D_2 Dopamine Receptor A1 Allele in Alzheimer Disease and Aging

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Background: The apolipoprotein E4 (*APOE*4*) allele is a major risk factor for the common forms of late-onset Alzheimer disease (AD), but does not account for all the genetic variation in late-onset AD; hence, other genetic markers must be examined. The D_2 dopamine receptor (*DRD2*) *A1* allele is associated with abnormal brain function and decreased DRD2s. These receptors are decreased in hippocampus and amygdala in AD, and allele frequencies may vary with age.

Objective: To study *APOE* and *DRD2* genotypes in patients with AD and cognitively intact controls of varying ages.

Design: The *DRD2* and *APOE* genotypes were examined in 832 unrelated white subjects, including 554 patients with AD (486 sporadic; 68 familial) and 278 controls. Logistic regressions tested *A1* allele effects on disease status and age, and *DRD2* linkage with AD was investigated in 60 families with late-onset AD.

Setting: University medical centers.

Subjects: Patients (mean±SD age, 74.6±8.1 years; range, 52-98 years) had probable AD, according to standard consensus diagnostic criteria; controls (mean±SD age, 69.2±8.6 years; range, 50-93 years) were cognitively intact.

Main Outcome Measures: Disease status, age, and DRD2 linkage with AD.

Results: No association between the *DRD2* and *APOE* alleles was found, and the presence of the *A1* allele did not increase the risk for AD. There was also no evidence of linkage between *DRD2* and AD. Age analyses, including both patients and controls, indicated a decrease in *A1* allele frequency with age.

Conclusions: The *A1* allele does not contribute to AD risk, alone or in combination with the *APOE*4* allele. The *DRD2 A1* allele frequencies decrease with age in both patients and controls. Thus, studies of *DRD2* disease association need to control for age.

Arch Neurol. 1997;54:281-285

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ALZHEIMER DISEASE (AD), the most common form of cognitive decline among elderly persons, afflicts 5% of people older than 65 years and accounts for the most striking rise in dementia incidence in the very old.[1,2] In the search for causes, many investigations have focused on genetic factors (**Table 1**). Discoveries to date include findings of mutations of genes on chromosome 1,[3,4] chromosome 14,[5] or less commonly, chromosome 21[6] as causes of the familial form of AD that begins before the age of 60 years. For the more common late-onset AD, evidence for chromosome 19 involvement[7] has been confirmed by studies[8-11] showing a strong association between the apolipoprotein E (*APOE*) locus on chromosome 19 and familial and sporadic AD. The *APOE*4* allele confers a major dose-related risk for late-onset familial and sporadic AD,[12] while *APOE*2* confers protection.[13] The *APOE*4* associations also have been reported for early-onset AD.[14]

Although the evidence supports *APOE* as a major risk factor in late-onset AD, some large, genetically informative, late-onset families have affected members without *APOE*4*, pointing to other genetic risk sources.[12] In fact, the available data indicate that APOE accounts for only 45% to 55% of the genetic variation observed in late-onset AD.[15] Additional genetic markers, therefore, require examination.

Several lines of evidence suggest possible involvement of the D_2 dopamine receptor (*DRD2*) gene (located in 11q23) in AD. The number of DRD2s in hippocampus and amygdala is decreased in brains with AD,[16,17] and studies of the *Taq* I polymorphism of the *DRD2* gene indicate that the less frequent *A1* allele is associated with decreased DRD2 binding sites.[18] Other studies suggest that the *A1* allele is associated with reduced visuospatial function,[19] as well as prolonged P300 latency,[20] a cognitive, event-related brain potential also prolonged in AD.[21] To our knowledge, we report herein the first study

SUBJECTS AND METHODS

Subjects for the association study were 554 patients with probable AD, according to the standard consensus diagnostic criteria.[23] No reported family history of AD or dementia was present in 486 patients (*A1*, sporadic cases), and another 68 unrelated patients had a family history of 2 or more first-degree relatives with dementia (*A1*, familial cases). The average (±SD) age at examination was 74.6±8.1 years (range, 52-98 years) for all patients (sporadic, 74.1±8.1; familial, 78.5±7.3) and the average (±SD) age at onset of dementia was 69.0±8.6 years (range, 44-94 years) for all patients (sporadic, 68.9±8.5; familial, 69.9±9.1). Sex ratios favored women who represented 62% of all patients (sporadic, 61%; familial, 62%).

Genotype and allele frequencies for patients were compared with those of 278 unrelated, cognitively intact controls aged 50 to 93 years (mean±SD, 69.2±8.6 years). Controls also had no family history of AD, and 55% were women.

To determine whether the *DRD2* gene is passed on through generations along with AD, linkage analysis was performed using 60 families with AD from the National Alzheimer's Disease Cell Bank of Indiana University, Indianapolis. Each family had 2 or more sampled affected relatives meeting standard clinical criteria for AD.[23] These families contained 133 genotyped, affected persons and 214 unaffected, at-risk, genotyped persons. The average (±SD) age at onset for affected relatives was 70.0±7.5 years, and 61% were women.

All subjects were white and were recruited from the National Institute on Aging Alzheimer's Disease Centers and affiliated clinics. Patients and controls were referred to these sites by other university and community physicians and staff, the local chapters of the Alzheimer's Association, and others in the community. Those recruited for the association studies came from the University of California, Los Angeles, Alzheimer's Disease Center and affiliates (Neuropsychiatric Institute and Hospital and West Los Angeles Veterans Affairs Medical Center: 19 sporadic cases of AD, 38 familial cases of AD, and 16 controls), the Joseph and Kathleen Bryan Alzheimer's Disease Research Center Memory Disorders Clinic at Duke University, Durham, NC (274 sporadic cases of AD, 188 controls), the Massachusetts General Hospital Memory Disorders Clinic, Charlestown (193 sporadic cases of AD, 74 controls), and the National Alzheimer's Disease Cell Bank of Indiana University (30 familial cases of AD). Mean subject ages, sex ratios, and allele frequencies did not differ significantly among recruitment sites (data not shown). All clinical diagnoses were made with investigators blinded to genetic data. Prior to study enrollment, informed consent was obtained from subjects or, if necessary, their legal guardians. All study protocols were approved by the human subjects protection committees at each participating site.

DNA was obtained from blood samples using standard techniques either from direct extraction or from lymphoblast cultures. The *APOE* and *DRD2* genotypes were determined as previously described.[10,19,24-26] Resulting gels and autorads were visually scored, and data entered into computerized database systems.

Allele frequencies were compared with Pearson χ^2 tests. A conditional logistic regression model was constructed to assess whether the risk of AD was associated with the presence of the *DRD2 A1* allele and the number of *APOE*4* alleles, while controlling for age at examination and sex. A logistic regression model also was used to determine the effect of age on *A1* allele presence controlling for disease status, number of *APOE*4* alleles, and sex. Because of the small number of subjects homozygous for the *A1* allele, the homozygous and heterozygous categories were collapsed.

To determine whether the DRD2 marker is linked to AD, 2-point lod scores (logarithm to base 10 of the odds in favor of linkage) were calculated as previously described.[7] By convention, a lod score of 3 (odds of 1000:1 in favor) indicates proof of linkage, while a lod score of −2 (100:1 against) is accepted as proof that linkage is not present. Affected relative pair linkage analysis was calculated using software (SimIBD) described by Davis et al.[27] A computer program (VITESSE)[28] was used in the lod score analysis. Both autosomal-dominant and autosomal-recessive models of inheritance were tested. Because of the late and variable age at onset in AD, a low-penetrance analysis was performed for each of the models examined. In a low-penetrance model, phenotypic information on disease status is included for affected persons only, while genotypic (marker) data are included on all participating family members.

Table 1. Genetic Discoveries in Alzheimer Disease*

Gene	Chromosome	Onset	% of Cases	Comments
APP	21	Early	<<1	Autosomal dominant
APOE	19	Late and early	50	Familial and sporadic
Presenilin 1	14	Early	<5	Autosomal dominant
Presenilin 2	1	Early	<<1	Autosomal dominant
Other	Unknown	Late	50	Unknown number of genes

**Percentage of cases indicates estimates of actual percentages; APP, amyloid precursor protein; APOE, apolipoprotein E; early, younger than 60 years; and late, 60 years of age or older.*

examining *DRD2* genotypes in patients with AD and cognitively intact controls of varying ages. Our aim is to determine whether the *DRD2 A1* allele increases risk for AD, alone or in combination with the *APOE*4* allele. Because allele frequencies may vary with age,[22] we also assessed the influence of age on *A1* allele frequency.

RESULTS

There was no significant difference in *A1* allele frequencies between the 486 sporadic AD cases and the 68 unrelated familial cases with AD (0.21 vs 0.14; χ^2, 3.7; *df*, 2; *P*=.16), so all other association analyses included both groups as 1 diagnostic group. The *DRD2 A1* allele frequencies were similar for the 554 patients with AD and 278 controls (0.21 vs 0.20) but higher for patients when groups were stratified according to *APOE*4* carrier status (non-*APOE*4* carriers, 0.24 vs 0.21; *APOE*4* carriers, 0.19 vs 0.17) (**Table 2**). The *A1* allele frequencies were similar for the 494 patients (0.20) and 201 controls (0.20) who were aged 65 years or older.

As expected, the *APOE*4* allele was overrepresented in the patients with AD compared with the controls (0.42

Table 2. *DRD2* Distribution in *APOE*4* Carriers and Non-*APOE4* Carriers for AD*

	Non–*APOE*4*, No. %		*APOE*4*, No. (%)		Total, No. (%)	
	AD	Control	AD	Control	AD	Control
DRD2 alleles						
A1	87 (0.24)	86 (0.21)	140 (0.19)	26 (0.17)	**227** (0.21)	**112** (0.20)
A2	277 (0.76)	316 (0.79)	604 (0.81)	128 (0.83)	**881** (0.79)	**444** (0.80)
Total	**364**	**402**	**744**	**154**	**1108**	**556**
DRD2 genotypes						
A1/A1	8 (0.04)	4 (0.02)	11 (0.03)	4 (0.05)	**19** (0.03)	**8** (0.03)
A1/A2	71 (0.39)	78 (0.39)	118 (0.32)	18 (0.23)	**189** (0.34)	**96** (0.34)
A2/A2	103 (0.57)	119 (0.59)	243 (0.65)	55 (0.72)	**346** (0.63)	**174** (0.63)
Total	**182**	**201**	**372**	**77**	**554**	**278**

**No significant differences in the D_2 dopamine receptor (DRD2) A1 allele frequencies are observed between apolipoprotein E4 (APOE*4) allele carriers and non-APOE*4 allele carriers. The DRD2 genotypes are in Hardy-Weinberg equilibrium. AD indicates Alzheimer disease.*

Table 3. Odds Ratios for Developing Alzheimer Disease for the *APOE* and *DRD2* Genotypes*

Genotype	Odds Ratio (95% Confidence Interval)	*P*
APOE		
X/X	1.00 (Referent)	...
4/X	4.61 (3.25-6.54)	<.001
4/4	32.05 (11.23-89.75)	<.001
DRD2		
2/2	1.00 (Referent)	...
1/1 or 1/2	1.36 (0.95-1.89)	.10

**Because of the small sample size, the A1/A1 and A1/A2 genotypes were collapsed (ie, 1/1 or 1/2). X refers to either the apolipoprotein 2 (APOE*2) or APOE*3 allele. Odds ratios are controlled for age at examination and sex. DRD2 indicates D_2 dopamine receptor; ellipses, not applicable.*

Table 4. Lod Scores for 60 Families With Late-Onset Alzheimer Disease for DRD2*

	θ						
Model	0.00	0.05	0.10	0.15	0.20	0.30	0.40
Dom	−3.73	−0.49	0.12	0.34	0.40	0.37	0.09
Rec	−12.23	−2.34	−0.73	−0.03	0.28	0.33	0.12

**Low-penetrance analyses, wherein phenotypic information on disease status was included for affected persons only. Theta values indicate distance from D_2 dopamine receptor (DRD2) marker; Dom, assumes dominant mode of inheritance for disease gene; and Rec, assumes recessive mode of inheritance for disease gene.*

vs 0.13; χ^2, 132.2; *df*, 2; $P<.001$), and the control frequency for *APOE*4* was not significantly different from those reported elsewhere. The distributions of the *APOE* and *DRD2* genotypes were in Hardy-Weinberg equilibrium for the patients and the controls (data not shown).

The logistic regression examining the main effects of the *APOE*4* allele and the presence of the *DRD2 A1* allele confirmed the dose-dependent effect of the *APOE*4* allele ($P<.001$) and found no effect of the *DRD2 A1* allele (**Table 3**). No significant interaction was found between the 2 genes on the risk of AD using a likelihood ratio test (χ^2, 0.34; *df*, 2; $P=.84$) (data not shown).

For the linkage analysis on the 60 families with late-onset AD, the 2-point lod scores are given in **Table 4**. Tight linkage was excluded with the *DRD2* locus for both age-adjusted and the low-penetrance analyses. In addition, results of the linkage analysis (SimIBD)[27] provided no evidence of linkage or association between AD and *DRD2* ($P=.68$).

To assess the influence of the presence of the *A1* allele on age, we used a logistic regression, controlling for diagnostic status, sex, and number of *APOE*4* alleles, and found a significant negative association between the presence of the *A1* allele and age ($\beta=-.022$; SE, 0.009; $P=.01$). The conditional odds ratio for a 10-year increase in age is 0.800 (95% confidence interval, 0.668-0.958). For both patients and controls, *A1* allele frequencies decreased at the age of 80 years or older (**Figure**).

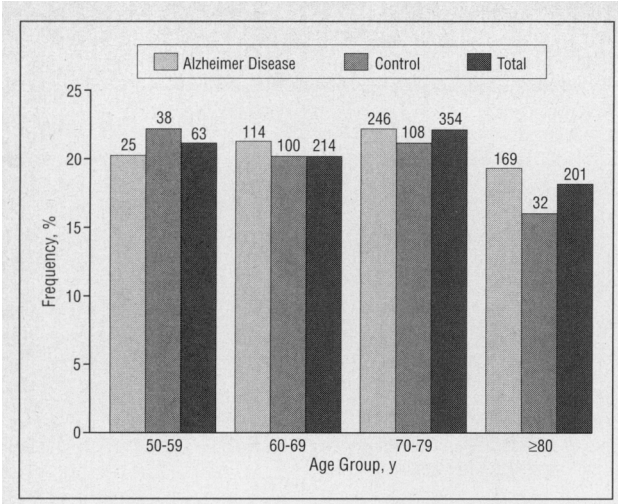
COMMENT

RISK FOR AD

These data are consistent with previously reported data sets,[10,29,30] indicating a dose-dependent effect for *APOE*4*. Because the *APOE*4* allele is neither necessary nor sufficient for the occurrence of AD, searches for other genetic risk sources are reasonable. Although the patients with AD and controls had similar *A1* allele frequencies (0.21 vs 0.20, Table 2), when subjects were stratified according to *APOE*4* carrier status, patients had higher *A1* allele frequencies than controls. The logistic regression, however, failed to demonstrate a significantly increased risk for AD from the *A1* allele. Moreover, there was no evidence of linkage between *DRD2* and AD. Together, these findings argue against an *A1* allele effect in AD.

AGE EFFECTS

We found a significant negative association between the presence of the *A1* allele and age using a logistic regression model. Moreover, the lack of a *DRD2* and *APOE* interaction indicates that the *A1* allele effect on age is independent of previously reported age effects for *APOE*4*.[22,31,32] The observation that *A1* allele frequency decreases with age suggests that the allele is



A1 *allele frequencies according to age group. Figures above bars indicate number of subjects.*

associated with reduced survival both in patients with AD and controls. Several hypotheses could explain such a result. The *DRD2* gene may be in genetic linkage disequilibrium with the actual longevity-reducing mutation. When 2 loci are close enough together on the genome so that recombination rarely occurs, such linkage disequilibrium can exist so that alleles are passed through generations in *cis* orientation. This leads to an increase in the linked *cis* allele, although it has no biological role in the disease of interest.

An alternate explanation is that the *DRD2* gene has a direct biological role in reducing survival. The precise mechanism is unknown, but the association of the *A1* allele with diminished DRD2 binding sites[18] suggests binding site availability as a possible mediating factor. Another potentially relevant factor is the observation in some studies that the *A1* allele is associated with alcoholism[33] and other substance dependencies,[34,35] and DRD2s appear to mediate response to such drugs of abuse as cocaine.[36] Physical illnesses (eg, cirrhosis) associated with alcoholism and other forms of substance abuse could be the critical mediating factor resulting in premature death and thus explaining the lower *A1* allele frequency in older subjects in the present study.

Regardless of the mechanism explaining these findings, such age-related changes in *A1* allele frequency could contribute to inconsistencies of previous disease association studies. For example, some studies of *A1* allele frequency in alcoholism have compared patients and controls of significantly different ages,[37] or else have not reported the ages of controls[38] or of both patients and controls.[39] One report[40] showing considerable variability in *A1* allele frequency in different ethnic groups did not report subject ages. Although the contribution of age to allele frequency may be minimal in some of these studies, failure to consider age could result in skewed findings and explain some of the inconsistencies from study to study.

In summary, these findings argue for controlling age in disease association studies involving the *DRD2 A1* allele. They also suggest several hypotheses requiring additional study. Investigations of other genetic polymorphisms within the *DRD2* gene, particularly those closer to the promotor region, might reveal allelic associations that more accurately reflect DRD2 binding site concentrations in the brain. Such studies also could provide more direct evidence for the possibility that DRD2 concentrations mediate the decrease in *A1* allele frequency associated with old age.

Accepted for publication November 11, 1997.

This study was supported by the following grants: University of California, Los Angeles: 1R29 MH46424, MH52453, and AG13308 from the Public Health Service (UCLA Clinical Research Center MO1 RR00856-21) and IRG94101 from the Alzheimer's Association (Dr Small); AG10123 from the UCLA Alzheimer's Disease Center; opportunity funds from UCLA Neuropsychiatric Institute (Drs Small and Noble); and the Charles A. Dana Foundation, New York, NY (Dr Small). Duke University Medical Center, Durham, NC: NS31153 (Drs Pericak-Vance and Haines), NS26630 (Dr Pericak-Vance), AG05128 (Drs Roses and Saunders), AG11268 (Dr Pericak-Vance), and a LEAD award for excellence in Alzheimer's disease (Dr Roses). Indiana University, Indianapolis: P50-AG0-5128 (Dr Conneally). Massachusetts General Hospital, Charlestown: a Zenith Award from the Alzheimer's Association (Dr Haines).

The views expressed are those of the authors and do not necessarily represent those of the Department of Veterans Affairs.

We thank the families and patients with AD without whose help and participation this work would not have been possible, and the Joseph and Kathleen Bryan Alzheimer's Disease Research Center at Duke University. We also thank Fawzy Fawzy, MD, for his support of this project and Richard A. Gatti, MD, and Thomas Belin, PhD, for their helpful suggestions.

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REFERENCES

1. Bachman DL, Wolf PA, Linn R, et al. Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. *Neurology.* 1992;42:115-119.
2. Brayne C, Gill C, Huppert FA, et al. Incidence of clinically diagnosed subtypes of dementia in an elderly population: Cambridge Project for Later Life. *Br J Psychiatry.* 1995;167:255-262.
3. Levy-Lahad E, Wasco W, Poorkaj P, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science.* 1995;269:973-977.
4. Rogaev EI, Sherrington R, Rogaeva EA, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature.* 1995;376:775-778.
5. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature.* 1995;375:754-760.
6. Goate A, Chartier-Harlin M-C, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature.* 1991;349:704-706.
7. Pericak-Vance MA, Bebout JL, Gaskell PC, et al. Linkage studies in familial Alzheimer disease: evidence for chromosome 19 linkage. *Am J Hum Genet.* 1991;48:1034-1050.
8. Alzheimer's Disease Collaborative Group. Apolipoprotein E genotype and Alzheimer's disease. *Lancet.* 1993;342:737-738.
9. Mayeux R, Stern Y, Ottman R, et al. The apolipoprotein epsilon 4 allele in patients with Alzheimer's disease. *Ann Neurol.* 1993;34:752-754.

10. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele E4 with late onset familial and sporadic Alzheimer's disease. *Neurology.* 1993;43:1467-1472.
11. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to B-amyloid and increased frequency of type 4 allele in late onset familial Alzheimer disease. *Proc Natl Acad Sci U S A.* 1993;90:1977-1981.
12. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science.* 1993;261:921-923.
13. Corder EH, Saunders AM, Risch MJ, et al. Apolipoprotein E type 2 allele and the risk of late onset Alzheimer's disease. *Nature Genet.* 1994;7:180-183.
14. Okuizumi K, Onodera O, Tanaka H, et al. ApoE-ε4 and early-onset Alzheimer's. *Nature Genet.* 1994;7:10-11.
15. Roses AD, Devlin B, Conneally PM, et al. Measuring the genetic contribution of APOE in late-onset Alzheimer disease (AD). *Am J Hum Genet.* 1995;57 (suppl):A202.
16. Joyce JN, Kaeger C, Ryoo H, Goldsmith S. Dopamine D2 receptors in the hippocampus and amygdala in Alzheimer's disease. *Neurosci Lett.* 1993;154:171-174.
17. Ryoo HL, Joyce JN. LOS of dopamine D2 receptors varies along the rostrocaudal axis of the hippocampal complex in Alzheimer's disease. *J Comp Neurol.* 1994;348:94-110.
18. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D_2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch Gen Psychiatry.* 1991;48:648-654.
19. Berman SM, Noble EP. Reduced visuospatial performance in children with D2 dopamine receptor A1 allele. *Behav Genet.* 1995;25:45-58.
20. Noble EP, Berman SM, Ozkaragoz TZ, Ritchie T. Prolonged P300 latency in children with the D_2 dopamine receptor A1 allele. *Am J Hum Genet.* 1994;54: 658-668.
21. Ball SS, Marsh JT, Schubarth G, et al. Longitudinal P300 latency changes in Alzheimer's disease. *J Gerontol.* 1989;44:195-200.
22. Schachter F, Faure-Delenef L, Guenot F, et al. Genetic associations with human longevity at the APOE and ACE loci. *Nature Genet.* 1994;6:29-32.
23. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-944.
24. Sambrook J, Fritsch EF, Maniatas T. *Molecular Cloning: A Laboratory Manual.* 2nd ed. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 1989: B24.
25. Hixson JE, Vernier DR. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with *Hha* I. *J Lipid Res.* 1990;31:545-548.
26. Wenham PR, Price WH, Blundell G. Apolipoprotein E genotyping by one-stage PCR. *Lancet.* 1991;337:1158-1159.
27. Davis S, Schroeder M, Goldin LR, Weeks DE. Nonparametric simulation-based statistics for detecting linkage in general pedigrees. *Am J Hum Genet.* 1996; 57:A190.
28. O'Connell JR, Weeks DE. The VITESSE algorithm for rapid exact multilocus linkage analysis via genotype set-recoding and fuzzy inheritance. *Nat Genet.* 1995;11:402-408.
29. Locke P, Conneally PM, Tanzi RE, et al. APOE and Alzheimer disease: examination of allelic association and effect on age at onset in both early- and late-onset cases. *Genet Epidemiol.* 1995;12:83-92.
30. Haines JL, Pritchard ML, Saunders AM, et al. No genetic effect of α^1-antichymotrypsin in Alzheimer disease. *Genomics.* 1996;33:53-56.
31. Rebeck GW, Perls TT, West HL, et al. Reduced apolipoprotein e4 allele frequency in the oldest old Alzheimer's patients and cognitively normal individuals. *Neurology.* 1994;44:1513-1516.
32. Corder EH, Saunders AM, Strittmatter WJ, et al. Apolipoprotein E, survival in Alzheimer's disease, and the competing risks of death and Alzheimer's disease. *Neurology.* 1995;45:1323-1328.
33. Pato CN, Macciardi F, Pato MT, et al. Review of the putative association of dopamine D2 receptor and alcoholism: a meta-analysis. *Am J Med Genet.* 1993; 48:78-82.
34. Smith SS, O'Hara BF, Persico AM, et al. Genetic vulnerability to drug abuse: the D2 dopamine receptor TaqI B1 restriction fragment length polymorphism appears more frequently in polysubstance abusers. *Arch Gen Psychiatry.* 1992; 49:723-727.
35. Noble EP, Blum K, Khalsa ME, et al. Allelic association of the D_2 dopamine receptor gene with cocaine dependence. *Drug Alcohol Depend.* 1993;33:271-285.
36. Self DW, Barnhart WJ, Lehman DA, Nestler EJ. Opposite modulation of cocaine-seeking behavior by D_1- and D_2-like dopamine receptor agonists. *Science.* 1996; 271:1586-1589.
37. Parsian A, Todd RD, Devor EJ, et al. Alcoholism and alleles of the human D_2 dopamine receptor locus: studies of association and linkage. *Arch Gen Psychiatry.* 1991;48:655-663.
38. Bolos AM, Dean M, Lucas-Derse S, Ramsburg M, Brown GL, Goldman D. Population and pedigree studies reveal a lack of association between the dopamine D_2 receptor gene and alcoholism. *JAMA.* 1990;264:3156-3160.
39. Comings DE, Comings BG, Muhleman D, et al. The dopamine D_2 receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA.* 1991;266:1793-1800.
40. Barr CL, Kidd KK. Population frequencies of the A1 allele at the dopamine D_2 receptor locus. *Biol Psychiatry.* 1993;34:204-209.