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D10S1423 Identifies a Susceptibility Locus for Alzheimer's Disease (*AD7*) in a Prospective, Longitudinal, Double-Blind Study of Asymptomatic Individuals: Results at 14 Years

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Abstract

Typical forms of Alzheimer's disease (AD) appear to be influenced by multiple susceptibility loci. This report describes the prospective, longitudinal, double-blind assessment of the age-specific risk of AD encountered by 325 asymptomatic first-degree relatives of AD probands who carried the D10S1423 (*AD7*) 234bp allele, the *APOE E4* allele, or both, after 14 years of systematic follow-up. A total of 30 incident cases of AD were detected during the first 3752 subject-years of surveillance. The effects of carrying either or both of the D10S1423 234bp and *APOE E4* alleles on the age-specific risk of developing AD were determined using Kaplan-Meier survival analysis. The risk of developing AD was the greatest for individuals who carried both alleles (Mantel-Cox statistic = 16.46, df = 3, p = 0.0009; Breslow statistic = 13.38, df = 3, p = 0.004). Cox proportional hazards models were developed to estimate the risk ratios for each genotype, controlling for the potential effects of age at recruitment, sex, and years of education. Only individuals who carried both risk alleles exhibited a risk ratio that differed significantly from 1 (risk ratio = 7.5, p = 0.002, 95% C.I. = 2.1 to 27.0). Neither age at recruitment, sex, nor years of education made significant contributions to the model, although women tended to be at greater risk (p = 0.06). Recent evidence that D10S1423 resides within open reading frame C10orf112, whose predicted product resembles a low-density lipoprotein receptor, suggests a molecular mechanism for this gene-gene interaction.

Keywords

Alzheimer's Disease; Genetics; D10S1423; *AD7*; C10orf112; Prospective; Longitudinal Study; Asymptomatic Individuals at Risk

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and mental impairment among the elderly (Alzheimer's Association, 2009). The defining features of AD include progressive, global cognitive impairment that develops in individuals whose brains manifest densities of senile plaques that exceed those expected for age (Khachaturian, 1985; Mirra et al., 1991). However, patients with this disorder manifest remarkable inter-individual variability in other clinical characteristics, including age at symptomatic onset; rate and

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pattern of progression; emergence of disturbances of mood, thought, perception, and behavior; development of extrapyramidal symptoms; and presence of a family history of AD-like dementia (Zubenko, 1997). Postmortem and genetic studies have also revealed considerable inter-individual variation in comorbid neuropathological findings, brain neurochemical abnormalities, and contributions from particular genetic factors (Zubenko, 1997). This level of heterogeneity suggests that AD, as currently defined, may more closely resemble a syndrome with multiple contributing etiologies than a disease with a unitary cause (Zubenko, 1997).

Although they are uncommon, the majority of cases of AD that become symptomatic before the age of 60 appear to arise from highly penetrant, autosomal dominant genetic lesions. These include mutations in the structural genes for the amyloid precursor protein located on chromosome 21 (Goate et al., 1991; Murrell et al., 1991), presenilin 1 located on chromosome 14 (Schellenberg et al., 1992; St. George-Hyslop et al., 1992; AD Collaborative Group, 1995; Sherrington et al., 1995), presenilin 2 located on chromosome 1 (Levy-Lahad et al.. 1995; Rogaev et al., 1995), as well as genetic lesions that result in Down's syndrome (Holland, 1994). More typical, later-onset forms of AD appear to be influenced by multiple susceptibility loci, combinations of which contribute to the development of this disorder by mechanisms that remain uncertain. One such locus, *APOE*, is the structural gene for an apolipoprotein involved in lipid transport and metabolism (Myklebost and Rogne, 1988). An association of the *APOE E4* allele with late-onset familial and sporadic AD has been observed in many populations throughout the world and is now well established (Saunders et al., 1993; Farrer et al., 1997).

Twin studies suggest that genetic factors may account for as much as 80% of the risk of AD (Gatz et al., 2006). However, the known AD susceptibility genes have been estimated to account for only a portion of the heritability of AD, underscoring the importance of continuing the search for additional AD risk loci. With this goal in mind, we reported the results of a systematic survey of the human genome for the identification of highly informative DNA polymorphisms (SSTRPs) that identify new AD risk loci (Zubenko et al., 1998a,b). In addition to the *APOE* locus, our survey detected five novel candidate susceptibility loci for AD, including D10S1423. An association of the D10S1423 234bp allele with AD has been reported in three independent samples of AD cases and controls (Boston, Pittsburgh, Bonn)(Zubenko et al., 1998a,b; Majores et al., 2000). Data from these case-control studies also suggest a strong synergistic interaction between the D10S1423 234bp and *APOE E4* risk alleles. Patients with autopsy-confirmed AD who carry the D10S1423 234bp allele have been reported to manifest substantially lower levels of cortical dopamine and relative preservation of cortical norepinephrine levels compared to non-carriers, a neurochemical finding that further supports a role for this anonymous genotype in the pathophysiology of AD (Zubenko et al., 1999).

The results of these association studies have been supported by a prospective, longitudinal, double-blind assessment of the age-specific risk of AD encountered by 325 asymptomatic first-degree relatives of AD probands who carried the D10S1423 234bp allele, the *APOE E4* allele, or both, after 11.5 years of systematic follow-up (Zubenko et al., 2001). A total of 18 incident cases of AD were detected during the first 3379 subject-years of this longitudinal study. The effects of carrying either or both of the D10S1423 234bp and *APOE E4* alleles on the age-specific risk of developing AD were determined using Kaplan-Meier survival analysis. The age-specific risk of developing AD was the greatest for individuals who carried both alleles (Mantel-Cox statistic = 20.12, df = 3, $p = 0.0002$; Breslow statistic = 13.36, df = 3, $p = 0.004$). Cox proportional hazards models were developed to estimate the risk ratios for each genotype, controlling for the potential effects of age at recruitment, sex, and years of education. In the resulting best fitting model, only individuals who carried both

risk alleles exhibited a risk ratio that differed significantly from 1 (risk ratio = 16.2, p = 0.008, 95% confidence interval = 2.1 to 128.3). In 2001, McKusick named the AD risk locus identified by the D10S1423 polymorphism *AD7* in Online Mendelian Inheritance in Man (MIM number 606187; 2005). This report describes the continuation of our prospective assessment of the age-specific risk of AD encountered by asymptomatic first-degree relatives in this cohort who carried the D10S1423 234bp allele, the *APOE E4* allele, or both, after 14 years (3752 subject-years) of systematic follow-up.

SUBJECTS AND METHODS

Recruitment of the AD High-Risk Cohort

The original AD high-risk cohort (ADHRC) consisted of 330 first-degree relatives of 189 demented probands who met NINCDS-ADRDA criteria for possible (n=35), probable (n=103), or definite (n=6) AD (McKhann et al., 1984) and/or *DSM-III-R* criteria(APA, 1994) for primary degenerative dementia of the Alzheimer's type (n=45). Members of the cohort were between the ages of 40 and 75 and were cognitively intact at the time of recruitment as determined by a review of medical and psychiatric history, a survey of current activities of daily living, a mental status examination, and the Mini-Mental State Examination (MMSE; Folstein et al., 1975). Subjects with any clinical evidence of cognitive decline or impairment, or a MMSE score of <27, were excluded. For 303 of the 330 subjects, the MMSE was augmented by the more detailed Mattis Dementia Rating Scale (MDRS; Mattis, 1976), and all individuals tested had MDRS scores in the range expected for healthy elderly controls (≥135). All members of the cohort provided written informed consent for participation in this study, which was approved by the Biomedical Institutional Review Board of the University of Pittsburgh.

Longitudinal Surveillance Protocol

Semi-structured telephone assessments were initiated on March 1, 1989, and performed approximately annually by a research nurse with specialized experience in geriatrics who remained blind to the laboratory data. The telephone assessments included a review of the items on the Family History Form of Huff and colleagues(1988; Zubenko et al., 1988) and a survey of the subjects' activities of daily living. Subjects and their identified "best" informants were encouraged to contact the research nurse if any evidence of a change in mental functioning occurred during the interim. To determine the sensitivity and specificity of the telephone assessments for the detection of individuals with newly emergent cognitive impairment, 202 members of the AD high-risk cohort were re-evaluated by in-person interviews. The telephone assessments detected subjects whose Clinical Dementia Rating scores (CDR; Hughes et al., 1982) exceeded 0 with a sensitivity of 82% and a specificity of 98%. These cross-sectional determinations seem likely to underestimate the sensitivity and specificity of the telephone assessments for identifying cases of progressive dementia when administered longitudinally over a period of years.

In-person assessments were performed when evidence suggestive of emergent cognitive dysfunction was reported during the telephone screen. If the presence of cognitive impairment suggested by the telephone screen was supported by a MMSE score <27, a MDRS score <135, a CDR score >0, or other clinical evidence obtained during the in-person evaluation, the subject was referred for a complete diagnostic evaluation. If no such evidence was detected, the frequency of the periodic telephone follow-up was increased to approximately every six months. Clinical diagnoses of AD among incident cases of dementia were established according to the *DSM-III-R* criteria and NINCDS-ADRDA criteria, as applied by board-certified specialists with added qualifications in geriatric psychiatry. Autopsies were performed by board-certified neuropathologists and

neuropathologic diagnoses were made according to generally accepted criteria (Tomlinson and Corsellis, 1984; Khachaturian et al., 1985; Mirra et al., 1991).

Laboratory Methods

Venous blood samples were obtained by antecubital phlebotomy by qualified clinical staff who coded the samples prior to transport to the laboratory. Lymphocytes were isolated under sterile conditions by centrifugation on an Histopaque 1077 step gradient according to the manufacturer's instructions (Sigma Chemical, St. Louis, MO). Lymphoblast cell lines were established by exposure of lymphocytes to Epstein Barr virus.

Genotyping of coded samples was performed by laboratory staff who were blind to sociodemographic and clinical information. Genomic DNA was isolated from lymphocytes or lymphoblasts using minor modifications of standard methods (Miller et al., 1988; Zubenko et al., 1993). Genotyping of the D10S1423 polymorphism was performed as previously described (Zubenko et al., 1998b), using polymerase chain reaction (PCR) methodology employing the oligonucleotide primer pair included in the CHLC Human Screening Set/Weber Version 6 (Research Genetics, Huntsville, AL). Following amplification, the resulting PCR products were resolved by electrophoresis under denaturing conditions, visualized by autoradiography, and sized by comparison to individuals of known genotypes from the CEPH panel, 1331-01 and 1331-02 (Coriell Institute, Camden, NJ). Genotyping of the *APOE* locus was performed using PCR methodology and the oligonucleotide primers (Gibco BRL, Gaithersburg, MD) described by Hixson and Vernier (1990). The radiolabeled products of each amplification were digested with endonuclease *Hha* I and the resulting fragments were resolved by electrophoresis under nondenaturing conditions. The labeled restriction fragments were visualized by autoradiography and allele assignments were made as previously described (Zubenko et al., 1994).

Statistical Analysis

Distributions of continuous variables among cases and non-cases were examined using the t statistic. Categorical variables were compared between cases and non-cases using the χ^2 statistic or Fisher's exact test as appropriate. Survival analyses employing the Kaplan-Meier product limit method and Cox proportional hazards models, with adjustment for covariates, were performed using SPSS Version 15.0 for Windows (SPSS, Chicago, IL).

RESULTS

A description of the AD high risk cohort and 30 incident cases of AD is presented in Table 1. The cohort was composed almost entirely of Caucasians and included approximately equal proportions of men and women. The subjects had a mean age of 56.1 years at the time of entry into the longitudinal study and a mean age of 68.2 years at the time of their most recent follow-up assessment. On average they had completed a high school education. Consistent with the criteria for entry into the study, all subjects were cognitively intact as reflected by a mean MMSE score approaching 30. As expected, the proportions of individuals in the high risk cohort who carried the D10S1423 234bp or *APOE E4* alleles, 40.6% and 46.8%, were approximately midway between those observed for autopsy-confirmed AD cases and controls reported in our genome survey (Zubenko et al., 1998b).

A total of 62 of the 189 probands with clinically diagnosed AD were autopsied during the course of this study and the diagnosis was histopathologically confirmed in 60 (96.8%) of these 62 cases. Of the two autopsied cases that did not meet histopathologic criteria for AD, one exhibited striatonigral degeneration and the other exhibited neuronal loss without findings to support a more specific diagnosis. To date, the annual rate of attrition from this

longitudinal study has averaged 2.3% and the most common source of attrition has been death.

A total of 64 incident cases of perceived memory impairment were detected by our surveillance protocol during the first 3752 subject-years of this longitudinal study. Thirty of these cases revealed objective evidence of cognitive impairment and developed progressive dementias that resulted in their inability to function independently. They manifested the onset of cognitive impairment at a mean age of 71.9 ± 6.9 years and the progression of their cognitive impairment has been monitored for an average of 5.6 years. In all 30 cases, medical and laboratory evaluations supported the diagnosis of AD. Following the death of one of these cases, for whom concurrent cerebrovascular disease was detected clinically, an autopsy was performed and the diagnosis of AD with multiple infarcts was determined by neuropathologic examination of the brain. The age-specific risk of AD in the ADHRC was determined using Kaplan-Meier survival analysis. As shown in Figure 1, the cumulative incidence of AD by age interval 81–85 years was 37.8% ± SE 7.5%.

The 30 incident AD cases were similar to the remaining members of the ADHRC in sex ratio, race, years of education, and cognitive performance on the MMSE at the time of recruitment (Table 1). The effects of carrying either or both of the D10S1423 234bp and *APOE E4* alleles on the age-specific risk of developing AD were determined using Kaplan-Meier survival analysis. As shown in Figure 2, the age specific-risk of developing AD was the greatest for individuals who carried both alleles (Mantel-Cox statistic = 16.46, df = 3, p = 0.0009; Breslow statistic = 13.38, df = 3, p = 0.004).

A Cox proportional hazards model was developed to estimate the risk ratios for each genotype, controlling for the potential effects of age at recruitment, sex, and years of education. In the resulting model described in Table 2, only individuals who carried both risk alleles exhibited a risk ratio that differed significantly from 1 (risk ratio = 7.5, p = 0.002, 95% C.I. = 2.1 to 27.0). Neither age at recruitment, sex, nor years of education made significant contributions to the model. However, female sex tended to be associated with increased risk of AD (risk ratio = 2.4, p = 0.06, 95% C.I. = 1.0 to 6.1).

DISCUSSION

This report provides continuing evidence from a prospective, longitudinal, double-blind study that the D10S1423 234bp and *APOE E4* alleles confer increased risk of AD among asymptomatic, first-degree relatives of AD probands, an effect that is most pronounced for individuals who carry both risk alleles (estimated risk ratio = 7.5). This principal finding supports earlier published results from this longitudinal study that were based on 18 incident AD cases detected after 11.5 year of systematic follow-up (Zubenko et al., 2001). After controlling for the potential effects of age at recruitment, sex, and years of education, only individuals who carried both risk alleles exhibited a significantly elevated risk of developing AD.

The molecular mechanism that underlies the synergistic interaction by which the D10S1423 234bp and *APOE E4* alleles contribute to the age-specific risk of AD may provide new insights into the pathophysiology of this common neurodegenerative disorder. As described in the National Center for Biotechnology Information human genome database (NCBI Build 35.1; http://www.ncbi.nlm.nih.gov/), the D10S1423 SSTRP resides within intron 10 of predicted open reading frame C10orf112. At its location deep within intron 10, it is unlikely that the D10S1423 SSTRP would directly affect the expression or properties of the predicted protein product of C10orf112. The C10orf112 gene model includes 39 predicted exons that encode seven low-density lipoprotein (LDL) receptor class a domains that mediate binding

of LDL receptors to lipoproteins, as well as nine MAM domains that are common components of membrane receptors. Recent molecular studies have revealed that 34 of the predicted 39 exons are expressed in human hippocampus (Zubenko and Hughes, 2009). These observations raise the possibility that the D10S1423 234bp allele may be in linkage disequilibrium with a regulatory or structural C10orf112 gene variant whose product interacts with the apoE4 lipoprotein to increase the age-specific risk of AD.

The selective expression of C10orf112 mRNA in human brain tissue is consistent with its involvement in the pathophysiology of AD (Zubenko and Hughes, 2009). Considerably lower expression was observed in heart tissue, and expression was undetectable in a wide range of other tissues. Selective expression of C10orf112 was also noted within brain regions. High levels of expression were observed in the hippocampus, and the occipital and parietal lobes, brain regions that undergo degeneration and manifest both senile plagues and neurofibrillary tangles in AD. However, little or no expression was observed in the frontal or temporal lobes, cortical regions that also undergo the typical degenerative changes that occur in AD, or in the cerebellum that is largely spared by this condition. We have previously suggested that the heterogeneous clinical, histopathological, neurochemical, and genetic features of AD more closely resemble a syndrome with multiple contributing etiologies than a disease with a unitary cause (Zubenko, 1997, 2000). The expression of C10orf112 in some, but not all, brain regions affected by AD is consistent with this hypothesis.

These findings may contribute to advancements in the therapeutics of AD in several important ways. Characterization of the molecular mechanisms that underlie the increased risk of AD conferred by the D10S1423 234bp and *APOE E4* alleles, and their synergistic interaction, may provide new molecular targets for therapeutic drug development. Furthermore, the continued elucidation of genetic factors that identify asymptomatic individuals at risk of developing AD will facilitate the design of therapeutic trials involving subjects who have the greatest likelihood of responding and for whom successful interventions would have the greatest impact. Finally, genotypic subtypes of AD may manifest greater pathogenic homogeneity than the syndrome of AD as a whole. As a result, this approach to reducing the variance in disease pathogenesis may be important for the discovery of drugs or other interventions that have beneficial effects on preventing, forestalling the onset, slowing the progression, or ameliorating the symptoms of dementia in some subtypes of AD but not others.

Our ongoing longitudinal study focuses on a cohort of initially asymptomatic individuals who were at increased risk of developing AD by virtue of their family history. After 3752 subject-years, our surveillance protocol has detected 30 incident cases of AD. More incident cases would have been detected during this interval by recruiting individuals with mild cognitive impairment or who had lived further into the age of risk. However, it is likely that many individuals with mild cognitive impairment, especially those who carry the *APOE E4* allele, are already manifesting early symptoms attributable to AD, the most common form of dementia. In contrast, our goal was to identify risk factors for events that contribute to the pathogenesis of AD at early times before symptoms emerge. Likewise, the recruitment of an older cohort would have limited our ability to detect risk factors that specifically influence the development of forms of AD that emerge at earlier ages.

After 3752 subject-years of this longitudinal study, our ADHRC had a mean age of 68.2 years and an accelerating incidence rate of AD is evident among its remaining members. As the cohort continues to age, we anticipate that the ADHRC and associated library of transformed cell lines will provide a unique resource for efficiently evaluating putative AD susceptibility alleles and other cellular biomarkers (individually and in combination) that

have moderate effects among asymptomatic subjects using the prospective, longitudinal, double-blind study design that we initiated two decades ago.

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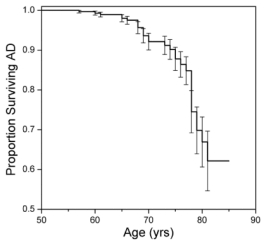

Figure 1.

Age-Specific Risk of AD Among Initially-Asymptomatic Relatives of AD Probands. Survival analysis was performed using the Kaplan-Meier method. Proportions of subjects in each age interval surviving AD are presented ± SE.

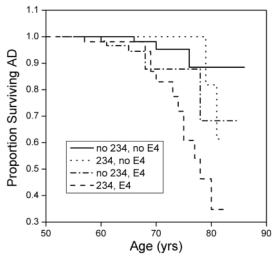

Figure 2.

Effects of D10S1423 and *APOE* Genotypes on Age-Specific Risk of AD Among Initially Asymptomatic Relatives of AD Probands. Survival analysis was performed using the Kaplan-Meier method. Mantel-Cox statistic = 16.46, df = 3, p = 0.0009; Breslow statistic = 13.38, df = 3, p = 0.004. Genotypes for the ADHRC members included in this analysis were: no 234 and no E4, n = 88; 234 and no E4, n = 60; no 234 and E4, n = 77; 234 and E4, n = 53.

Table 1

Sociodemographic, Clinical, and Genetic Characteristics of the AD High-Risk Cohort (ADHRC) and Incident AD Cases

Characteristic	ADHRC (N=325)[a]	Incident AD Cases (N=30)	Remaining ADHRC (N=295)	Statistic	df	P value
Current Age (yrs, mean±SD)[b]	68.2±7.7	74.8±7.1	67.5±7.5	t=5.12	323	<0.001
Sex (women/men, %women)	191/134, 58.8	18/12, 60.0	173/122, 58.6	χ^2=0.02	1	0.89
Race (white/black, %white)	314/11, 96.6	27/3, 90.0	287/8, 97.3	Exact test	--	0.07
Education (yrs, mean±SD)[c]	13.6±2.6	13.2±2.8	13.6±2.6	t=0.79	297	0.43
MMSE at recruitment (mean±SD)	29.6±0.8	29.1±1.4	29.6±0.7	t=1.89	30.74	0.07

[a] Excludes four relatives of two autopsied probands who did not meet histopathologic criteria for AD, and one individual who was subsequently determined not to be a blood relative of an identified AD proband.

[b] If dead, age at death; if lost to follow-up, age at loss.

[c] Excludes 26 (8.0%) members of the total cohort for whom educational history was not available.

Table 2

Cox Proportional Hazards Model Predicting the Incidence of AD Within the ADHRC

Characteristic	Risk Ratio	P Value	95% C.I.
234+, E4−	0.9	0.89	0.2 to 4.5
234−, E4+	3.3	0.09	0.8 to 12.9
234+, E4+	7.5	0.002	2.1 to 27.0
Sex (M=1, F=2)	2.4	0.06	1.0 to 6.1
Age at entry (yrs.)	1.0	0.38	0.9 to 1.1
Education (yrs.)	1.1	0.11	1.0 to 1.4

Risk ratios for genotypes are relative to 234−, E4−.