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Linkage of Frontotemporal Dementia to Chromosome 17: Clinical and Neuropathological Characterization of Phenotype

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Summary

Frontotemporal dementia is a behavioral disorder of insidious onset and variable progression. Clinically, its early features reflect frontal lobe dysfunction characterized by personality change, deterioration in memory and executive functions, and stereotypical and perseverative behaviors. Pathologically, there is degeneration of the neocortex and subcortical nuclei, without distinctive features such as plaques, neurofibrillary tangles, or Pick or Lewy bodies. Within-family variation in neuropathology and clinical phenotype is observed. In cases where family aggregation is observed, it is inherited as an autosomal dominant, age-dependent disorder. Family studies recently have identified two dementia loci: chromosome 17 for disinhibition-dementia-parkinsonism-amyotrophic complex and pallido-ponto-nigral degeneration and chromosome 3 for familial nonspecific dementia. We describe a family (DUK1684) with clinically and neuropathologically confirmed, autosomal dominant, non-Alzheimer disease dementia. Linkage analysis of this family showed evidence for linkage to chromosome 17q21, with a multipoint location score ($\log_{10}$) of 5.52. A comparison of the clinical and pathological features in DUK1684 with those of the other chromosome 17–linked families, together with the linkage data, suggests that these families are allelic. These studies emphasize that genetic linkage analysis remains a useful tool for differentiating disease loci in clinically complex traits.

Introduction

The degenerative dementias are a clinically and genetically heterogenous group of disorders including Alzheimer disease (AD), prion diseases (Creutzfeld-Jacob disease), Huntington disease, Pick disease (PD), and frontotemporal dementia (FLDEM). FLDEM is characterized by behavioral and neuropsychological features reflecting frontal lobe dysfunction. Neuropathological findings reveal a nonspecific degeneration of the neocortex and subcortical nuclei, without the distinct features (plaques, neurofibrillary tangles, or other inclusions) that characterize other dementias, such as AD or PD (Brun et al. 1994). The changes in behavior and personality that are observed within this clinical category may not present as a distinct phenotype and may even suggest "unrelated clinical diagnoses," such as schizophrenia, amyotrophy, depression, or dysphasia, among affected family members (Lynch et al. 1994). In cases where there is evidence of familial aggregation, FLDEM appears to be inherited as an autosomal dominant disorder with age-dependent penetrance.

Recent studies based on single-family reports have shown two distinct chromosomal loci for non-AD FLDEM. A large family with disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC) was linked to a locus on chromosome 17q21 (Lynch et al. 1994; Wilhelmsen et al. 1994). A second family, inheriting a phenotype called "rapidly progressive autosomal dominant parkinsonism and dementia with characteristic pallido-ponto-nigral degeneration" (PPND), has been linked to the same region as has DDPAC (Wijker et al. 1996). A third family with nonspecific dementia has been linked to chromosome 3 (Brown et al. 1995). The identification of additional families linked to either location will aid us in identifying the gene(s) responsible and in understanding the clinical and neuropathological variation observed in this disease classification.

We have ascertained a large, multigenerational family (DUK1684) with the clinical and neuropathological characteristics of FLDEM. We report evidence for linkage to chromosome 17q21 in this family. In addition, we describe the clinical and pathological phenotype observed in this family and compare and contrast these findings with the DDPAC and PPND families.

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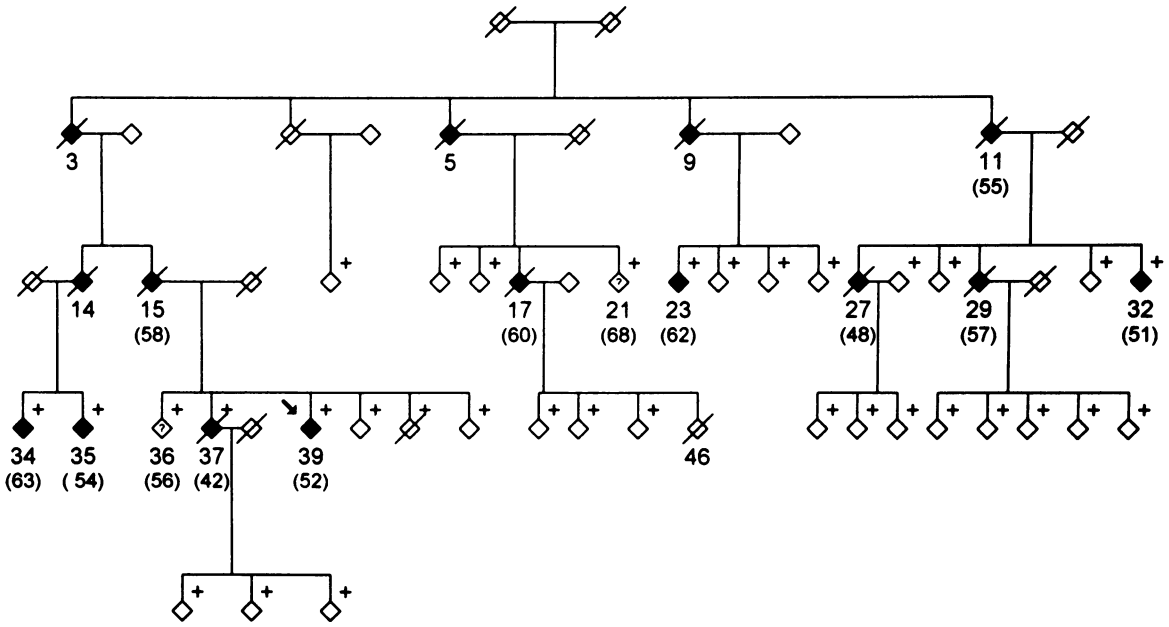

Figure 1 Pedigree of family DUK1684. Blackened symbols denote affected subjects. (Note that, to protect patient confidentiality, traditional male and female symbols have not been used.) A question mark (?) indicates that diagnosis was uncertain; the number in parenthesis indicates the age (in years) at onset; a diagonal slash (/) through a symbol indicates that the individual is deceased; and a plus sign (+) indicates that the individual was examined by Bryan ADRC personnel and that DNA was available.

Subjects and Material

Family Ascertainment

The family (DUK1684; fig. 1) was ascertained through referral to the Joseph and Kathleen Bryan Alzheimer Disease Research Center (Bryan ADRC) at Duke University Medical Center. Procedures for the recruitment of subjects were approved by the institutional review board. For family members unable to provide informed consent, permission for participation was obtained from next of kin. Records also were obtained on deceased affected individuals and on family members distant from the Bryan ADRC. The pedigree has been modified, for reasons of confidentiality.

Evaluation of affected individuals included a review of medical history, a standard neurological examination, and neuropsychological testing. Subjects first were categorized as demented or nondemented, according to DSM-IIIR criteria (American Psychiatric Association 1987). Diagnoses were assigned in cases of cognitive compromise by use of standard clinical criteria for neurological practice. Diagnoses of AD (McKhann et al. 1984) or vascular dementia (Roman et al. 1993), the most common forms of progressive dementia, were assigned according to NINCDS-ARDA criteria. FLDEM was assigned according to the criteria of Brun et al. (1994).

Autopsy pathology reports were available for review for two individuals (subjects 27 and 29). Slides were reviewed in one case (subject 29). In subject 37, the entire brain was sent to the Kathleen Bryan Brain Bank, for both gross and microscopic study.

Molecular Analysis

Simple-tandem-repeat polymorphisms were typed on individual family members by use of PCR (Vance et al. 1996). After PCR, the fragments were separated on denaturing sequencing gels. The gels were stained with Syber Green (Molecular Probes) and were scanned on a FluorImager SI (Molecular Dynamics). The fragments were sized by use of a 10-bp DNA ladder (Gibco-BRL). The genotyping results were entered into the PEDIGENE database, where all clinical, family history, and marker data are stored and managed in a secured, limited-access system (Haynes et al. 1995).

Linkage Analysis

The linkage analysis was performed by use of the VITESSE program package (O'Connell and Weeks 1995). Autosomal dominant inheritance with age-dependent penetrance was assumed for the trait locus, with a gene frequency of .0001 for the dementia allele.

At-risk individuals in the FLDEM family were assigned probabilities of carrying the dementia gene that were based on familial data on age at onset. Specifically, a penetrance curve for affection status was calculated

from the sample mean and variance ($\mu = 54.9 \pm 5.68$), under the assumption of a normal distribution for age at onset. Two individuals (subjects 21 and 36) were designated as probably affected, on the basis of clinical examination and medical history. In the linkage analysis, they were assigned an 80% probability of carrying the dementia gene. Spouses (i.e., married-in individuals) were assumed to be normal, with respect to disease status, for this rare autosomal dominant disease.

In addition to the age-adjusted analysis, a low-penetrance "affecteds only" analysis was performed as a conservative approach in evaluating linkage. A low-penetrance analysis incorporates phenotypic data on affected family members only. This approach precludes linkage exclusion based on potential crossovers in older "normal" at-risk individuals who may actually carry the disease gene but have not yet expressed it.

The markers used were the same as those used in the reports on the DDPAC locus on chromosome 17 and on the nonspecific dementia gene on chromosome 3 (Wilhelmsen et al. 1994; Brown et al. 1995). Marker-allele frequencies were calculated from a series of 100 unrelated Caucasian controls. Frequencies for these markers and for others are available via anonymous ftp (site: dnadoc.mc.duke.edu in the /pub/ALLELE_FREQ directory). Both two-point and multipoint linkage analyses were performed. The maps used in the multipoint location analyses were as reported elsewhere (Gyapay et al. 1994).

Results

Clinical Description and Neuropathology

The clinical findings are summarized in table 1. The proband (DUK1684/39; fig. 1) had onset of symptoms at age 52 years. The patient's early difficulties included "depression," personality change, and multiple physical complaints, including difficulty with walking. Other family members described the patient as severely amotivational, apathetic, and, at times, explosively irritable. These behaviors have resulted in occupational and social compromise.

On neuropsychological evaluation, the proband showed impairments in naming, visuoperception, and executive functions, but the rapid forgetting and apraxia typical of AD were not observed (Welsh et al. 1992). Brain magnetic-resonance imaging (MRI) was normal, with no sign of structural abnormalities. Resting-state fluorodeoxyglucose (FDG) positron-emission tomography (PET) showed reduced uptake in the anterior portion of the frontal and temporal lobes but no diffuse hypometabolism and no reduction of the parietotemporal cortices as is typical in AD (Rapoport 1993). In the 4 years since the initial evaluation, the patient has become more "childlike."

In four affected individuals in DUK1684 (subjects 3, 5, 9, and 11), there is limited anecdotal history of dementia and, in some, repetitive behaviors, but there is no clinical information. Among those for whom clinical information is available (table 1), initial symptoms were cognitive in five (subjects 14, 15, 17, 32, and 34), behavioral in five (subjects 23, 27, 29, 37, and 39), and extrapyramidal in one (subject 35). The average age at onset is 54.9 years (range 45–63 years). In five individuals on whom data are available, average disease duration was 9.2 years. Although impaired memory abilities are reported, problems with judgment and problem solving, perseveration, lack of insight, and poor social awareness are more prominent.

Two individuals (subjects 21 and 36) had signs suggestive of dementia. Neuropsychological testing revealed in each a mild cognitive syndrome, placing them in an ambiguous category. Subsequent reports from other family members document a decline in function in each during the past 18 mo. However, they do not show the full clinical phenotype seen in the definitively affected family members. Hence, for the linkage analysis, subjects 21 and 36 were assigned a probability of 80% of carrying the disease phenotype. These individuals, together with other at-risk family members, will be re-evaluated annually.

Limited pathology reports available on subjects 27 and 29 show a similar pattern of cell loss. Microscopically, neuronal loss and gliosis were most prominent in the temporal lobe, the third nerve nucleus, and the substantia nigra. Senile plaques, tangles, and Pick bodies were not seen.

A full neuropathological study was performed on subject 37. Gross examination of the brain showed mild atrophy of the frontal, parietal, and occipital lobes, with moderate atrophy of the temporal lobe. There was severe ventricular dilatation. Microscopic examination revealed that the distribution of cell loss was moderate to severe in the midbrain, amygdala, and entorhinal cortex, with variable involvement in the neocortex. The substantia nigra showed severe neuronal loss and moderate pigment incontinence. Lewy bodies and other inclusions were absent, and a few eosinophilic-degenerating neurons were present. Sections of the medulla and pons showed moderate degeneration of the locus ceruleus. The spinal cord was not available.

Linkage Analysis

The possibility that DUK1684 is an allelic variant of AD was tested. Reported mutations in the presenilin 1 and 2 genes (PS1 and PS2) and in amyloid precursor protein (APP) were tested (Goate et al. 1991; Schellenberg et al. 1992; Levy-Lahad et al. 1995). Since the entire sequences of the presenilin genes are not known,

Table 1

Clinical Features of DUK1684

Individual	Age at Onset (years)	Duration (years)	First Symptom	Frontal Lobe Dementia[a]	Autopsy	CT/MRI[b]	PET	Extrapyramidal Signs[a]						Frontal Lobe Release	Pyramidal Signs[a]
								Rigidity	Bradykinesia	Postural Instability	Tremors	Dystonia	Masked Facies		
15	58	10	Cognitive	3											
14			Cognitive	3											
17	60	8	Cognitive	3											
27	48	9	Behavioral		Yes					1					
29	56	6	Behavioral		Yes			2					1	Yes	1
23	62	4[c]	Behavioral	2											
32	51	6[c]	Cognitive	2		MRI[d]			1	1					
39	52	4[c]	Behavioral	2		MRI normal	1/Frontal				1		1	Yes	1
35	63	4[c]	Extrapyramidal	2		MRI[e]			3		1		1	Yes	1
34	54	8[c]	Cognitive	2		CT[f]		1	1	2			1	Yes	1
37	45	13	Behavioral		Yes	CT[g]		3				2	1	Yes	1
36	56		Behavioral	?											
21	68		Cognitive	?											

NOTE.—A blank cell denotes that no information was available or that the procedure was not performed.

[a] Severity code: 1 = mild; 2 = moderate; and 3 = severe.

[b] CT = computed tomography.

[c] Individual is still living.

[d] Moderate anterior temporal atrophy.

[e] Sulcal prominence.

[f] Mild ventricular dilatation.

[g] Mild global atrophy.

Table 2

Two-Point LOD Scores between FLDEM and Chromosome 3 Marker Loci

Type of Analysis and Marker	LOD Score at Recombination Fraction of						
	.00	.05	.10	.15	.20	.30	.40
Age adjusted:							
D3S1284	−3.27	−1.38	−.88	−.60	−.43	−.23	−.10
D3S1577	−.30	−.31	−.20	−.26	−.22	−.11	−.04
D3S1552	.18	.13	.09	.07	.04	.02	.00
D3S1603	−6.70	−2.67	−1.86	−1.40	−1.08	−.56	−.19
Low penetrance:							
D3S1284	−3.01	−1.02	−.64	−.45	−.34	−.20	−.10
D3S1557	.16	.12	.09	.06	.04	.02	.00
D3S1552	.43	.37	.31	.25	.20	.10	.04
D3S1603	−5.17	−2.12	−1.46	−1.06	−.76	−.35	−.11

NOTE.—The recombination fraction for males was assumed to be equal to that for females.

we also examined linkage to the respective chromosomal regions. No mutations were observed, and linkage to these regions was excluded (data not shown).

The two-point LOD scores for the chromosome 3–linked dementia markers are presented in table 2 (both age adjusted and for affecteds only). No significant evidence of linkage was found. Although slightly positive scores were found for D3S1552, multipoint linkage analysis (multipoint location score ≤ -2.00) confirmed exclusion of this region (data not shown).

The chromosome 17 marker data are presented in table 3 (both age adjusted and for affecteds only). A peak two-point LOD score of 2.89 was obtained for D17S791, highly suggesting linkage to this region. Multipoint linkage analysis with the markers D17S800, D17S791, and D17S806 resulted in a peak multipoint location score ($\log_{10}$) of 5.53, thereby establishing linkage to this region (fig. 2). The most likely location for the gene in this family, on the basis of the likelihood analysis, is at the D17S791 locus.

Haplotype analysis (data not shown) showed several unaffected individuals who carry portions of the disease haplotype. The current age of many of these individuals is well below the mean age at onset in this family. However, several older "unaffected" crossover individuals, whose risk of carrying the disease gene is relatively low,

Table 3

Two-Point LOD Scores between FLDEM and Chromosome 17 Marker Loci

Type of Analysis and Marker	LOD Score at Recombination Fraction of						
	.00	.05	.10	.15	.20	.30	.40
Age adjusted:							
D17S800	−.90	−.71	−.59	−.49	−.40	−.21	−.07
D17S791	2.89	2.62	2.32	2.01	1.69	1.04	.39
GP3A	.24	.26	.26	.24	.22	.16	.09
D17S806	−1.62	1.88	1.80	1.59	1.34	.80	.27
D17S790	−1.94	1.34	1.44	1.37	1.20	.72	.21
D17S787	−7.25	−2.62	−1.86	−1.36	−.96	−.41	−.11
Low penetrance:							
D17S800	−.42	−.36	−.31	−.26	−.21	−.12	−.05
D17S791	1.80	1.61	1.41	1.20	.98	.54	.16
GP3A	.41	.33	.26	.20	.15	.07	.02
D17S806	−1.25	.39	.57	.58	.53	.31	.09
D17S790	−.98	1.21	1.27	1.19	1.04	.65	.24
D17S787	−2.38	−1.94	−1.51	−1.16	−.88	−.45	−.18

NOTE.—The recombination fraction for males was assumed to be equal to that for females.

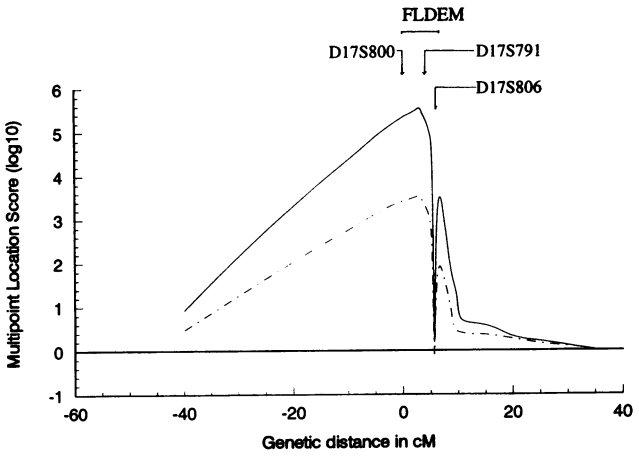

Figure 2 Multipoint location analysis (log_{10}) for placement of the disease gene on chromosome 17 (multipoint location score 5.53, at peak recombination fraction). The unbroken line represents results of age-adjusted analysis; and the broken line represents results of low-penetrance analysis.

also were identified and contributed to the disease sublocalization in the multipoint analysis. The two individuals (subjects 21 and 36), classified at 80% risk in retrospect, both carry the disease-allele haplotype. No crossovers were identified, in either at-risk or affected individuals, for the most tightly linked marker, D17S791.

Discussion

We have identified a family, inheriting a progressive neurodegenerative disease with FLDEM and extrapyramidal features, that is linked to chromosome 17q21. Phenotypically, this family and the previously linked DDPAC and PPND families share a broad but common clinical spectrum of early personality change, dementia, and parkinsonism, suggesting that these families are allelic (table 4).

The neuropathological findings seen on autopsy are similar in all three families and can account for the major symptoms of FLDEM observed in each family. Although similar areas were not always analyzed, the neuronal loss observed in the midbrain (substantia nigra) would result in extrapyramidal features, whereas the degeneration of limbic structures would result in dementia and disinhibition.

There are some differences among the three families, with regard to timing and degree of clinical involvement of various systems. Some of this clinical variation may reflect the stage, in disease progression, at which affected individuals are examined. In the family that we studied, early behavioral and cognitive features are prominent, and clinical parkinsonism and motor involvement are less evident. In DDPAC, the behavioral changes (i.e., disinhibition) are prominent, and amyotrophy, seen in a single individual, is noted. The suggestion that PPND presents a distinct phenotype seems based on the end-stage features of disease progression (Wijker et al. 1996). At the same time, the limited behavioral variation observed in DUK1684 may reflect a small sample size and the limited information available on deceased affected individuals. Similarly, the heterogeneity seen in age at onset can be influenced by family history and awareness, since reports of symptoms come from other family members. Clinical and pathological findings are useful in differentiating diseases in which the phenotypes are nonoverlapping. However, in FLDEM the clinical features are diverse and involve functions, such as personality change and foresight and planning, that are difficult to assess with traditional neuropsychological tests. In these circumstances, linkage analysis is a useful tool for classifying disease phenotypes.

In summary, the clinical and pathological similarities and the evidence for linkage to the same region of chromosome 17 suggest that the cause of disease in these

Table 4

Clinical Features of Chromosome 17–Linked Families with Non-AD Dementia

	DUK1684	DDPAC	PPND
Age at onset (years) [Range]	54.9 [45–63]	45 [27–56]	43 [32–58]
Duration (years) [Range]	9.2 [6–13]	13 [5–23]	8 [2–17]
Total no. affected	15	13	32
No. autopsied	3	6	6
Initial symptom[a] (no. of subjects)	D (5), PC (5), PD (1)	PC (11), PD/PC (2)	D (5), PC (7), PD (11), PD/PC (3)
Extrapyramidal signs[b]	1–3	2–3	2–3
Pyramidal signs[b]	1	0–2	1
CT/MRI[b]	0–2	2–3	1–2
PET (hypoactivity)	1/Frontal	3/Frontal	3/Frontal

[a] D = dementia; PC = personality change; and PD = parkinsonism.
[b] 0 = Normal; 1 = mild; 2 = moderate; and 3 = severe.

families is allelic. Understanding the variation observed in the clinical phenotype of these diseases (DDPAC, PPND, and FLDEM) awaits the identification and characterization of the gene.

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