

Linkage of Familial Amyotrophic Lateral Sclerosis With Frontotemporal Dementia to Chromosome 9q21-q22

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AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a progressive disease characterized by degeneration of both upper and lower motor neurons. Typically, it develops as a pure motor syndrome. However, in rare cases (probably <5%) ALS arises concurrently with other neurodegenerative phenotypes such as frontotemporal dementia (FTD)¹⁻³ or other extrapyramidal or cortical and subcortical syndromes.¹ While most cases of ALS occur in unrelated individuals (sporadic ALS), familial inheritance is observed in about 10% of cases (FALS).⁴ Analogously, cases of neurodegenerative overlap syndromes may also arise on a familial basis. Thus, pedigrees have

Context Occasionally, 2 or more major neurodegenerative diseases arise simultaneously. An understanding of the genetic bases of combined disorders, such as amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD), will likely provide insight into mechanisms of these and related neurodegenerative diseases.

Objective To identify loci that contain genes whose defects cause ALS.

Design A genome-wide linkage analysis of 2 data sets from an ongoing study begun in the mid-1980s at 4 university research centers.

Subjects An initial subset of 16 families (549 people) potentially informative for genetic analysis, in which 2 or more individuals were diagnosed as having ALS, identified from a Boston data set of 400 families and 4 families potentially informative (244 people) subsequently identified from a Chicago data set of more than 300 families to test a hypothesis based on findings from the Boston families.

Main Outcome Measures Linkage calculations assuming autosomal dominant inheritance with age-dependent penetrance (a parametric logarithm-of-odds [lod] score of 1.0 or greater required for further study of a potential locus); crossover analysis involving the ALS-FTD locus.

Results In a set of families in which persons develop both ALS and FTD or either ALS or FTD alone, a genetic locus that is linked to ALS with FTD located between markers D9S301 and D9S167 was identified on human chromosome 9q21-q22. Families with ALS alone did not show linkage to this locus. Crossover analysis indicates this region covers approximately 17 cM.

Conclusion These data suggest that a defective gene located in the chromosome 9q21-q22 region may be linked to ALS with FTD.

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been reported with ALS-FTD^{1,5} and with combinations of ALS, Parkinson disease (PD), and dementia.^{4,6,7} Recently, genetic analyses have documented that several pedigrees with FTD, extrapyramidal manifestations suggestive of PD, and amyotrophy (a combination designated here as FTD-PD) arise from mutations in the *MAPT* gene, which encodes the tau protein.⁶⁻¹¹

The cause of most cases of ALS is unknown. About 25% of FALS cases are caused by defects in the gene encoding copper-zinc cytosolic superoxide

dismutase (*SOD1*).^{12,13} To define the pathogenesis of other FALS cases, we conducted genome-wide linkage analysis involving 16 pedigrees. In the course of this screening, we identified a new locus for a subtype of ALS in which, in the same family and often in the same individuals, ALS is conjoined with FTD.

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METHODS

Family Data

Families included in this study fulfilled the El Escorial criteria for the diagnosis of ALS,¹⁴ with the exception that we included rare pedigrees with other neurodegenerative features such as FTD. The combined Boston and Chicago data sets now include more than 700 collected families (each with at least 2 individuals diagnosed as having ALS). Families known to have mutations in *SOD1* were excluded from this study. Simulated linkage analysis with the program SIMLINK¹⁵ was used to identify an initial screening subset of 16 families potentially informative for genetic analysis from the 400 families in the Boston collection. This subset of families includes 549 people, of whom 93 were affected with either ALS or ALS and FTD. DNA was available from 305 persons, including 36 affected individuals and 44 "married-in" spouses. Because of the late onset and short duration of this disease, many individuals were not available for study. Based on findings from the Boston families as described in the "Results" section, 4 families from the Chicago data set were subsequently analyzed. These Chicago families include 244 people, of whom 38 were affected with ALS or FTD or both. The institutional review boards of the involved institutions approved this study. Informed consent was received from all participating patients. To protect patient confidentiality, the haplotype data essential for assessing the limits of candidate gene location are summarized herein in tabular form. Full pedigree and haplotype information was provided to reviewers and is available to genetics researchers from the authors on request as appropriate.

Marker Analysis

DNA was isolated from whole blood or cultured lymphoblasts and analyzed by polymerase chain reaction (PCR) amplification using standard techniques. Markers spaced across the entire genome were selected from the Cooperative Human Linkage Center Human screening set, Weber version 8 and 8A

(Center for Medical Genetics, Marshfield, Wis), and the ABI Prism screening set (Perkin Elmer, Foster City, Calif). Additional markers used to narrow the region of interest were chosen based on mapping information publicly available from the Whitehead Institute/MIT Center for Genome Research.¹⁶ Primers for PCR were obtained as Map Pairs from Research Genetics (Huntsville, Ala) or custom synthesized by Research Genetics or GIBCO (Gaithersburg, Md). For allele identification, the PCR products were separated and scored using automated DNA sequencing equipment from LiCor (Lincoln, Neb) or Perkin Elmer. Haplotype construction was done by hand and confirmed using SimWalk2 version 2.54.¹⁷

Linkage Analysis

The MLINK and LINKMAP subprograms of the program LINKAGE (FASTLINK, version 4.0, National Center for Biotechnology Information)¹⁸⁻²⁰ and the program VITESSE (Division of Statistical Genetics, University of Pittsburgh, Pittsburgh, Pa)²¹ were used to calculate pairwise and multipoint logarithm-of-odds (lod) scores for linkage between markers and disease locus. A parametric lod score of 1.0 or greater was required for further study of a potential locus. Allele frequencies for the markers were estimated using married-in members of the study families as a representative control population ($n=44$). These frequencies were compared with data generated in other screening projects, and no significant differences were seen. Penetrance of the disease was assumed to be 90% by age 70 years, and intermediate risk classes based on age were assigned as previously described.²² Pedigrees (including haplotypes) were displayed using Cyrillic (version 2.1; Cherwell Scientific, Palo Alto, Calif).

RESULTS

Initial Marker Screening and Linkage Analysis

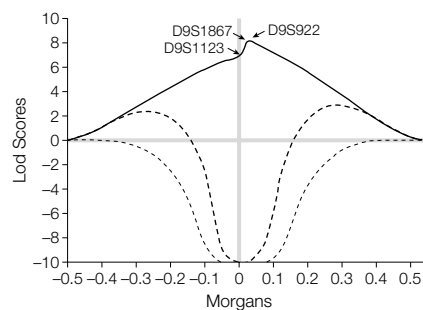
To screen the genome efficiently for new FALS loci, we instituted a 2-pronged approach, with screening of

independent data sets at 2 sites (Boston and Chicago). In the Boston data set, the marker D9S1122 gave an overall lod score of 3.34 at $\theta=0.10$ (θ indicates recombination fraction) when examined in 16 families, thus reaching our criterion (lod score >1.0) for further study. Two markers (D9S301 and D9S922) located about 7 cM to either side of D9S1122 were selected for further testing. These markers map to the chromosome 9q21-q22 region.²³

Family F222 had a lod score of 1.10 at $\theta=0$ for marker D9S922 and a score of 0.48 at $\theta=0$ for marker D9S1122, and family F17 had lod scores of 2.08, 0.07, and 3.15 with markers D9S301, D9S1122, and D9S922, respectively, at $\theta=0$. When we reviewed the records for these families, selected from our set solely on the basis of this analysis, we found that in each family several patients developed motor neuron disease concurrently with progressive dementia. In family F222, 1 patient was diagnosed with ALS and FTD while 2 showed only motor neuron symptoms. For 3 other persons, the clinical records and other available information confirmed a diagnosis of ALS accompanied by dementia symptoms but were inconclusive as to the type of dementia. In family F17, 2 patients were diagnosed with ALS and FTD while 2 had ALS alone. One patient had ALS accompanied by dementia symptoms. Information about possible dementia is unavailable for the affected person in the earliest generation. The mean (SD [range]) age of onset for affected individuals in these 2 families was 53.8 (8.2 [40-62]) years with an average (SD [range]) duration of 3.8 (4.0 [1.3-15]) years, with most persons surviving 4 years or less and 1 patient surviving 15 years. In the other 14 ALS families in the Boston linkage analysis subset, which showed no linkage to these markers, there were no individuals with both ALS and FTD.

The dementia specified as FTD in these families was characterized by socially inappropriate, impulsive behavior and a general deterioration in ability to perform routine daily tasks. These behavioral changes occurred months be-

Figure. Multipoint Analysis for Markers D9S1123, D9S1867, and D9S922



Lod indicates logarithm of odds. The line with the long dashes represents analysis of the complete data set; the line with short dashes, analysis of the nondementia subset; and the solid line, data from the subset of 5 families with amyotrophic lateral sclerosis and frontotemporal dementia.

fore any significant changes in memory. The affected persons generally did not appreciate the significance of these subtle changes in personality. Examination of these patients documented a combination of corticospinal and lower motor neuron features in conjunction with signs of frontal release. Imaging studies were consistent with frontotemporal atrophy. Pathological studies confirmed the presence of frontotemporal atrophy and also revealed frontotemporal gliosis, vacuolar changes in the corresponding cortex, rare Pick bodies, and a relative paucity of amyloid plaques and neurofibrillary tangles. In our view, these combined findings fulfill the Lund-Manchester criteria for a diagnosis of FTD²⁴ arising concurrently with motor neuron disease.

To test the hypothesis that these chromosome 9 markers identify a locus that is linked specifically to ALS with FTD, the Boston data set was augmented by 4 potentially informative ALS families from the Chicago branch of our consortium (centers located at Harvard, Duke, Vanderbilt, and Northwestern Universities). These included 3 families with members having ALS concurrent with dementia and 1 with ALS unaccompanied by dementia. In family F9748, 5 patients were diagnosed as having ALS-FTD while 3 had ALS alone. In family F9969, 2 patients were diag-

nosed as having ALS-FTD while 3 had ALS alone and 2 others had FTD alone. In family F638, 1 patient was diagnosed as having ALS-FTD while 2 had ALS alone and 1 other had FTD alone. For 2 other persons in family F638, the clinical records and other available information confirmed a diagnosis of ALS accompanied by dementia symptoms but were inconclusive as to the type of dementia. For these 3 families, which include 108 persons, of whom 21 had ALS or FTD or both, a total of 16 DNA samples were available, 11 from affected persons. The mean (SD [range]) age of onset for affected individuals in these 3 families was 54.6 (12.4 [38-82]) years, with most persons having onset at or before age 65 years and 1 person having onset at age 82 years, and with an average (SD [range]) duration of 6.2 (6.3 [2-24]) years, with most persons surviving 6 years or less and with 3 patients surviving 12, 13, and 24 years, respectively. In family F379 (n=136), 17 persons were affected with ALS, and DNA was collected from 60 persons (11 affected). No members of this family showed symptoms of dementia. The mean (SD [range]) age of onset for affected persons in this family was 50.7 (13.2 [36-71]) years with an average (SD) duration of 2.5 (1.6) years. Overall, the disease parameters (age of onset and duration) for the families we studied are typical of all ALS cases, both sporadic and familial.⁴

The expanded data set was examined for heterogeneity using admixture analysis.²⁵ For the families with ALS and FTD, the hypothesis of linkage with heterogeneity assuming $\alpha = .65$ was 13 times more likely than the hypothesis of linkage with homogeneity and 4.0×10^4 times more likely than the null hypothesis of no linkage. The 3 Chicago families with members having ALS and dementia showed linkage to this locus while the nondementia family did not show linkage, thus confirming our hypothesis that this locus is associated with ALS with concurrent FTD. Accordingly, we tested additional markers between D9S301 and D9S922 and telomeric of D9S922. For

the 5 ALS-FTD families, peak multipoint lod scores of 8.08 and 8.12 were obtained at markers D9S1867 and D9S922, respectively (for the marker set D9S1123, D9S1867, and D9S922) (FIGURE). Two-point lod scores for the markers are shown in TABLE 1 for all 16 families in the Boston data set and for the subset of ALS-FTD families.

Crossover Analysis of the ALS-FTD Locus

For all families, haplotypes representing individual chromosome fragments were assembled. No single haplotype was consistently inherited with ALS in the non-FTD families, confirming that they are not linked to this chromosome 9 locus. The alleles comprising the linked haplotypes were dissimilar between the ALS-FTD families, suggesting independent origins for the disease-associated chromosomes. Although 3 of the 5 linked families show no evidence of crossovers occurring across this region, we can partially define the limits of the ALS-FTD locus based on crossover events observed in families F222 and F17. Genotype data are shown in TABLE 2 for affected individuals and an unaffected obligate carrier of the disease-associated chromosome.

A crossover observed in affected individual (individuals are identified as generation:individual throughout) II:3 in family F222 (Table 2) determines the centromeric border of the ALS-FTD region. The disease-associated allele for marker D9S301 in this family is allele 1. Individual II:3 has inherited allele 8 for this marker from affected parent I:1 and shares the family disease-associated haplotype for markers telomeric of D9S301. Thus, we concluded that the crossover seen in individual II:3 occurred between markers D9S301 and D9S927, establishing D9S301 as the centromeric limit of the disease locus.

The telomeric boundary of the region is less firmly established. Individual IV:4 in family F17 is affected. Thus, unaffected individual III:1, the parent of IV:4, is an obligate carrier of the disease-associated chromosome. Indi-

vidual III:1 shares the family disease haplotype for markers centromeric of marker D9S167 and carries alleles 10 and 11 for D9S167 (Table 2). While we could not determine whether allele 10 or 11 was physically associated with the disease chromosome (phase) in individual III:1, neither allele 10 nor allele 11 is the disease-associated allele 5 observed for D9S167 elsewhere in this family. This implies that a crossover has occurred at some point centromeric to this marker. Although DNA from individual IV:4 is not available, we can partially reconstruct this genotype using data available from other persons (spouse and 2 children). However, both children have inherited the same chromosome from their affected parent IV:4, and this is not present in III:1. It is most likely to be the chromosome that IV:4 inherited from the married-in parent (spouse of III:1). Thus, we cannot explicitly determine whether individual IV:4 inherited the modified disease-associated haplotype observed in III:1. If we assume that IV:4 did inherit it, the crossover centromeric of D9S167 would establish this marker as the telomeric border of the ALS-FTD locus.

We estimate the genetic distance between D9S301 and D9S167 as 17 cM, corresponding to approximately 14 cR.^{23,26}

COMMENT

These data define a new locus for a variant of FALS that arises in conjunction

with frontotemporal dementia. This locus was identified via systematic genomic screening of families ascertained only for ALS. The fact that the families with linkage in the Boston data set share the unusual ALS-FTD phenotype strengthens our confidence in the validity of this result. Moreover, the initial linkage was independently verified in a second data set that included 3 ALS-FTD families. This 2-stage approach can be viewed as hypothesis generating and hypothesis testing. The lod scores in the first data set reach classic levels of significance without lim-

iting the analysis to the ALS-FTD subset and without including the Chicago ALS-FTD families. Testing the ALS-FTD hypothesis in the second data set with inclusion of the Chicago families generated higher scores, greatly increasing our confidence in this result.

The combination of FTD with ALS has been described.^{1-3,27-29} Such cases arise both on a sporadic basis and as autosomal dominantly inherited traits.⁵ However, genetic loci for ALS-FTD have not been reported. While it is possible that the families presented herein are phenotypic variants of the FTD-PD tauo-

Table 1. Pairwise Lod Scores for Familial Amyotrophic Lateral Sclerosis (FALS) and Chromosome 9 Markers*

Markers	Recombination Fraction, θ						
	0	0.05	0.10	0.15	0.20	0.30	0.40
Boston 16-Family Data Set, Age Corrected							
D9S301	-16.70	-3.25	-0.45	0.85	1.40	1.29	0.48
D9S927	-10.64	-0.19	0.88	1.73	1.99	1.57	0.62
D9S1122	0.37	3.04	3.34	3.21	2.86	1.80	0.67
D9S1123	-15.87	-4.61	-2.53	-1.35	-0.62	0.03	0.09
D9S1867	-26.10	-4.03	-0.66	0.88	1.56	1.54	0.65
D9S922	-23.53	-4.10	-0.68	0.96	1.70	1.67	0.70
D9S167	-30.98	-5.45	-1.43	0.50	1.41	1.58	0.66
Subset of 5 FALS-FTD Families, Age Corrected							
D9S301	3.33	3.97	3.69	3.24	2.72	1.56	0.49
D9S927	4.10	3.92	3.57	3.14	2.65	1.60	0.60
D9S1122	3.56	3.30	2.96	2.58	2.15	1.25	0.43
D9S1123	1.43	1.63	1.58	1.44	1.24	0.76	0.31
D9S1867	5.47	4.92	4.33	3.71	3.08	1.80	0.62
D9S922	6.41	5.95	5.39	4.76	4.06	2.52	0.96
D9S167	3.81	4.73	4.46	4.00	3.43	2.09	0.72

*FTD indicates frontotemporal dementia; lod, logarithm of odds.

Table 2. Haplotype Data Defining the Limits of the Chromosome 9 Locus*

Markers	Family F222†					Family F17†				
	I:1 (A-d)‡	II:1 (A)‡	II:2 (A-F)‡	II:3 (A-d)§	III:1 (A)	IV:1 (A-d)	IV:2 (A-F)‡	IV:3 (A-F)	III:1 (Un)	IV:4 (A)‡
D9S301	1 8	1 7	1 7	8 7	1 6	6 7	6 6	6 1	6 7	? 6
D9S927	3 5	3 5	3 5	3 5	3 3	5 12	5 3	5 10	5 5	? 5
D9S1122	2 4	2 3	2 3	2 3	2 4	3 2	3 2	3 4	3 3	? 1
D9S1123	4 3	4 3	4 4	4 4	4 4	3 2	3 5	3 1	3 6	? 4
D9S1867	2 1	2 7	2 9	2 9	2 9	1 2	1 9	1 6	1 8	? 2
D9S922	3 2	3 1	3 2	3 2	3 1	1 4	1 1	1 2	1 2	? 3
D9S167	3 11	3 6	3 1	3 1	3 10	5 1	5 3	5 7	10 11	? 4

*Disease-associated haplotypes shown in boldface. Pedigree data from which these haplotypes were derived are available from the authors on request as appropriate. Diagnosis code: A indicates amyotrophic lateral sclerosis (ALS); A-F, ALS and frontotemporal dementia (FTD); A-d, ALS and dementia that cannot be confirmed as FTD; Un, unaffected obligate carrier; and ?, unknown. Data are presented as sets of alleles.

†Individual family members are identified by generation:individual. Disease status is given in parentheses.

‡Indicates a reconstructed genotype (haplotypes inferred based on pedigree analysis).

§Individual with observed crossover determining centromeric border of the ALS-FTD region.

||Individual with proposed crossover determining possible telomeric border of the ALS-FTD region. It was not possible to determine whether allele 10 or 11 was physically associated with the disease chromosome.

pathy kindreds with amyotrophy, FTD, and parkinsonism,³⁰ in our view, 3 findings refute that possibility. First, while amyotrophy is observed in some tauopathy cases, it is not usually the predominant, presenting clinical feature. Second, unlike the tauopathy cases that map to the tau-gene locus (*MAPT*) on chromosome 17q, the disease in these families maps to chromosome 9q. Moreover, genetic analysis in these families revealed recombinations between polymorphisms at the tau locus and the inherited ALS-FTD trait (B.A.H., P.C.S., and R.H.B., unpublished data, 1999). Finally, at autopsy, a striking deposition of neurofibrillary tangles³¹ is usually seen in FTD-PD cases. Such tangles were only rarely evident in multiple regions of the brains of persons from each of the 5 families described here. Although the data do not suggest involvement of tau gene mutations in these ALS-FTD families, we cannot exclude the possibility that the primary genetic defect in these families is related to a pathway involving a tau-like protein or the tau protein itself.

Our results extend our understanding of the genetic bases of both ALS and dementia. To date, loci for ALS have been confirmed or suggested on chromosomes 21q (*SOD1* gene),¹² 11 (neurofilament heavy subunit gene),³² the X chromosome,³³ distal 9q,³⁴ 2q (childhood onset, recessive ALS),³⁵ and 15q15.1-q21.1 (juvenile, recessive ALS).³⁶ The previously defined ALS locus on chromosome 9³⁴ is at the extreme telomere of the chromosome and thus is genetically distinct from that defined by our linkage. Moreover, the earlier locus was identified in kindreds with juvenile-onset ALS with a slow course and no dementia, clearly clinically distinct from the characteristics of the ALS-FTD families discussed herein. Loci encoding genes or factors related to dementia have previously been identified on chromosomes 21q (amyloid protein),³⁷ 14 (presenilin 1),³⁸ 1 (presenilin 2),^{39,40} 19 (apolipoprotein E),⁴¹ 12 (α -macroglobulin)^{42,43} and 3.⁴⁴ It thus appears that our new locus for ALS-FTD also

defines a new dementia-related chromosomal address.

We have examined existing databases for possible candidate disease genes in our new ALS-FTD locus. One gene that maps near this region is the tyrosine kinase receptor *trkB*, a receptor for the neurotrophin family of proteins.⁴⁵ Analysis of a known polymorphism within this gene has shown that it lies telomeric of the ALS-FTD locus (B.A.H., P.C.S., and R.H.B., unpublished data, 1999). Other known genes mapping within the candidate region include those for cytosolic aldehyde dehydrogenase (*ALDH1*), annexin 1 (*ANX1*), CDC28 protein kinase 2 (*CKS2*), glucosaminyl transferase 1 (*GCNT1*), and heterogeneous nuclear ribonucleoprotein K (*HNRPK*).⁴⁶ Also, a locus for choreoacanthocytosis has been mapped to this region by linkage studies, with a maximum lod score at marker D9S1867.⁴⁷ The 2 diseases affect both motor functions and classes of cortical neurons; further study will show whether choreoacanthocytosis and ALS-FTD are genetically related.

Finally, we note that most of our families with inherited ALS still are not genetically associated with any of the identified ALS loci (B.A.H., T.S., J.L.H., and R.H.B., unpublished data, 2000). It thus appears that inherited ALS will show a high degree of genetic heterogeneity, as well as clinical diversity. This has implications for genetic linkage analysis strategies, rendering the conventional approach of establishing linkage with multiple large families exceedingly difficult. It remains to be determined whether the multiple genes involved in inherited ALS define sets of functionally significant, interacting genes. If this is the case, an understanding of the functions of the associated proteins and pathways may provide further insight into the pathogenesis of these diseases and ultimately lead to new approaches to treatment.

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