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Genome Screen of Late-Onset Alzheimer's Extended Pedigrees Identifies TRPC4AP by Haplotype Analysis

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Alzheimer's disease is a complex progressive neurodegenerative disorder with profound cognitive decline. Multiple susceptibility genetic variants have been identified with equivocal replication. While rare, collections of extended pedigrees with multiple affected family members are invaluable for genome-wide screens. We have used two extended pedigrees, having 14–15 siblings with four to five affected late-onset Alzheimer's disease patients in each, to identify the gene, transient receptor potential cation channel, subfamily C, member 4 associated protein (TRPC4AP), on chromosome 20q11.22, as relevant for the disease. Multiple significant SNPs in this gene were found with the initial genome scan (after Bonferroni correction). Additional SNPs were assessed in the families and in the controls which were also significant by haplotype analysis. Moreover, 36% of the patients' haplotypes in our collection of late-onset patients had the same haplotype. These results suggest that TRPC4AP is involved with the disease in these late-onset Alzheimer's families. The results also confirm the use of the genome-wide association study for identifying new genetic variants of complex diseases. © 2008 Wiley-Liss, Inc.

Key words: complex disease; genome-wide association study; extended pedigrees

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INTRODUCTION

Late-onset Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive decline and distinct neuropathology. Many putative susceptibility genetic variants have been associated with the disease in case/control studies. However, unequivocal replications have been limited. Mutations in several genes in pedigrees with early-onset Alzheimer's disease have been identified which include those in presenilin 1, presenilin 2, and the amyloid precursor protein; the apolipoprotein E4 polymorphism is a risk factor which increases susceptibility for the disease [Goate et al., 1991; Corder et al., 1993; Van Duijn et al., 1994; Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995]. Collectively these genes account for less than 25% of the disease prevalence. Family history is an important risk factor for the disease. Based on twin studies, heritability for the disease has been estimated at 79%, with no difference (after controlling for age) between men and women in prevalence or heritability [Gatz et al., 2006].

Large pedigrees of members living with late-onset Alzheimer's disease are rare. Our studies have identified two large families in which there are multiple members affected with late-onset Alzheimer's disease who are still living. The families are Caucasian of European descent and are described in the Methods section. We have used these families for a genome-wide scan with the Affymetrix GeneChip® Human Mapping 500 K Array Set. A significant set of SNPs in the gene, transient receptor potential cation channel, subfamily C, member 4 associated protein (TRPC4AP), was identified, after Bonferroni correction; further studies included analyzing an additional panel of SNPs in this gene in each family. A haplotype of 10 SNPs in TRPC4AP was significant for the disease in these two families. Sequencing identified 10 additional SNPs for this haplotype. Moreover, in our database of unrelated Alzheimer's patients and control spouses, 36% of the patients had this haplotype.

Additional Supporting Information may be found in the online version of this article.

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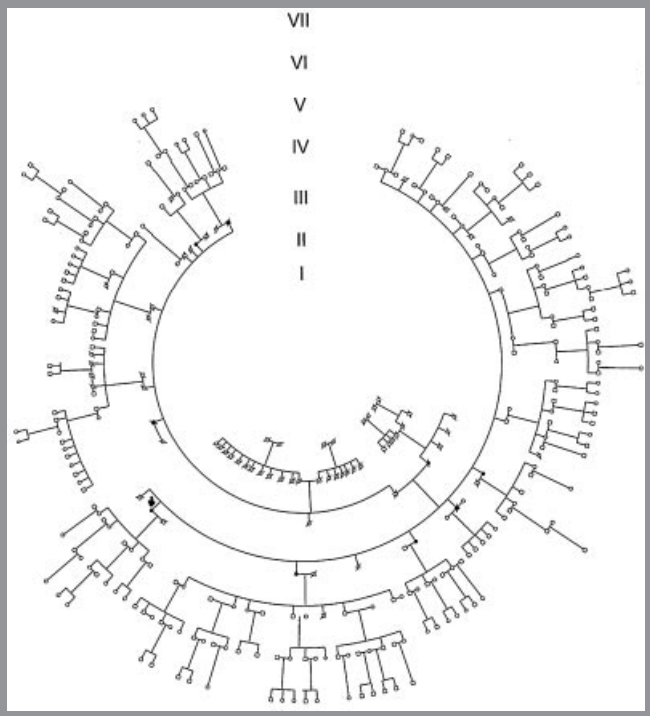

FIG. 1. Pedigree for Family 1.

METHODS

Clinical Phenotypes

Family 1. The proband was one of 15 siblings, 5 affected with Alzheimer's disease (Fig. 1). The patient developed memory loss at age 70. At age 77, the patient had a recorded Mini-Mental State Examination (MMSE) of 19/30, with an anomia for low frequency words and difficulty following serial commands. The magnetic resonance imaging (MRI) scan of the brain showed cerebral atrophy with several bright spots in the periventricular region, consistent with arteriosclerotic disease. Moderate prominence of the ventricles was noted. The electroencephalogram (EEG) was unremarkable. There was no history of alcohol or tobacco use. Blood work showed an elevated cholesterol (234 mg/dl), low density lipoprotein (LDL) (149), and a B12 deficiency which was treated. The patient's cognitive functions continued to worsen and the patient died recently at age 82 in a nursing facility. One sibling developed memory loss at age 72. At age 75, the MMSE was 20/30. Blood work, including thyroid function and B12, was unremarkable. The computed tomography (CT) scan of the brain revealed mild volume loss with no evidence of strokes, hemorrhage, or lesions. The patient has no history of alcohol use, but does use snuff. The patient is currently living with a child. A second sibling developed memory loss at age 70. The blood work was unremarkable with a normal EEG. The CT scan of the brain revealed generalized atrophy, but no acute abnormality. The patient has no history of alcohol use, but also uses snuff. The patient is living with a spouse. A third sibling developed memory loss at age 66. An MRI scan of the brain at age 67 revealed mild diffuse cerebral atrophy and small vessel disease. The blood work, including thyroid function and B12, showed a low B12 which was treated. The EEG was abnormal because of a mild slowing. This sibling never attended school but held a job as a telephone repair person. The patient had a history of drinking beer and using snuff. The patient died recently at age 74 in a nursing facility. A fourth sibling developed memory problems at age 65. At age 73, the patient scored a 21/30 on the MMSE. The blood work, including thyroid function was normal, but the sibling is being treated for hypothyroidism. The MRI scan of the brain at age 68 revealed a normal scan. There is no history of alcohol use, but the sibling does use snuff. The patient lives with a child. There are 7 siblings who currently are ages 60–73 with no signs of memory loss at this time. The proband's father died at age 58 of colon cancer and the mother at age 78 with signs of dementia. The proband's father's sibling developed memory loss around age 85 and died at age 93 in a nursing facility. A second sibling of the proband's father developed memory problems at age 89 and lives in a nursing facility. A third sibling of the proband's father also had dementia, but no medical records are available. A sibling of the mother is 84 and has no signs of memory loss. We have DNA on all of the siblings, the father's two affected siblings, the mother's unaffected sibling, most of the children and spouses for a total of 69 samples. All participants or the authorized representatives of the patients gave consent for the study, in accordance with the Institutional Review Board guidelines.

Family 2. The proband was one of 14 siblings, 6 affected with Alzheimer's disease or dementia (Fig. 2). The patient developed memory loss at age 76. At age 77 the patient had an MMSE of 24/30.

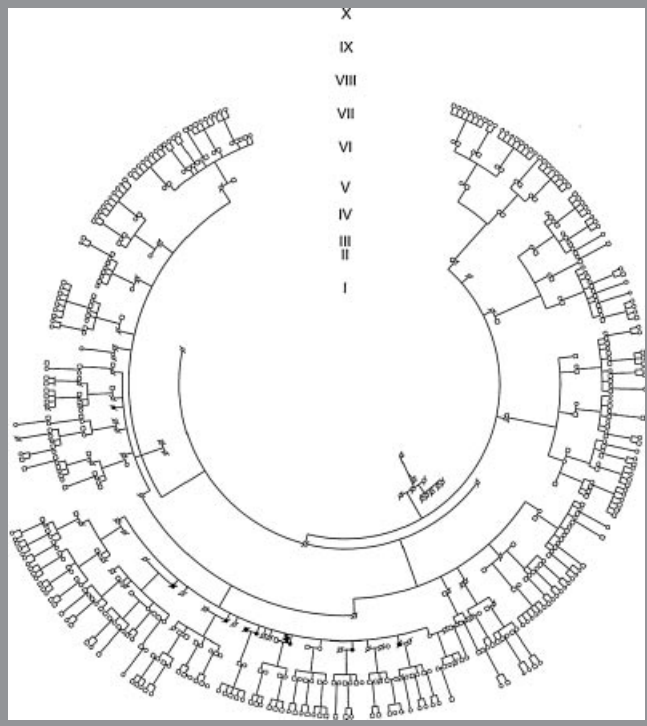

FIG. 2. Pedigree for Family 2.

The blood work, including thyroid function and B12 levels, were unremarkable. The CT scan of the brain at age 80 years showed age related atrophy with prominent ventricles. There is no history of tobacco use and occasional to moderate alcohol use. The patient who was a school teacher and administrator lives at home with a spouse, as the cognitive functions continue to deteriorate. One sibling developed memory problems at age 80. The patient's blood work, including thyroid function, was unremarkable. There is possible alcohol abuse. The patient currently lives in a nursing facility with progressive worsening of cognitive functions. A second sibling developed memory problems at age 55. This sibling suffered head trauma and was unconscious for a time earlier in life. There was a hospital admission for paranoia at age 63. A CT scan of the brain at age 60 showed mild to moderate, deep and diffuse cortical atrophy. The blood work was unremarkable. Alcohol abuse was indicated. The patient continued the decline in cognitive functions and died at age 65. A third sibling developed memory loss at age 80. No medical records were available. There was no alcohol abuse. The patient died at age 84. The fourth sibling developed symptoms at age 69 and in addition to a decline in cognitive functions was aggressive and had hallucinations. The patient died at age 72. Medical records were unavailable. The fifth sibling is an identical twin to an unaffected sibling. The affected sibling developed symptoms at age 71 and is currently in a nursing home at age 82. A sixth sibling is currently showing signs of mild cognitive impairment. The proband's father died in an accident at age 58. He had 4 siblings, one of whom died in an insane asylum at age 60. The proband's mother died of leukemia at age 80. She had 5 siblings, one with possible dementia who died at age 88. There was no alcohol abuse in the parents. We have DNA on 5 siblings, 3 of those who were/are affected, the one with possible MCI, and from the children and spouses for a total of 71 samples. All participants or the authorized representatives of the patients gave consent for the study, in accordance with the Institutional Review Board guidelines.

Subjects. We also screened 199 patients and 85 spouses from our community based samples for the haplotype. We obtained medical records on each patient and made the clinical diagnosis according to NINCDS-ADRDA criteria [McKhann et al., 1984] which included a documented progressive decline in cognitive function and appropriate blood work to rule out other medical conditions, including thyroid and vitamin B12 deficiencies. In addition, we included in the diagnosis, results from a CT scan or MRI of the brain which indicated cortical atrophy, but no evidence of strokes or tumors. The patients were Caucasian, of European descent. Spouses of patients and of siblings were of similar age, ethnic background, and similar environmental exposure who served as controls. All participants or the authorized representatives of the patients gave consents for the study, in accordance with the Institutional Review Board guidelines. The standard power for the association analysis is 0.88 [Ambrosius et al., 2004].

Genotyping. Genomic DNA was extracted using the Qiagen Q1Aamp DNA blood midi kit (Qiagen, Inc., Valencia, CA) and suspended in low EDTA TE buffer. Aliquots were quantitated using the NanoDrop spectrophotometer (NanoDrop Technologies, Wilmington, DE). For stage 1, we had five patients, 5 siblings, and 1 spouse from family 1 and four patients, 2 cousins, and 2 spouses from family 2 for the initial microarrays. Samples were diluted to 50 ng/μl and sent to Precision Biomarker Resources, Inc. (Evanston, IL) for genotyping, according to the manufacturer's specifications (Affymetrix, Santa Clara, CA), using the GeneChip® 500 K Mapping Array Set, consisting of two arrays (Nsp I, ~262,000 SNPs and Sty I, ~238,000 SNPs). Genotype calls were obtained from the Bayesian Robust Linear Model with Mahalanobis distance classifier genotype calling algorithm (BRLMM) on the Affymetrix platform. Among the 500,568 SNPs on the microarrays, 469,218 had call rates ≥95% with HWE $P > 0.001$, and were further analyzed. Gender calls were in accordance with the X chromosome genotype data and the known gender. Genotypic association was performed using the trial version of HelixTree software (Golden Helix, Bozeman, MT). Allelic and haplotype association were performed using the HaploView software (www.hapmap.org) [Barrett et al., 2005]. Bonferroni corrections were made using the 500,568 samples for multiple testing.

For stage 2 of the project, we selected additional SNPs in the gene, TRPC4AP, from the NCBI SNP database (www.ncbi.nlm.nih.gov/snp). Three of the most significant SNPs from the microarray data and those seven selected from the database were genotyped in 69 samples from family 1 and 71 samples from family 2, using fluorescent-detected single base extension with the SNaPshot Multiplex kit (Applied Biosystems, Foster City, CA) as described (Table SI) [Huang and Poduslo, 2006]. Controls were the unaffected spouses in the families and our selection of 85 spouse controls.

Sequencing. Patients, unaffected spouses and unaffected siblings were used for the sequencing in search of the mutation causing the disease in these families. Primers for the exons and junction areas were selected for TRPC4AP from the Ensemble Probe database (www.ensemble.org/homo_sapiens/exonview?db=core&exon=&transcript=enst00000252015&flanking=50&sscn=25&fullseq=yes&submit=go) (Table SII). Samples were sequenced according to the VariantSEQr® protocol (Applied Biosystems) using the BigDye® Terminator Ready Reaction Mix v 3.1 and the ABI 377 sequencer. SeqScape® v 2.5 was used for analysis (Applied Biosystems).

RESULTS

In stage 1, genotypic analysis of the microarray data involved analyzing the affected Alzheimer's patients' family samples against the control CEPH data with genotypic analysis, located on the Affymetrix website: (www.affymetrix.com/support/technical/sample_data/500k_hapmap_genotype_data.affx). The CEPH controls (60 samples) that were used were the unrelated parents. There were 6 SNPs on chromosome 20q11.22 that were significant, after Bonferroni correction for 500,568 SNPs, with *P* values ranging from 1.23E-04 to 9.98E-05 (Table I). Several SNPs on other chromosomes had significant *P* values after Bonferroni correction, but most were not in identified genes. All of the six significant SNPs on chromosome 20q11.22 were located in the gene for TRPC4AP.

The genotypes and frequencies of the four SNPs with the lowest *P* values for the Alzheimer's patients compared with the CEPH controls are listed in Table II. While all of the patients have homozygous genotypes for the SNPs, most of the controls have either heterozygous (50%) or opposite homozygous (37–38%) genotypes.

TABLE I. Association Studies With Alzheimer's Patients Versus CEPH Controls

Probe Set ID	dbSNP RS ID	Chip	Physical position	Chromosome	Cytoband	P	aP	FDR (aP)	bP
SNP_A-2161805	rs6087664	Nsp	33089877	20	q11.22	5.63E−11	4.73E−10	6.65E−06	9.98E−05
SNP_A-1793643	rs6088692	Sty	33102249	20	q11.22	5.63E−11	4.73E−10	3.21E−06	8.99E−05
SNP_A-1961453	rs6120816	Nsp	33108019	20	q11.22	6.99E−11	5.84E−10	7.70E−06	1.23E−04
SNP_A-2059637	rs1885119	Nsp	33109310	20	q11.22	5.63E−11	4.73E−10	6.65E−06	9.98E−05
SNP_A-2208157	rs2065108	Sty	33170483	20	q11.22	3.85E−10	3.10E−09	1.68E−05	5.89E−04
SNP_A-2153441	rs6088727	Sty	33177300	20	q11.22	3.85E−10	3.10E−09	1.68E−05	5.89E−04

For stage 2, 10 SNPs were analyzed in each member of both families. Haplotype analysis of the ten SNPs revealed a common haplotype for the affected siblings (Table III) which consisted of (as read from the forward strand and not the reverse coding strand) rs1058003: rs3746430: rs3736802: rs6088677: rs6087660: rs4911460: rs6087664: rs13042358: rs6120816: rs1885119: G:T:T:C:T:G:C:G:G:T.

All 5 of the affected siblings in Family 1, and 4 of the five affected siblings in Family 2, for which we have DNA, have this haplotype. Moreover, in all of the affected siblings, the genotype is homozygous for these SNPs. Genotypes for the control samples are generally heterozygous. Unaffected sibling 5 in Family 2 and siblings 6, 8, and 10 in Family 1 also exhibit the haplotype of the affected siblings; they are younger in age and do not currently have any cognitive problems. Affected sibling 2 in Family 2 has the homozygous genotypes for the last six SNPs, suggesting recombination between the fourth and fifth SNPs.

Each of the 19 exons and their intron/exon boundaries were sequenced. Additional SNPs were identified, most of which were from the SNP website (http://www.ncbi.nlm.nih.gov/sites/entrez?itool=gene_full_report&dbfrom=gene&cmd=link&linkname=gene_snp&idsfromresult=26133). Additional SNPs in linkage disequilibrium with the disease were found in and near exon 3 (rs1998233), exon 5 (rs4911463 and rs49114620), exon 6 (rs2281626), exon 11 (rs1885117 and rs1885116), exon 14 (rs2273636), exon 15 (rs6060151), exon 16 (rs4911169 and rs4911168 and rs3746431), and exon 17 (rs752449) (Table SIII). SNPs in the patient samples that were unchanged from the control samples were in and near exon 2 (rs11480829), exon 4 (rs7354623 and rs7354641) exon 6 (rs11907019 and rs17092225), exon 8 (rs6060169), exon 9 (rs11905247 and rs11478027), exon 11 (rs6088675 and rs4387881), exon 12 (rs6058157), exon 13 (rs6141525, rs12625215, rs6120789, rs 6088673, rs6088674), exon 14 (rs13045538 and rs2273637), exon 15 (rs11696609, rs14329, rs11552600, rs6060152), exon 16 (rs17092212), exon 17 (rs752448) and exons 18 and 19 (rs17092208, rs11481073, rs11482185, and rs11552601). Several unidentified SNPs were found in exons 2 and 16, but were not significant for the disease. We did not find any mutations in the coding regions and are in the process of sequencing the introns as it has been shown that most introns and intergenic regions are also transcribed and may play regulatory roles [Gingeras, 2007]. The sequencing of exon 9 revealed that the TRPC4AP is isoform 1 (exon 9 is shorter in isoform 2). Further studies revealed that DNA from all of the samples were isoform 1. The only sequencing variant found was a frameshift insertion in intron 18 which was also found in the controls.

We also screened 199 patients and 85 control spouses from our sample set for the haplotype (G:T:T:C:T:G:C:G:G:T) and found that 36% of the patients' haplotypes were this haplotype compared with 26% of the control spouses ($P = 0.0282$; OR = 1.56; 95%CI = 1.05–2.32).

The haplotype (G:T:T:C:T:G:C:G:G:T) for the disease extends from 33,054,747 to 33,120,760 bp in the gene. This haplotype is found in one block which contains all 19 exons (Fig. S1).

DISCUSSION

Most genetic studies of late-onset Alzheimer's disease that focus on genome-wide association studies involve analyzing several hundred to thousands of samples. In our study we used samples from two large extended pedigrees with multiple affected members with late-onset disease. Analyzing the affected only siblings versus the CEPH unrelated parent controls with the GeneChip® 500 K Mapping Array Set provided evidence that several SNPs in the candidate gene, TRPC4AP, on chromosome 20 were significant, after Bonferroni correction. In the second stage, additional SNPs were analyzed in both of the extended pedigrees against our control unaffected spouses, which provided the haplotype (G:T:T:C:T:G:C:G:G:T) for the disease. Sequencing the 19 exons provided information on additional SNPs that were also relevant to the disease, as well as information on the frameshift insertion in intron 18.

TABLE II. Genotypes of the Chromosome 20q11.22 SNPs From the Microarrays

	A-2059637	A-2161805	A-1961453	A-1793643
AD	BB (100%)	AA (100%)	AA (100%)	AA (100%)
CEPH controls	AA (38.3%)	AA (13.3%)	AA (13.6%)	AA (13.3%)
	AB (48.3%)	AB (48.3%)	AB (49.2%)	AB (48.3%)
	BB (8.3%)	BB (38.3%)	BB (37.3%)	BB (38.3%)

TABLE III. Haplotype/Genotype Analysis of TRPC4AP in Two Extended Families

SNP	Proband (AD)	Sibling 1 (AD)	Sibling 2 (AD)	Sibling 3 (AD)	Sibling 4 (AD)	Sibling 5	Sibling 6	Sibling 7	Sibling 8	Sibling 9	Sibling 10	Sibling 11	Spouse	Spouse	Spouse	Spouse	Spouse	Spouse	Spouse	Spouse	Spouse
Family 1																					
rs1058003	G	G	G	G	G	AG	G	AG	G	AG	G	AG	A	AG	A	AG	A	A	G	A	AG
rs3746430	T	T	T	T	T	CT	T	CT	T	CT	T	CT	C	CT	C	CT	C	C	CT	C	CT
rs3736802	T	T	T	T	T	T	T	T	T	T	T	T	CT	T	C	T	T	C	CT	CT	CT
rs6088677	C	C	C	C	C	C	C	C	C	C	C	C	CT	C	CT	C	CT	CT	CT	CT	CT
rs6087660	T	T	T	T	T	CT	T	CT	T	CT	T	CT	C	CT	C	CT	C	C	T	C	CT
rs4911460	G	G	G	G	G	A	G	AG	G	AG	G	AG	A	AG	A	AG	A	A	G	A	AG
rs6087664	C	C	C	C	C	G	C	CG	C	CG	C	CG	G	CG	G	CG	G	G	C	G	CG
rs13042358	G	G	G	G	G	G	G	G	G	G	G	G	AG	G	A	G	G	A	G	AG	AG
rs6120816	G	G	G	G	G	CG	G	CG	G	CG	G	CG	C	CG	C	CG	C	C	G	C	CG
rs1885119	T	T	T	T	T	CT	T	CT	T	CT	T	CT	C	CT	C	CT	C	C	T	C	CT

SNP	Proband (AD)	Sibling 1 (AD)	Sibling 2 (AD)	Sibling 3 (AD)	Sibling 4 (MCI)	Sibling 5	Spouse	Spouse	Spouse	Spouse	Spouse	Spouse
Family 2												
rs1058003	G	G	G	G	G	G	AG	G	AG	G	A	A
rs3746430	T	T	CT	T	T	T	C	C	CT	CT	C	C
rs3736802	T	T	CT	T	T	T	C	C	T	CT	C	CT
rs6088677	C	C	CT	C	C	C	CT	CT	C	CT	CT	CT
rs6087660	T	T	T	T	T	T	CT	T	CT	T	C	C
rs4911460	G	G	G	G	G	G	AG	G	AG	G	A	A
rs6087664	C	C	C	C	C	C	CG	C	CG	C	G	G
rs13042358	G	G	G	G	G	G	AG	G	G	G	A	AG
rs6120816	G	G	G	G	G	G	CG	G	CG	G	C	C
rs1885119	T	T	T	T	T	T	CT	T	CT	T	CT	C

The gene TRPC4AP (transient receptor potential cation channel, subfamily C, member 4 associated protein) or TRUSS (tumor necrosis factor receptor-associated ubiquitous scaffolding and signaling protein) on chromosome 20q11.22 has 19 exons and a length of 90,411 bases with two alternative transcripts; however, there are at least 17 spliced variants listed in GenBank. Thus the gene locus is complex as it may produce several proteins. According to AceView, there may be 20 different mRNAs. The one known protein which was encoded by mouse TRUSS has 797 amino acids with a mass of 90,852 Da. The protein is expressed in heart, liver, testis, and brain [Soond et al., 2003]. The protein interacts with TNF-R1 (the tumor necrosis factor receptor 1), making the complex insensitive to stimulation with TNF-α. In addition, the protein may be involved with the activation of transcription factors such as NF-κB and may serve as a scaffolding protein that links TNF-R1 to components of the IκB-kinase complex [Soond et al., 2006]. The protein may also function in the TNF-α induced Jun NH_2-terminal kinases (JNK) and the transcription factor (AP-1) activation [Soond et al., 2006]. TNF is a proinflammatory cytokine which may be involved with the pathology of Alzheimer's disease. The neurotoxicity in Alzheimer's disease may indeed be mediated by inflammatory processes in the brain; proinflammatory cytokines, such as TNF-α, may be released from activated microglia which could lead to the neuronal apoptosis found in the disease process. The protein may also have a MHC class 1 binding function [Antoniou et al., 2002]. The transient receptor potential (TRP) cation channels are part of a superfamily of 28 channels subdivided into six subfamilies. Most of the channels provide entry for calcium ions which are involved in the regulation of many calcium-dependent cell functions. Dysfunctions of the channels are thought to cause human disease or contribute to the progression of the disease [Nilius, 2007]. It has been suggested that the transient receptor potential channels may be involved with Alzheimer's disease by possibly disrupting calcium homeostasis [Yamamoto et al., 2007].

Thus we have identified SNPs significant for the disease by haplotype analysis in the gene for TRPC4AP on chromosome 20q11.22 that may well be causing the disease in two extended pedigrees with late-onset Alzheimer's disease, as well as in unrelated late-onset Alzheimer's disease patients. The use of extended pedigrees provides an invaluable tool for genome screens to identify new genes which may be involved in the pathogenesis of complex diseases, such as Alzheimer's disease.

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