Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neuroscience Letters 379 (2005) 199–204
Neuroscience Letters
www.elsevier.com/locate/neulet

An autosomal genomic screen for dementia in an extended Amish family

A.E. Ashley-Koch[a,*], Y. Shao[a], J.B. Rimmler[a], P.C. Gaskell[a], K.A. Welsh-Bohmer[a], C.E. Jackson[b], W.K. Scott[a], J.L. Haines[c], M.A. Pericak-Vance[a]

[a] *Center for Human Genetics, Department of Medicine, Duke University Medical Center, 595 La Salle Street, Box 3445, Durham, NC 27710, USA*
[b] *Henry Ford Hospital, Detroit, MI, USA*
[c] *Vanderbilt University, Nashville, TN, USA*

Received 21 October 2004; received in revised form 7 December 2004; accepted 27 December 2004

Abstract

Apolipoprotein E (APOE) is the only universally confirmed susceptibility gene for late-onset Alzheimer disease (LOAD), although many loci are believed to modulate LOAD risk. The genetic homogeneity of isolated populations, such as the Amish, potentially provide increased power to identify LOAD susceptibility genes. Population homogeneity in these special populations may reduce the total number of susceptibility genes contributing to the complex disorder, thereby increasing the ability to identify any one susceptibility gene. Dementia in the Amish is clinically indistinguishable from LOAD in the general population. Previous studies in the Amish demonstrated a significantly decreased frequency of the APOE-4 susceptibility allele, but significant familial clustering of dementia [M.A. Pericak-Vance, C.C. Johnson, J.B. Rimmler, A.M. Saunders, L.C. Robinson, E.G. D'Hondt, C.E. Jackson, J.L. Haines, Alzheimer's disease and apolipoprotein E-4 allele in an Amish population, Ann. Neurol. 39 (1996) 700–704]. These data suggested that a genetic etiology independent of APOE may underlie the dementia observed in this population. In the present analysis, we focused on a large, multiplex, inbred Amish family (24 sampled individuals; 10 of whom are affected). We completed a genomic screen to identify novel LOAD loci ($n = 316$ genetic markers), using both model-dependent "affecteds-only" analysis (dominant and recessive) and model-independent affected relative pair analysis. Interesting results (lod > 1.5 or $p < 0.01$) were obtained for markers on eight chromosomes (2q, 5q, 6q, 7p, 8p, 8q, 11p, 18p, 18q, and 19q). The highest overall score was a multipoint lod score of 3.1 on chromosome 11p. Most regions we identified were not previously detected by genomic screens of outbred populations and may represent population-specific susceptibilities to LOAD. These loci are currently under further investigation in a study of LOAD including additional Amish families.

Keywords: Alzheimer disease; Genome screen; Linkage analysis; Complex disease; Isolated population

Alzheimer disease (AD) is the most common form of dementia in older adults. The etiology of AD likely involves a complex web of genetic and environmental factors. Four genes have been implicated in AD susceptibility [9,18,34], including the apolipoprotein E locus (APOE) which is a susceptibility gene for late-onset AD (LOAD; onset >60 years of age) [2,31]. Jointly, these four genes explain less than 50% of the total genetic variation in AD, suggesting that additional unidentified AD loci exist [5].

To identify additional AD loci, several genomic screens have been performed in LOAD families. One screen identified a potential LOAD locus on chromosome12 [26], which was subsequently confirmed in three independent data sets [6,22,30]. More recent genomic screens have shown evidence for two additional AD loci on chromosome 9 [10,27] and chromosome 10 [16]. The chromosome 9 locus has been confirmed in an independent set of families [6]. The chromosome 10 locus has been examined in detail [25], and may be associated with plasma Abeta42 levels, a potential biomarker for LOAD [4]. Most recently, it has been suggested that a locus on chromosome 10 may be controlling the age of onset of AD [19], either independently or jointly with risk. Due to variation in the localization of the linkage signals, it is unclear if the linkage peak for susceptibility to AD [25] is the same peak as that observed for age at onset of AD [19].

* Corresponding author. Tel.: +1 919 684 1805; fax: +1 919 684 0900.
E-mail address: aakoch@chg.duhs.duke.edu (A.E. Ashley-Koch).

0304-3940/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2004.12.065

One of the challenges to identify specific genes contributing to AD is that any one gene is likely to contribute only a modest to moderate effect on AD susceptibility and searching for such effects can be arduous. The genetic homogeneity of an isolated population may provide increased power to identify loci with moderate effect, since the total number of susceptibility genes that contribute to LOAD should be reduced. This approach has already proven useful for AD in a genome-wide analysis of a Finnish population [12], as well as an Arab population [7]. In the Finnish population, a total of eight chromosomal regions were identified (1p36, 2p22, 3q28, 4p13, 10p13, 13q1, 18q12, and 19p13). In the Arab population, the most significant evidence for allelic association was observed on chromosomes 2, 9, and 10, with some evidence for association on chromosome 12 in the region implicated by outbred LOAD populations. In our continuing efforts to dissect the etiology of AD, we have performed a genomic screen of late-onset dementia in a large family from the Indiana Amish population to both identify novel loci, and possibly to refine the localization of putative AD loci identified in previous genomic screens [10,16,22,25,26,27].

The Amish population in the present analysis resides within three counties in northern Indiana and one county in southern Michigan. The population descended from founders who migrated to the region in 1853 from Switzerland. The Amish community provides a homogeneous population for genetic analysis as religious and cultural factors isolate the community from the general population [13]. A previous examination of individuals in this Amish community who were 65 years of age and older found a lower prevalence of dementia compared with other regionally located Caucasian populations [14,15]. Further examination revealed a significantly decreased frequency of the APOE-4 susceptibility allele suggesting that the decreased prevalence of AD in this population could be attributed, at least in part, to the lower frequency of the APOE-4 allele [28]. The individuals in this community affected with dementia tended to aggregate into large, multiplex inbred families. One of these families was investigated in the present analysis.

The present analysis focused on a large multiplex Amish family with demential, identified in previous analyses [28]. All available family members were examined and included in the analysis. In total, DNA samples were available on 24 individuals, including 10 affected individuals (Fig. 1).

All participating family members were given the Mini-Mental State examination (MMSE) (new version) to screen for initial evidence of cognitive impairment [8]. MMSE scores of 24–30 are considered within the normal range. All family members scoring below 24 on the MMSE were evaluated for signs of dementia. Due to cultural beliefs in the Amish population, autopsy confirmation of diagnosis was not possible. Thus, classification of dementia relied on personal history and clinical examination [28].

The clinical evaluation of dementia requires the objective verification of cognitive status, usually accomplished by informant interview and mental status testing. In the Amish population, the clinical examination is conducted in the home and is constrained by several factors unique to the population

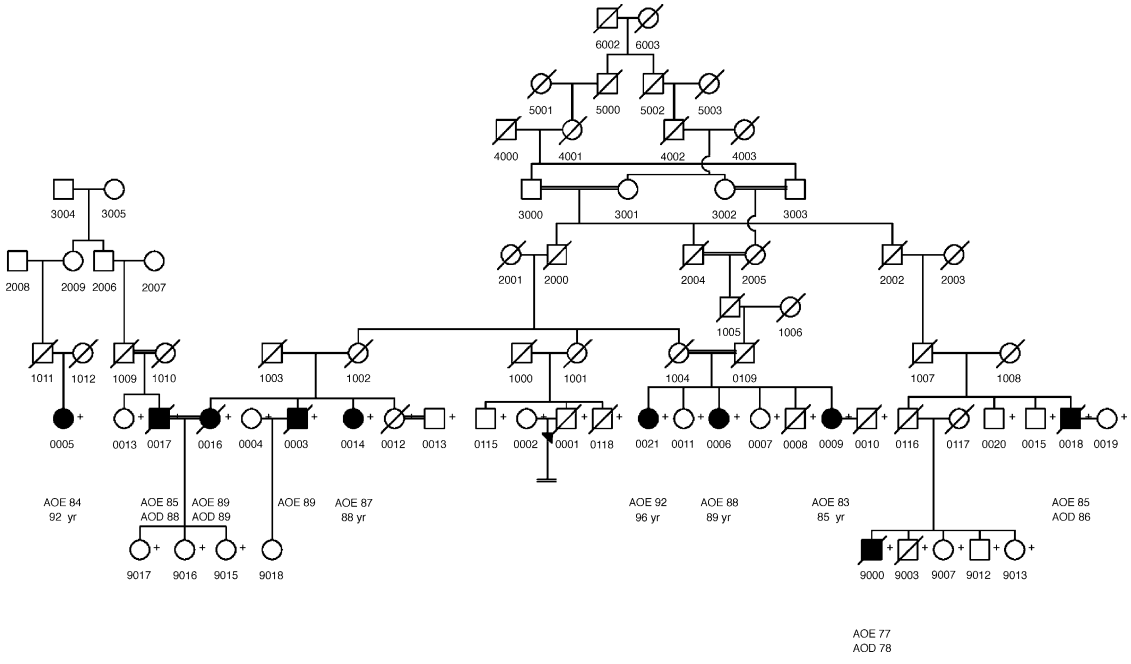

Fig. 1. Pedigree of family 1683. Individuals with clear symbols are phenotypically normal, and those with filled symbols are affected with dementia. Those individuals for whom DNA was available are noted with a "+" in the top right corner of the individual symbol. The individual numbers are listed directly below the individual symbols. Below the individual numbers are the age of exam (AOE), and age of death (AOD) or current age for the affected family members. The double marriage lines indicate consanguineous matings, although for simplicity of the figure, not all relations are fully defined. For computational ease, the pedigree was broken into two sections between individuals 17 and 16.