Linkage of the Gene for an Autosomal Dominant Form of Juvenile Amyotrophic Lateral Sclerosis to Chromosome 9q34

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Summary

We performed genetic mapping studies of an 11-generation pedigree with an autosomal dominant, juvenile-onset motor-systems disease. The disorder is characterized by slow progression, distal limb amyotrophy, and pyramidal tract signs associated with severe loss of motor neurons in the brain stem and spinal cord. The gene for this disorder, classified as a form of juvenile amyotrophic lateral sclerosis (ALS), is designated "ALS4." We performed a genomewide search and detected strong evidence for linkage of the ALS4 locus to markers from chromosome 9q34. The highest LOD score (Z) was obtained with D9S1847 $(Z = 18.8$, recombination fraction of .00). An analysis of recombinant events identified D9S1831 and D9S164 as flanking markers, on chromosome 9q34, that define an ∼5-cM interval that harbors the ALS4 gene. These results extend the degree of heterogeneity within familial ALS syndromes, and they implicate a gene on chromosome 9q34 as critical for motor-neuron function.

Introduction

Amyotrophic lateral sclerosis (ALS [MIM 105400]), also known as "Lou Gehrig disease," denotes a widely recognized, heterogeneous group of progressive neurological disorders associated with degeneration of motor neurons in the cerebral cortex, brain stem, and spinal cord (Williams and Windebank 1991). Although ALS is most commonly encountered as a sporadic condition that is presumed not to have been inherited, ∼5%–10%

of patients have similarly affected relatives; this indicates that genetic factors play an important role in the development of some motor-neuron disorders (Strong et al. 1991). Inherited forms of ALS are classified as "familial ALS" (Mulder et al. 1986). The clinical phenotypes of sporadic and familial ALS can be virtually indistinguishable; however, pathological studies in pedigrees with familial ALS have documented more extensive, subclinical involvement of the nervous system, including degeneration of the posterior columns, Clarke's column, and spinocerebellar tracts (Engel et al. 1957; Brownell et al. 1970; Tanaka et al. 1984).

The gene for an autosomal dominant form of familial ALS (ALS1) maps to chromosome 21q22.1-22.2 (Siddique et al. 1991) and is associated with mutations in the copper-zinc superoxide dismutase (SOD-1) gene (Rosen et al. 1993). ALS1 patients typically have an adult-onset illness that progresses rapidly and leads to death, from respiratory collapse and pneumonia, within 3–5 years of onset, although ALS1 families in which disease progression has exceeded 10 years have been described (Williams and Windebank 1991).

Childhood- or adolescent-onset forms of familial ALS carry the designation "juvenile ALS." Ben Hamida et al. (1990) described 17 Tunisian kindreds with various forms of early-onset ALS. The mean age at onset was 12 years, and illness progressed slowly. Patients with juvenile ALS may have normal life spans, but neuromuscular impairment is typically severe. Autosomal recessive forms of juvenile ALS map to either chromosome 2q33-35, designated "ALS2" (Hentati et al. 1994), or chromosome 15q12-21, designated "ALS5" (Hentati et al. 1997). The molecular bases of ALS2 and ALS5 are unknown. Although ALS1 and ALS2 share the clinical feature of motor-neuron degeneration, they are clinically and genetically distinct disorders. The identification of pedigrees with adult-onset, autosomal dominant ALS that is neither linked to chromosome 21 nor associated with mutations in SOD-1 suggests the existence of additional loci for familial ALS; this form has been designated "ALS3" (Siddique et al. 1991).

Here, we report analysis of a large pedigree with a
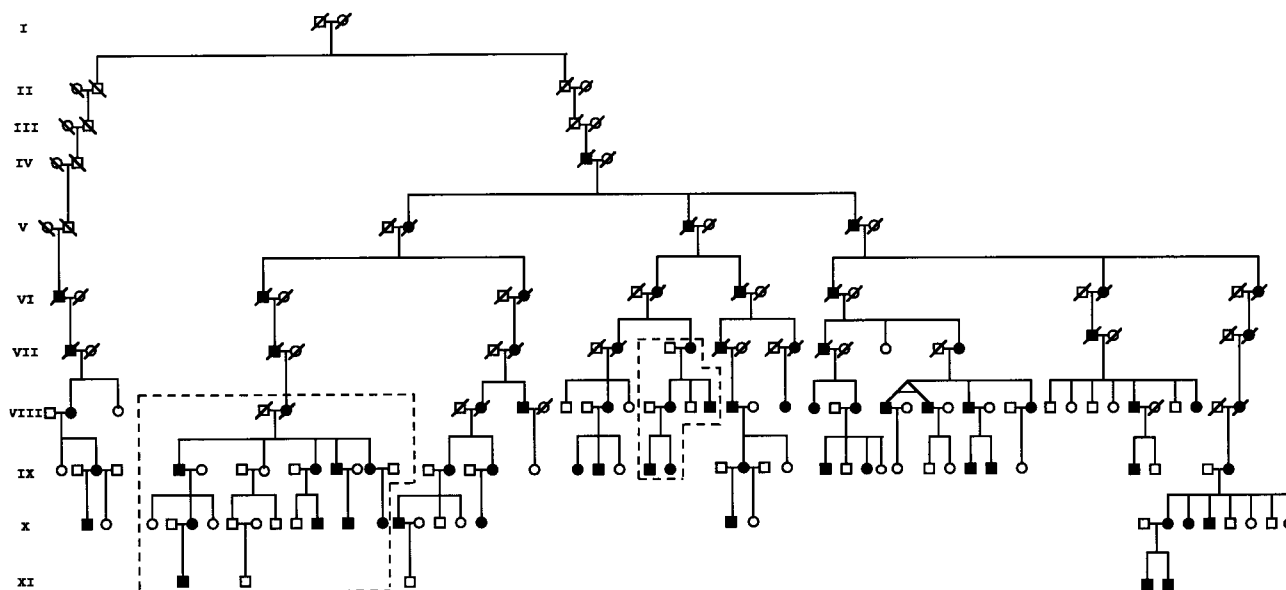
Figure 1   Pedigree K7000, which segregates an autosomal dominant form of juvenile ALS. Females are indicated by circles and males by squares. Blackened figures denote affected individuals, and slashed figures denote deceased individuals. Genotypes for chromosome 9 markers were determined for all living persons shown. Haplotypes for boxed portions of the pedigree are presented in figure 3*A* and *B*.

slowly progressive, autosomal dominant form of juvenile ALS. The gene for this disorder, designated "ALS4," maps to chromosome 9q34 and is genetically distinct from previously mapped familial ALS syndromes.

Subjects and Methods

Description of Pedigree

We studied an 11-generation pedigree (K7000; fig. 1) that was originally described in 1964 (Myrianthopoulos et al. 1964). Ancestors of this kindred were traced to 17th-century England, and the disorder was documented in eight generations, including 52 affected persons living in southern Maryland and nearby states. Autosomal dominant inheritance was confirmed by the presence of male-to-male transmission. In the present study, diagnosis of early-onset selective upper– and lower–motor-neuron involvement was established by the patient's history, the clinical findings, and the results of electrophysiological tests. Affected persons typically manifested symptoms in the 2d decade of life (mean age at onset, 17 years). They initially had difficulty walking; this was followed by weakness and wasting of small muscles of the hands and distal lower extremities. By the 4th or 5th decade, affected persons had significant proximal weakness and were frequently wheelchair-bound, and by the 6th decade, they had lost useful hand function. Bulbar muscles were not symptomatically involved. Neurological examinations were performed by four neurolog-

ical examinations were performed by four neurolog-
(D.R.C., J.W.G., B.A.R., and M.S.). Forty-nine affected and 34 at-risk individuals were evaluated by means of a standardized examination that assessed mental, cranial nerve, sensory, motor, deep-tendon reflex, and cerebellar status. Intelligence was normal. There was pathological hyperreflexia in 86% of affected individuals, and 17% had extensor plantar responses. In many affected individuals, weakness of the toe and foot extensor muscles prevented interpretation of the plantar response. Detailed sensory examinations, including tests for both large- and small-fiber–type sensory functions, were performed in 49 subjects: 44 had normal sensory examination results, and 5 older individuals (mean age, 51 years) had slight elevation of the vibratory threshold in the feet. Six subjects had normal skin biopsies, for quantitation of intraepidermal sensory nerve fibers, in accordance with methods described elsewhere (McCarthy et al. 1995).

Electrophysiological Studies

Sensory- and motor-nerve–conduction studies of the upper and lower extremities were performed, in five moderately to severely affected patients, according to standard methods (Kimura 1989). Sensory responses were normal, and motor-nerve–conduction studies showed absent or reduced-amplitude compound muscle-action potentials in all five subjects, with normal motor-nerve–conduction velocities. Needle electromyography showed evidence of chronic partial denervation; distal

muscles were more abnormal than were proximal muscles.

Neuropathological Description

Pathological examination of the brain, spinal cord, and nerve roots was performed on an 88-year-old woman (individual VII-10) who died of respiratory failure after an ischemic stroke. Gross inspection of the spinal cord demonstrated atrophy of the ventral and dorsal roots. Microscopic evaluation of the spinal cord parenchyma disclosed loss of anterior horn cells and pallor of the dorsal columns. The severity of anterior horn-cell loss varied from section to section but was greater at lumbosacral levels, where ~50% of the anterior horn cells were missing. Many remaining neurons showed chromatolysis. Inspection of the ventral and dorsal roots revealed numerous axonal swellings, some of which stained positive for phosphorylated neurofilaments. Microscopic evaluation of the brain disclosed numerous axonal spheroids in the dentate nucleus and nucleus gracilis, and rare ubiquitin-positive cytoplasmic inclusions were found in neurons of the inferior olivary nucleus. In this patient, no definite neuropathological changes were seen in upper motor neurons or their axons. Prominent axonal swellings were noted in the intracranial portions of the third and fourth cranial nerves.

Genetic Markers

Under a protocol of informed consent, blood samples were obtained, by venipuncture, for isolation of DNA and establishment of permanent cell lines, by standard methods. One hundred fifty PCR-based markers that identified loci spaced at ~10-cM intervals (version 6, Research Genetics) were used to search the genome for linkage (Weber and May 1989). Genetic maps and primer sequences for markers were obtained from internet sources, including the Genome Database (Gyapay et al. 1994) and the Cooperative Human Linkage Center (Murray et al. 1994). Methods for obtaining genotypes have been described elsewhere (Pellegrino et al. 1996). One hundred seven individuals were genotyped, including 52 affected and 37 at-risk individuals.

Linkage Analysis

Pairwise LOD scores (Z) and multipoint location scores were calculated, between marker loci and ALS4, by use of the computer program LINKAGE, version 5.1 (Lathrop et al. 1985). Zscores were calculated under a model of autosomal dominant inheritance. Penetrance of the ALS4 gene was taken as .99, and equiprobable male and female recombination fractions (θs) were assumed. The frequency of the mutant allele was taken as .0001. Equal gene frequencies were taken for marker alleles (use of marker allele frequencies estimated from a pool of 30 unrelated individuals had no significant effect on the LOD-score calculations). Unaffected at-risk individuals, aged <21 years, and individuals for whom neurological findings were equivocal were typed "unknown" for the trait phenotype; thus, these individuals provided marker information only. For multilocus analysis, location of the ALS4 gene was tested against a fixed map of seven markers in chromosome 9q34 (D9S1821, D9S260, D9S1831, D9S1847, D9S1830, D9S164, and D9S1818), and genetic distances were taken from published sources (Gyapay et al. 1994; Murray et al. 1994; Dib et al. 1996). Haldane's equation was used to convert θs to genetic distances (Ott 1985). Calculations were carried out on a VAX 6520 computer.

Results

Linkage to regions known to harbor the loci for previously mapped motor-neuron syndromes was initially excluded. ALS4 does not map to the regions of ALS1 or ALS2. Linkage to D21S223 (which is closely linked to ALS1) was excluded ($Z = -2.0$, $\theta = .1$). Marker D2S72 was tested for linkage to ALS2, on chromosome 2q (Hentati et al. 1994), and linkage was excluded ($Z = -2.0$, $\theta = .20$). Markers from the spinal muscular-atrophy (SMA)–gene region, on chromosome 5q11.2-13.3, were tested, including D5S435 (which maps within 1 cM of the SMA locus) (Brzustowicz et al. 1990; Wirth et al. 1994), and no evidence for linkage was found ($Z = -2.15$, $\theta = .1$). Furthermore, deletion of exons 7 and 8 of the survival motor-neuron (SMN) gene, which is associated with ~90% of SMA cases (Lefebvre et al. 1995), was not detected in an affected person from pedigree K7000 (P Bingham, personal communication). Linkage to the region of an autosomal dominant form of SMA, on chromosome 7p (Christodoulou et al. 1995), was tested and excluded ($Z = -2.0$, $\theta = .15$) with marker D7S795. Therefore, the neurological disorder segregating in pedigree K7000 is genetically distinct from these previously mapped motor-neuron syndromes, including forms of ALS.

To map ALS4, we performed a genomewide search, testing 150 PCR-based DNA markers (data available on request). Linkage was initially detected with markers D9S158 ($Z_{max} = 6.12$, $\theta = .059$) and D9S915 ($Z_{max} = 4.82$, $\theta = .038$), which map to distal chromosome 9q34 (Hudson et al. 1995). Additional markers in this region were tested, to refine the map position of ALS4 and to identify flanking markers (listed in table 1). The highest Z score was obtained with marker D9S1847 ($Z = 18.84$, $\theta = .00$). Haplotypes were constructed and a multilocus analysis, based on marker orders derived from published maps of chromosome 9 (Gyapay et al.

Table 1

*Z Scores at Various Recombination Fractions, for Markers on Chromosome 9q, in Pedigree K7000*

	Z Score at $\theta =$								
Marker	.00	.01	.05	.1	.2	.3	.4	Z_{max}	θ
D9S1821	−9.28	−2.22	1.73	2.96	3.14	2.32	1.12	3.25	.157
D9S260	−11.82	−2.50	1.01	2.04	2.17	1.54	.72	2.28	.155
D9S1831	−17.82	−.65	4.38	5.62	5.11	3.33	1.33	5.71	.124
D9S1863	1.83	6.08	6.67	6.25	4.69	2.90	1.22	6.67	.045
D9S1847	18.84	18.51	17.13	15.33	11.51	7.53	3.52	18.84	.000
D9S1830	11.03	11.07	10.46	9.34	6.84	4.29	1.88	11.08	.006
D9S164	4.69	9.04	9.74	9.24	7.24	4.75	2.12	9.74	.046
D9S1818	−2.26	5.13	6.55	6.44	4.97	2.99	1.09	6.60	.065
9qter									

1994; Murray et al. 1994; Dib et al. 1996), was performed. The results of the multilocus analysis are shown in figure 2; these results provide additional support for localization of ALS4 to chromosome 9q34. The highest probability for a location of ALS4 occurred in the region of markers D9S1847 and D9S1830 (peak location score >20.0). An analysis of crossovers seen in affected individuals, between ALS4 and markers within this region, was used to define a candidate interval for ALS4 (fig. 3A and B). Individual VIII-17 is an affected male in whom a crossover occurred, between D9S1831 and D9S1847 (fig. 3A). For affected individual IX-11, genotypes from deceased parents, needed to determine phase, are unavailable; however, there is an apparent crossover between D9S1830 and D9S164 (fig. 3B). These results suggest that ALS4 is telomeric to D9S1831 and centromeric to D9S164, defining an ~5-cM interval within chromosome 9q34 (see fig. 4).

Discussion

The designation "ALS" refers to a group of progressive disorders that affect upper and lower motor neurons, without sensory changes, and that lack other known causes (Brooks 1994). Although ALS is frequently associated with rapid progression and early death, a diagnosis of ALS does not require any specific duration of disease (provided there is progression), and patients may survive for many years. Given the clinical pattern of progressive, selective motor-system dysfunction, with pyramidal tract signs, affected members of pedigree K7000 conform to this recognized clinical ALS phenotype.

The results of the present analysis support the localization of a gene, on chromosome 9q34, for this autosomal dominant form of juvenile ALS. These findings extend the degree of genetic heterogeneity within juvenile ALS and other phenotypically similar disorders that are characterized by onset during adolescence and predominant motor-systems deterioration. More impor-
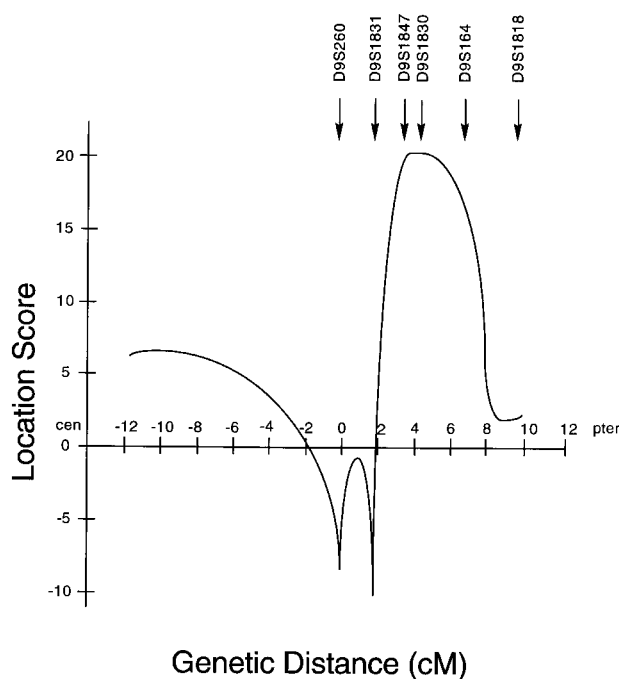

Figure 2   Multilocus analysis, with the ALS4 gene, against a fixed genetic map of linked markers. Order of markers and distances are taken from published sources (Gyapay et al. 1994; Murray et al. 1994; Dib et al. 1996). The highest probability for location of ALS4 is in the region of D9S1847 and D9S1830.

tantly, this observation implicates the existence, on chromosome 9, of yet another gene that is critical for the normal function of motor neurons.

It can be speculated that the gene for ALS4 may involve an abnormality in a neuron-specific component, or, as proposed for SOD-1 in ALS1, that it could result from mutations in a more widely or even ubiquitously expressed protein that has a function that is crucial to motor neurons (Brown 1995). The discovery of SOD-1 mutations that lead to ALS has provided many novel insights into the biology of motor neurons. It remains
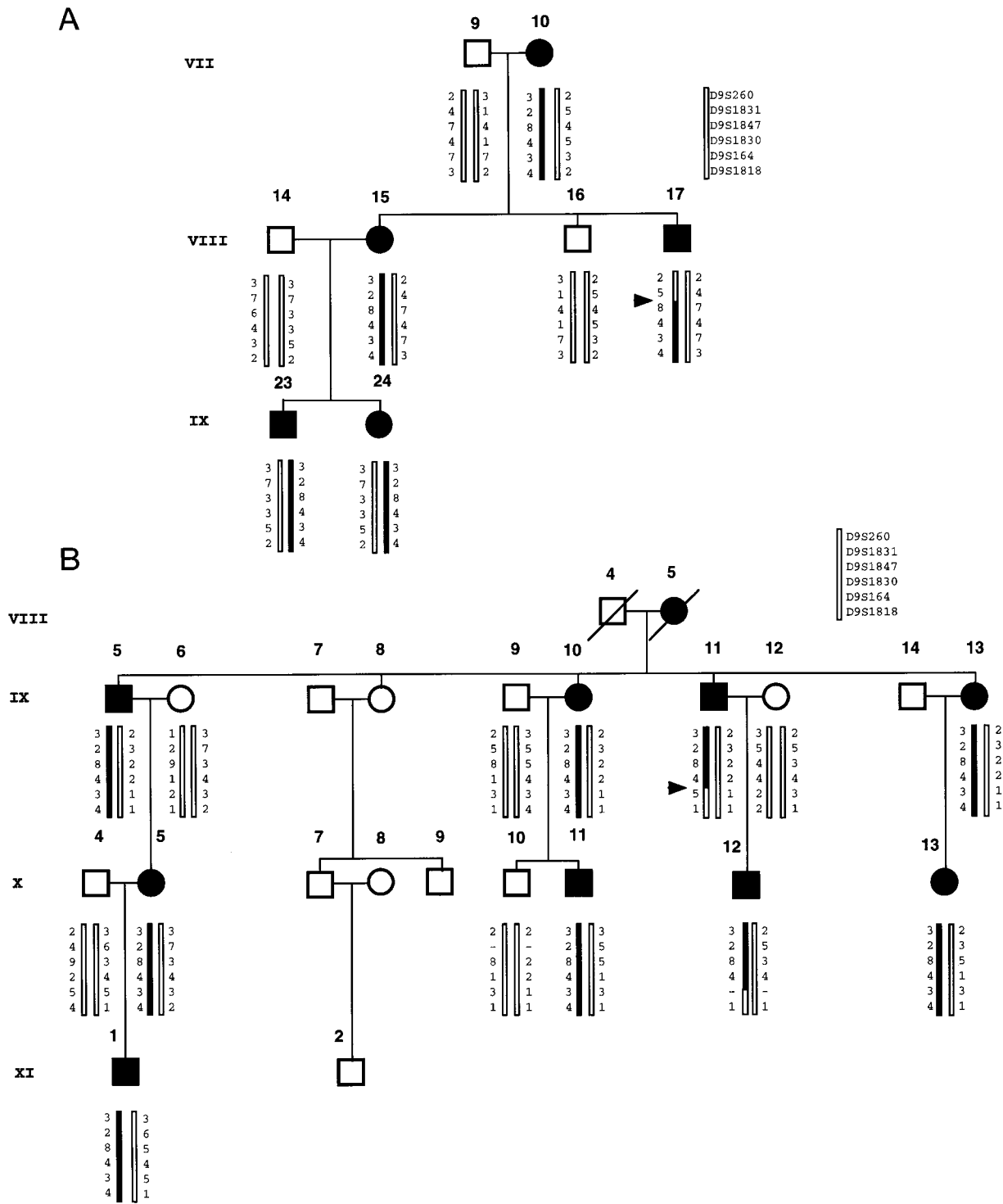
Figure 3   Recombinant events localize the ALS4 gene on chromosome 9q34 and define a 5-cM interval. Two portions of pedigree K7000 (boxed in fig. 1) that contain crossovers, within chromosome 9q34, that localize ALS4 between markers D9S1831 and D9S164 are shown. *A,* For individual VIII-17, a crossover occurred between D9S1831 and D9S1847. *B,* For individual IX-11, a crossover occurred between D9S1830 and D9S164.
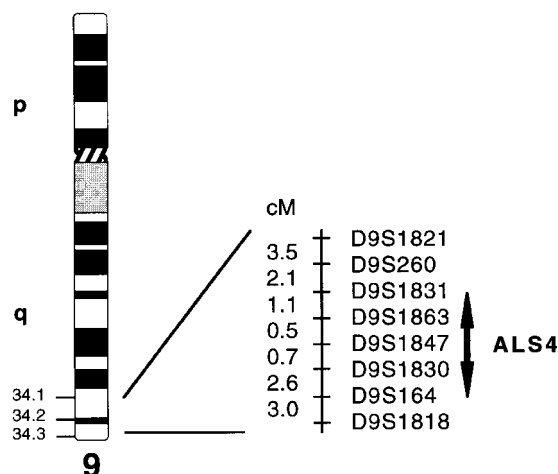
Figure 4 Ideogram of chromosome 9 that shows the map placement of markers in band 9q34 and the interval containing the ALS4 locus. Genetic distances are given in centimorgans.

unclear, however, how mutations in SOD-1 actually lead to progressive motor-neuron loss. It is not certain that all familial-ALS mutations cause dysfunction in proteins involved in free-radical scavenging. There is mounting evidence that cellular excitotoxicity may play a prominent role in the pathogenesis of sporadic ALS, and it would be reasonable to expect that mutations in this pathway might also lead to inherited motor-neuron dysfunction (Bristol and Rothstein 1996). Clearly, given the similarities and differences between ALS4 and other forms of inherited ALS, identification of the underlying defect will provide important new clues to the understanding of possible mechanisms that lead to motor-neuron dysfunction and death. Mapping and the eventual identification of the ALS4 gene are critical steps toward development of additional animal models for investigation of motor-neuron degeneration.

The clinical and neurophysiological phenotype of selective motor impairment seen in individuals from pedigree K7000 predicted that pathological disturbances might be limited to the motor systems. Interestingly, neuropathological evaluation of the brain and spinal cord of an 88-year-old woman in pedigree K7000 disclosed evidence of more widespread damage to the nervous system. In addition to motor-neuron degeneration, axonal swellings and reactive astrocytes were present throughout the spinal cord gray matter, particularly the dorsal root exit zones. These multisystem neuropathological findings observed in ALS4 are consistent with the spectrum of non–motor-system changes recognized in other forms of autosomal dominant, adult-onset, more rapidly progressive familial ALS (Engel et al. 1957; Hirano et al. 1967). Therefore, clinical designation of the pedigree-K7000 neurological disorder as a juvenile ALS

syndrome is warranted. Clearly, in familial ALS, other regions of the nervous system may be affected at a neuropathological level, despite a clinical phenotype that suggests only motor-neuron dysfunction. As mentioned above, a selective vulnerability of motor neurons to the consequences of a mutant gene might explain this observation. Nevertheless, the discrepancy between clinical motor-neuron phenotype and observed neuropathological features in familial ALS merits further investigation, and identification of a gene for ALS4 may provide insight into this interesting paradox.

In addition to ALS4, two other neurological disorders are known to map to the region of chromosome 9q34. These are tuberous sclerosis 1 (TSC1), the gene region for which overlaps that of the ALS4 locus (van Slegtenhorst et al. 1997), and torsion dystonia (TYD1), the gene for which is located centromeric to ALS4 (Pericak-Vance et al. 1995). Several plausible ALS4 candidate genes that map to this region of chromosome 9 include the death-associated protein kinase (DAPK1) gene (Feinstein et al. 1995), a calcium channel (L-type, α1 polypeptide; CACNL1A5) (Dirong et al. 1995), the N-methyl-D-aspartate receptor (GRIN-1) (Brett et al. 1994), and a kinesin-related gene (ATSV) (Furlong et al. 1996). ATSV is an especially attractive candidate, given the observation of axonal swelling in ALS4, which might suggest impaired axonal transport as a primary pathogenetic mechanism that leads to dysfunction of motor neurons and other cell types.

The clinical and genetic nosology of inherited disorders that affect motor systems is complex and evolving. In particular, the overlap of phenotypic features found in familial motor-neuron diseases, hereditary spastic paraplegias, and hereditary peripheral polyneuropathies (e.g., Charcot-Marie-Tooth neuropathy; CMT) has impeded classification and recognition of juvenile ALS (Ben Hamida et al. 1990). For example, the pedigree-K7000 disorder was initially reported as a variant of CMT, despite the presence of upper–motor-neuron dysfunction and the absence of sensory-nerve impairment (Myrianthopoulos et al. 1964). Similarly, numerous other reports have documented autosomal dominant syndromes of progressive limb amyotrophy, hyperactive deep-tendon reflexes, extensor plantar responses, and minimal or no sensory-nerve impairment, including peroneal muscular atrophy with pyramidal features (CMT type V; Harding and Thomas 1984), familial spastic paraplegia with amyotrophy of the hands (Silver syndrome; Silver 1966), and others (Refsum and Skillicorn 1954; Cross and McKusick 1967; Lander et al. 1976; Van Gent et al. 1985). Regardless of the diagnostic terminology for pedigree K7000, the results of this analysis show that an important gene for motor-neuron function maps to chromosome 9q34. As a clinical entity, this mapped form of autosomal dominant juvenile ALS in pedigree K7000

may be an underrecognized disorder. It will be crucial to test other kindreds that have motor-neuron disorders, with phenotypes similar to those seen in pedigree K7000, for linkage to the ALS4 region on chromosome 9q34.

Acknowledgments

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