

ORIGINAL INVESTIGATION

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A familial case of Alzheimer's disease without tau pathology may be linked with chromosome 3 markers

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Abstract Alzheimer's disease is the most common form of dementia that occurs in later years. The diagnosis is confirmed by the pathological findings of β A4-amyloid-containing neuritic plaques and neurofibrillary tangles, the former being present in sufficient quantity commensurate with age. Other forms of dementia are more difficult to diagnose clinically; their pathology is noted for the lack of plaques and tangles. A patient with a family history of dementia presented with the clinical signs of Alzheimer's disease which lasted for 13 years. At autopsy the brain tissue had β A4-amyloid-containing neuritic plaques, but no neurofibrillary tangles (i.e., the tissue was negative for staining with the tau antibody). Genetic analysis of DNA from family members revealed no linkage with chromosome 17 markers, indicating that this was not frontotemporal dementia. However, there was linkage with chromosome 3 markers. Thus, this form of Alzheimer's disease with a pathology of plaques only is linked with markers on chromosome 3.

Introduction

Alzheimer's disease is the most common form of dementia and generally occurs in later life. The clinical symptoms include an insidious onset and gradual progression of memory loss and cognition. The criteria used by our group for the diagnosis of Alzheimer's disease is that es-

tablished by the NINCDS-ADRDA group and consists of evidence of a progressive decline in memory and normal routine blood studies (McKhann et al. 1984). We also include a CT scan or MRI, which shows atrophy but no evidence of strokes or tumors. Pathologically, the most characteristic features of Alzheimer's disease are the presence of β A4-amyloid-containing neuritic plaques and neurofibrillary tangles; the plaques must be present in a sufficient number to exclude normal aging (Mirra et al. 1993). Mutations in genes on chromosomes 21 (exons 16 and 17 of the amyloid precursor protein) and 14 (presenilin 1) are associated with early onset disease; mutations in a gene on chromosome 1 (presenilin 2) with a Volga German and an Italian kindred; and the risk factors apolipoprotein E4 (APOE4) and CIA (APOC1 A) on chromosome 19 with both early and late onset disease (Goate et al. 1991; Lannfelt et al. 1993; Saunders et al. 1993; Levy-Lahad et al. 1995; Rogaev et al. 1995; Poduslo et al. 1998; Sherrington et al. 1995).

Our DNA Bank recently enrolled a family in which four siblings had the characteristic clinical signs of Alzheimer's disease. At autopsy the proband's brain had the presence of plaques but lacked tangles. Thus the clinical diagnosis was called into question. There have been reports of Alzheimer's patients having only plaques at autopsy (Terry et al. 1987; Graeber et al. 1997). The frontotemporal dementias are another group of neurodegenerative disorders with progressive dementias that can be confused clinically with Alzheimer's disease and have been linked with markers on chromosome 17 (Wilhelmsen et al. 1994; Brun and Passant 1996; Pasquier and Petit 1997). A nonspecific dementia has been linked with markers on chromosome 3 (Brown et al. 1995; Brown 1998). We analyzed the DNA from the presented family for the known mutations, as well as for the markers on chromosomes 17 and 3 involved with other dementias, to determine the diagnosis in this family.

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Materials and methods

Ascertainment

The family was ascertained through referral from the local Alzheimer's support group in El Paso, Texas. Procedures for recruitment, requests for medical records on affected siblings, and consent forms were approved by the institutional review board at Texas Tech. The medical records were reviewed and the diagnosis made according to NINCDS-ADRDA criteria (McKhann et al. 1984). The CERAD criteria were used to make the diagnosis of Alzheimer's disease at autopsy (Mirra et al. 1993).

Molecular analysis

Markers on chromosomes 17 and 3 were amplified by the polymerase chain reaction using the Perkin Elmer GeneAmp 9600. The reaction mix consisted of 1.00 μ l 10 \times PCR buffer, 1.00 μ l 2.5 mM dNTP, 1.00 μ l 2.5 mM MgCl₂, 0.25 μ l each primer 1 and 2, 4.47 μ l ddH₂O, 0.08 μ l Amplitaq Gold, 2.00 μ l 20–50 ng DNA. The amplification consisted of 95°C for 5 min; 95°C for 15 s; 55°C for 15 s; 72°C for 30 s; steps 2–4 for 10 cycles followed by 89°C for 15 s; 55°C for 15 s; 72°C for 30 s; steps 6–9 for 20 cycles followed by 72°C for 10 min. The samples were analyzed on an ABI 377 DNA Sequencer. The APOE and APOCI alleles were analyzed as described (Poduslo et al. 1998). The mutations in exons 16 and 17 of the amyloid precursor protein and in presenilin 2 were also analyzed (Lannfelt et al. 1993; Goate et al. 1991; Levy-Lehad et al. 1995). The tau mutation was analyzed as described (Poorkaj et al. 1998).

Linkage analysis

Simulation studies were done using the FASTSLINK software package with the unlinked markers D3S1313 (heterozygosity, 0.6898) and D3S1577 (heterozygosity, 0.5740) with 1000 replicates (Ott 1989; Weeks et al. 1990). Linkage analysis was performed using the FASTLINK software package, using pairwise and multipoint analysis in Mlink (Cottingham et al. 1993; Schaffer et al. 1994; Lathrop et al. 1994; Terwilliger and Ott 1994). The liability classes were assigned as described (Farrer and Cupples 1994) and the gene frequency was set at 0.001. Normal allele frequencies were obtained from analysis of approximately 100 unaffected (Caucasian) spouses enrolled in the DNA Bank.

Results

Clinical findings

The patient (of Caucasian descent) was one of 10 siblings; 3 others also had memory problems and one deceased sibling had Parkinson's disease. One of the children of an affected sibling had beginning signs of memory loss. The mother, who died in her 30s, was one of 9 siblings, 3 of whom had memory problems.

The proband, a retired water flood operator for an oil company, was in good health until the age of 65 years. He then had the insidious onset of short-term memory loss associated with spells of feeling as if "everything went blank", during which time he was noted to be disoriented and confused. He also had difficulty adding and subtracting, had poor concentration, trouble with facial recognition of recent acquaintances, and difficulty with geographi-

cal orientation, becoming confused and making wrong turns, even within a few blocks of home.

Past medical history was negative for heart disease, hypertension, cardiac disease, or strokes. Evaluation at age 66 years revealed him to be disoriented with respect to time, with difficulty performing serial 7's and copying figures. He also performed poorly on tests of short-term memory.

General and neurological exams were significant only for mild gegenhalten. Complete blood count (CBC), blood chemistries, thyroid function tests, vitamin B12 and folic acid levels, rapid protein reagin (RPR), EKG, and chest radiographs were within normal limits. A CT scan of the head revealed mild, generalized cerebral cortical atrophy. The cerebrospinal fluid had 4 cells/ μ l (2 WBCs, 2 RBCs), a protein concentration of 28 mg/dl, a glucose concentration of 70 mg/dl, nonreactive venereal disease research laboratory (VDRL) tests, and negative bacterial and fungal cultures. The patient was diagnosed with probable senile dementia of the Alzheimer's type.

His cognitive functions gradually worsened and 4 years into the illness he was noted to have parkinsonian symptoms (weak monotone voice, difficulty getting up from a chair, and a short shuffling gait with stooped posture). He could, however, stay home while his wife worked and was noted to have no behavioral problems. Shortly before his death at age 78 years, he was unable to speak or feed himself and was bedbound.

Case 2

This female sibling had the insidious onset of memory problems beginning at age 74 years with gradual worsening. Over time she lost the ability to balance the checkbook, would get lost easily, had word-finding difficulties, and could not carry out skilled motor acts such as operating the washing machine.

Three years into the illness, mental status examination revealed the patient to be alert and disoriented. She had poor general knowledge, difficulty with simple calculations, constructional problems, dysnomia, and striking apraxia. Her affect was inappropriately jovial. Neurological exam was significant only for grasp reflexes and gegenhalten. A CT scan showed mild cerebral cortical atrophy. Electroencephalogram revealed mild generalized slowing in the theta range. CBC, blood chemistries, thyroid function tests, and erythrocyte sedimentation rate were within normal limits. The course was relentlessly progressive and the patient died at age 90 years. No autopsy was obtained.

Case 3

This female sibling developed memory problems at age 72 years and is currently 82 years old. Symptoms at onset included loss of interest, crying, multiple somatic complaints, recent memory loss, impaired judgment and in-

Table 1 Simulation study

Thetas	Average	Standard deviation	Minimum	Maximum
Locus order 1 2 3				
0.500 0.220	0.000000	0.000000	0.000000	0.000000
0.400 0.220	-0.002369	0.032443	-0.050862	0.172861
0.300 0.220	-0.021886	0.115940	-0.205722	0.516540
0.200 0.220	-0.085704	0.229399	-0.468294	0.881282
0.100 0.220	-0.224121	0.356663	-0.766040	1.242367
Locus order 2 1 3				
0.000 0.220	-0.481089	0.443129	-0.866753	1.594988
0.044 0.193	-0.374035	0.432589	-0.861752	1.451417
0.088 0.160	-0.319112	0.419487	-0.855977	1.374412
0.132 0.120	-0.301347	0.418120	-0.852536	1.281680
0.176 0.068	-0.332418	0.439281	-0.857409	1.434272
0.220 0.000	-0.455140	0.481331	-0.866704	1.729372
Locus order 2 3 1				
0.220 0.000	-0.455140	0.481331	-0.866704	1.729372
0.220 0.100	-0.212422	0.375326	-0.760017	1.359903
0.220 0.200	-0.078731	0.240243	-0.469793	0.953692
0.220 0.300	-0.018281	0.121892	-0.207698	0.543642
0.220 0.400	-0.001258	0.034296	-0.050906	0.179769

Table 2 Number of replications with a multipoint lod score greater than a given constant

Constant	Number	Percent
1.000	36	3.600
2.000	0	0
3.000	0	0

sight, and difficulty with interpersonal relationships. As the illness progressed, she could not handle the check-book and would get lost easily.

Three years into the illness she could interpret only simple proverbs and had difficulty with simple similarities. Mathematical abilities were impaired and she had some mild dysnomia. There was no apraxia, no delusions, nor hallucinations. A neurological exam was significant for mild gegenhalten. The vitamin B12 level was low at 165 pg/ml with a normal Schilling's test. Blood chemistries, CBC, and thyroid function tests were normal. RPR, HIV, and antinuclear antibody tests were negative.

Neuropathology of the patient's brain showed generalized cerebral atrophy involving all lobes. There was spongiosis throughout the cortex and neuronal loss in layers 2 and 6 with reactive astrocytosis. There was a profound loss of pyramidal neurons in the CA1 and subiculum with a lesser loss in the entorhinal cortex and relative preservation in CA2, CA3, and CA4. There was also neuronal loss and reactive gliosis in the amygdala. The Bielschowsky silver stain showed diffuse plaques without definite central cores or neuritic pullens, numbering more than 20 per high power field (200 ×). The β A4-amyloid antibody stained many, but not all, of the diffuse plaques. The tissue sections were negative for staining with the tau antibody. The frozen tissue was analyzed for prion protein and was negative by Western blot analysis and by genetic analysis.

Table 3 Two point lod scores between chromosome 17 markers and the disease locus

Marker	Lod score at theta =				
	0.1	0.2	0.3	0.4	0.5
D17S791	0.77	0.62	0.36	0.11	0.00
D17S787	-0.20	-0.06	-0.02	-0.00	0.00
D17S808	-0.23	-0.11	-0.04	-0.01	0.00
D17S806	-0.53	-0.19	-0.05	-0.00	0.00
D17S790	-0.52	-0.15	-0.01	0.01	0.00
D17S932	-0.54	-0.24	-0.10	-0.02	0.00
D17S934	-0.22	-0.00	0.05	0.02	0.00
D17S579	-0.91	-0.41	-0.16	-0.04	0.00
D17S931	-0.38	-0.08	0.00	0.01	0.00
D17S797	-0.21	-0.05	0.00	0.01	0.00
D17S810	0.07	0.13	0.12	0.05	0.00
D17S1861	-0.23	0.00	0.03	0.01	0.00
D17S1868	-0.19	-0.04	-0.00	0.00	0.00

The proband and his siblings did not have mutations in exons 16 or 17 of the amyloid precursor protein gene nor in the presenilin 2 gene (data not shown). Mutations in presenilin 1 (generally found in patients with a much earlier age of onset) were not assessed as the age of onset in the proband was later (age 65 years). Simulation studies were done using the unlinked markers D3S1313 and D3S1577 with 1000 replicates (Table 1). The simulation showed that with the DNA samples available from the family with unlinked markers, 3.6% of the available samples would produce a Lod score of 1.0 and none would have a Lod score of 2.0 (Table 2).

Two point Lod scores were done for the 13 markers on chromosome 17 that were reported in the area linked with frontotemporal dementia (Table 3). There was a low level of linkage between the marker D17S791 and the disease in this family (0.77 at a theta of 0.1).

We examined the val-279-met mutation in exon 12 (Poorkaj et al. 1998) in this family. The mutation was not evident as expected since the autopsy tissue was negative for staining with the tau antibody.

Two point Lod scores were done for 18 markers on chromosome 3 in this family (Table 4). The highest Lod score was obtained for marker D3S1569 (1.48 at a theta of 0.01), with Lod scores below 1 for markers D3S3546 and D3S1292. Doing multipoint analysis with the disease locus, the highest Lod score was 4.17 if the disease locus was placed between D3S1569 and D3S3554 (Table 5). The Lod score was 2.79 if the disease locus was placed between D3S3546 and D3S3554. The locations in Kosambi cM for the markers D3S1295, D3S1313, D3S1577, D3S1595, D3S1603, D3S1271, D3S1591, D3S1558, D3S1292, D3S3554, D3S1764, D3S3612, D3S1309, D3S3694, D3S3546, D3S1569, D3S1550, and D3S1744 according to the Center for Medical Genetics, Marshfield, Wisconsin, are 77.01, 78.64, 109.22, 112.42, 115.09, 117.76, 121.67, 133.93, 146.60, 152.62, 152.62, 153.74, 153.74, 153.74, 154.48, 158.38, 159.80, 161.04 (<http://www.marshmed.org/genetics/cgi-bin/MarkerSearch.pl>).

Table 4 Two point lod scores between chromosome 3 markers and the disease locus

Marker	Lod score at theta =					
	0.01	0.1	0.2	0.3	0.4	0.5
D3S1295		-0.01	0.07	0.05	0.02	0.00
D3S1313		-0.22	-0.10	-0.04	-0.01	0.00
D3S1577		-0.72	-0.41	-0.17	-0.04	0.00
D3S1595		0.19	0.19	0.11	0.03	0.00
D3S1603		-0.51	-0.28	-0.12	-0.03	0.00
D3S1271		-0.22	-0.15	-0.07	-0.02	0.00
D3S1591		-0.19	-0.08	-0.03	0.00	0.00
D3S1558		-0.12	-0.04	-0.01	0.00	0.00
D3S1292	0.46	0.54	0.44	0.27	0.09	0.00
D3S3554	0.33	0.24	0.16	0.08	0.02	0.00
D3S1764		-0.44	-0.17	-0.05	-0.01	0.00
D3S3612		-0.30	-0.14	-0.06	-0.02	0.00
D3S1309		-0.24	-0.01	0.04	0.02	0.00
D3S3694		-0.59	-0.30	-0.12	-0.03	0.00
D3S3546	0.82	0.70	0.54	0.33	0.11	0.00
D3S1569	1.48	1.19	0.83	0.45	0.13	0.00
D3S1550		0.00	0.00	0.00	0.00	0.00
D3S1744		-0.62	-0.33	-0.13	-0.03	0.00
Postulated order						
D3S1292		D3S3546		D3S1569		D3S3554
Theta	0.13		0.09		0.03	

Table 5 Multipoint lod scores with chromosome 3 markers and the disease locus

Locus order	Thetas	Lod score
D3S3546=Disease-D3S1292	0.127-0.001	2.300229
D3S1569=Disease-D3S1292	0.128-0.072	1.825610
D3S1569=Disease-D3S3546	0.108-0.001	1.864439
D3S3546=Disease-D3S3554	0.002-0.001	2.793453
D3S1569=Disease-D3S3554	0.050-0.001	4.169593

Table 6 Association studies with APOE and APOCI

	Spouse frequencies	Family frequencies	PAD
APOE alleles			
2	0.082	0.0625	0.028
3	0.800	0.7031	0.574
4	0.118	0.2340	0.398
APOCI alleles			
A	0.209	0.2969	0.436
B	0.791	0.7031	0.564

Association studies were also done to determine the frequencies of the alleles of APOE and APOCI in this family (Table 6). The patient was APOE 3/4 and APOCI AB. The frequency of APOE4 in the affected individuals in this family was 23% as compared with 12% in the control spouses. That for APOCI A was 30% versus 21% in the controls. Linkage analysis of APOE and APOCI against the disease gene gave Lod scores of 0.49.

Discussion

Neurodegenerative dementias are the most common diseases that affect older adults. They are clinically and genetically heterogeneous and can be difficult to diagnose. While the most common form is Alzheimer's disease, about 10% of patients have other forms, such as frontotemporal dementias (Gustafson et al. 1997). The proband in our family was given the diagnosis of senile dementia of the Alzheimer's type, based on a progressive loss of memory, temporal-parietal symptoms (visuospatial and calculation difficulties), routine blood work, and a cranial CT scan, which initially was normal and then showed atrophy. However, at autopsy, the pathology of the brain showed the presence of diffuse β A4-amyloid-containing plaques but no neurofibrillary tangles.

Frontotemporal dementias linked to chromosome 17 are generally characterized by behavioral and personality changes that reflect frontal lobe dysfunction. Early on, constructional, calculating, and memory functions are relatively preserved. However, there is frequently a reduction in speech, culminating in mutism (Foster et al. 1997). Pathological changes show frontotemporal atrophy with spongiosis and gliosis, but without the plaques and tangles that are characteristic of Alzheimer's autopsy tissue (The Lund and Manchester groups 1994). These clinical signs and pathology were different from those found in the proband in our study.

The nonspecific dementia that mapped to chromosome 3 in the family from Denmark had clinical symptoms of confusion, restlessness, mental disintegration, and speech disturbances as well as changes in personality and early

apathy (Brown et al. 1995). Pathologically, there were no plaques or tangles. There were no Pick bodies, but there was occasional atrophy of the frontal and/or temporal lobes. Some individuals had marked white matter demyelination and gliosis (Brown et al. 1995). The proband in our study had a different clinical presentation and pathology.

The frontotemporal dementia (originally called disinhibition-dementia-parkinsonism-amyotrophy complex) was originally mapped to chromosome 17, 17q21–22, to a 12 cM region between D17S800 and D17S787 (Wilhelmsen et al. 1994). The highest Lod scores were obtained for markers D17S806, D17S791, and D17S934 which were all in the 12 cM area (Yamaoka et al. 1996; Heutink et al. 1997). The highest Lod score obtained with this family (0.77) was with marker D17S791, which was not significant. The tau gene is a candidate gene for frontotemporal dementia even though it is outside of the 12 cM area between D17S800 and D17S787. Four mutations have been identified as linked with the disease (Poorkaj et al. 1998; Hutton et al. 1998). We only examined the val-279-met mutation in this family because the autopsy tissue was negative for staining with the tau antibody. The mutation was not evident.

There have been several reports of a Danish family with nonspecific dementia that was linked with markers on chromosome 3 (Brown et al. 1995; Brown 1998). The locus was mapped to a 12 cM region between D3S1598 and D3S1572; the highest Lod score (4.2) was obtained for marker D3S1603. In our study family, the highest Lod score was 1.48 with marker D3S1569. Multipoint analysis gave a Lod score of 4.17 between markers D3S1569 and D3S3554. Our linked markers are somewhat downstream from those of the Danish family (> 40 cM from D3S1603). The marker D3S1569 was in the exclusion area for the Danish family (Lod score –5.77 at theta 0.00). Thus, there is evidence of linkage in this family with markers on chromosome 3.

APOE 4 and APOCI A are known to be risk factors for Alzheimer's disease (Saunders et al. 1993; Poduslo et al. 1998). While both allele frequencies were slightly increased in this family, the frequencies of E4 and CI A were considerably less than in these Alzheimer's patients. This is in contrast with the study of 21 unrelated patients with frontotemporal dementia who had frequencies of 28% for APOE 4 (Gustafson et al. 1997).

There has been a report suggesting that 30% of elderly Alzheimer's patients may not have neurofibrillary tangles in the neocortex at autopsy (Terry et al. 1987). In this report, neuritic plaques were present as expected in the elderly patients. After a careful study of a number of parameters, the group concluded that the patients without the neurofibrillary tangles also had senile dementia of the Alzheimer's type. They also concluded that the presence of tangles was associated with a greater severity of the disease.

Our study family fits into this category of having senile dementia of the Alzheimer's type, but without the characteristic neurofibrillary tangles. From our studies we conclude that this form of Alzheimer's disease with neuritic

plaques, but without neurofibrillary tangles, is linked with markers on chromosome 3, especially D3S1569 and D3S3554. Additional markers and candidate genes are now being analyzed.

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