIn white subjects, adjusted for age, sex, body mass index, depression, APOE ε4, hypertension, stroke, self-rated health, alcohol use, and smoking. In black subjects, adjusted for age, sex, body mass index, stroke, diabetes, self-rated health, and smoking.

^bp Value for trend for the fixed effect of COMT genotype in a repeated-measures mixed-effects regression model.

present study suggests that this relationship may not extend to an elderly population and may indeed be the reverse. It is hypothesized that the ideal level of dopamine for optimal cognitive function may be lower in older adults due to a reduction in dopamine receptors with age.²⁹ Interestingly, one study showed COMT enzyme activity to be more than 30% lower in the postmortem brain of patients with dementia compared to normal controls. Furthermore, decreased COMT activity in the prefrontal cortex of patients with dementia was associated with increased severity of disease and poorer cognition.³⁰ Thus, lower enzyme activity, which is commonly found in the Met/Met genotype, seems to be associated with cognitive impairment in late life.

Although the underlying mechanism for the association between COMT and cognitive function remains unclear, alterations in dopaminergic function is a likely pathway. Reduced enzyme activity decreases the degradation and increases the concentration of dopamine in the brain, which further enhances cognitive function. From this, it has been hypothesized that the Met allele, associated with reduced enzyme activity compared to the Val allele, is related to higher dopaminergic function and thus better cognitive outcome. However, studies have shown that the effects of dopamine on cognitive function can be expressed as an inverted u-shaped dose-response curve, in which too much or too little dopamine results in poor cognitive function. Indeed, Val/Val carriers who are given amphetamines (increasing low baseline dopamine levels) do as well as Met/Met carriers on a working memory task. However, when Met/Met carriers are given amphetamines, they perform more poorly than Val/Val carriers.³¹

COMT may also influence other physiologic factors that can influence cognition. A recent population-based study³² found an association between COMT genotype and estimates of abdominal obesity in middle-aged white men, with Met/Met carriers displaying the highest waist-to-hip ratio and sagittal abdominal diameter compared to other groups. Met/Met carriers were also found to have higher blood pressure and heart rate compared to Val/Val carriers. All of these factors have been noted as potential mid- and late-life risk factors that may determine cognitive impairment in late life.³³⁻³⁷ While we adjusted for several cardiovascular risk factors and disease, we still found an association between COMT genotype and cognitive decline. Future studies should further investigate the relationship between COMT and cognitive function and assess whether it is mediated/moderated by central obesity or other cardiovascular risk factors.

Strengths of the present study include the Health ABC cohort, which includes both black and white men and women, thus allowing generalizability of results to a diverse population of well-functioning elders. We were able to test for genotype-by-race and genotype-by-sex interactions, which were not found to be significant. Furthermore, we were able to adjust for potential confounders, such as BMI, health status (e.g., stroke), and health-related behaviors (e.g., smoking). However, additional neurocognitive tests would have been optimal, to assess all cognitive domains in late life. Furthermore, as COMT rs4680 was the only SNP analyzed in the present study, we cannot be certain that these associations are specific to this SNP, or whether they are due to a complex interaction of functional loci within the gene. It may be that the Val¹⁵⁸Met SNP interacts with other SNPs to determine phenotype.³⁸ Further, the Val¹⁵⁸Met SNP is the only common missense polymorphism in this region of the COMT gene (exon 4), but is in linkage disequilibrium with several synonymous substitutions which have been postulated to modulate COMT activity by altering mRNA secondary structure. Thus the effect of COMT on cognition may reflect this linkage disequilibrium rather than the Val>Met substitution itself.³⁸

Although the mediating mechanism remains unclear, supporting the influence of COMT genotype on cognitive function is informative for potential treatment or prevention programs that aim at controlling COMT enzymatic activity in the brain through pharmacologic interventions. Studies have shown that COMT inhibitors may improve cognitive function in patients with Parkinson disease.³⁹ Furthermore, drug-by-COMT genotype interactions have been reported in the effect of COMT inhibitors on cognitive function in healthy individuals.⁴⁰ In a randomized control trial that assessed the effects of tolcapone (COMT inhibitor) on cognitive function in healthy young adults, tolcapone improved cognitive performance on an episodic memory task in Val/Val carriers but worsened performance in Met/Met carriers.⁴⁰

Altogether, the present findings suggest COMT genotype is associated with change in global and executive cognitive function over an 8-year period in a biracial cohort of elderly men and women. We report an association between the Val allele and maintenance of cognitive function in black and white elders. Additional studies are needed to confirm the negative impact of the Met allele on cognitive decline in late life.

AUTHOR CONTRIBUTIONS

Study design and concept was by A.J.F. and approved by K.Y. The manuscript was written by A.J.F. and reviewed by K.Y. Analyses were per-

formed by K.L. and interpreted by A.J.F. and K.Y. Final approval of submitted version was by all coauthors. Statistical analysis was conducted by K.L.

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DISCLOSURE

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New Guideline Addresses Issue of Driving with Dementia

A new evidence-based clinical guideline published by the American Academy of Neurology in the April 20, 2010, edition of the journal *Neurology*® urges people with dementia who drive to proceed with caution and prepare to give up their keys eventually. Accepting the driving risks associated with dementia requires careful thought by all involved. In time, however, nearly all people with dementia will have to give up driving. It is important for doctors to discuss this with patients and caregivers soon after diagnosis. Physicians should consider multiple information sources to evaluate driving safety (e.g., cognitive tests, on-road driving tests). It is important that the decision to stop driving be directed by a doctor trained and experienced in working with people with dementia and their families. Visit www.aan.com/go/practice/guidelines for more information.