LETTER TO JMG

A novel locus for late onset amyotrophic lateral sclerosis/ motor neurone disease variant at 20q13

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Motor neurone disease includes a heterogeneous group of disorders with motor neurone involvement, such as amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, and primary lateral sclerosis. Amyotrophic lateral sclerosis is the most common adult onset form of motor neurone disease and involves the lower and upper motor neurones. It is characterised by progressive muscle weakness and atrophy, with fasciculations associated with hyperreflexia and spasticity. One of the proposed mechanisms for amyotrophic lateral sclerosis is degeneration of the motor neurone because of abnormal levels of toxic products that accumulate in the cell. Death usually occurs by respiratory failure about 2–3 years after the first symptoms.[1] About 10% of cases are familial amyotrophic lateral sclerosis, and several loci have been associated with this disease. To date, the only two genes identified have been the zinc–copper superoxide dismutase 1 (*SOD1*) gene, which is located on chromosome 21 (ALS1, MIM105400), and the *Alsin* gene, which is located at 2q33 (ALS2, MIM 205100).[2–4] Autosomal dominant forms of amyotrophic lateral sclerosis also have been linked to 18q21 (ALS3, MIM 606640), 9q34 (ALS4, MIM 602433), and 15q15.1–q21.1 (ALS5, MIM 602099) and amyotrophic lateral sclerosis–frontotemporal dementia (MIM 105550) to 9q21-22.[5–9] Moreover, mutations in *Dynein* are associated with motor neurone degeneration and defects in retrograde transport. This gene acts in the cellular division, trafficking, and transport of several proteins, such as *SOD1*.[10 11]

More recently, two new loci have been associated with amyotrophic lateral sclerosis. One of them, reported by three independent groups, is on chromosome 16; the other is at 20p.[12–14]

We report a Caucasian Brazilian family with 26 members distributed in three generations affected by a late onset autosomal dominant motor neurone disease. Clinical and neurological examination of 11 living members was compatible with the diagnosis of Caucasian amyotrophic lateral sclerosis and motor neurone disease and long survival.

Key points

- Motor neurone disease includes a heterogeneous group of disorders with motor neurone involvement, such as amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, and primary lateral sclerosis.
- Amyotrophic lateral sclerosis is the most common adult onset form of motor neurone disease and involves lower and upper motor neurones. It is characterised by progressive muscle weakness and atrophy, with fasciculations associated with hyperreflexia and spasticity.
- One proposed mechanism for amyotrophic lateral sclerosis is degeneration of the motor neurone because of abnormal levels of toxic products that accumulate in cells. Death usually occurs by respiratory failure about 2–3 years after the first symptoms.
- About 10% of cases are familial amyotrophic lateral sclerosis, and several loci have been associated with this condition. To date, the only two genes identified have been the zinc–copper superoxide dismutase 1 (*SOD1*) gene, which is located on chromosome 21 (ALS1, MIM105400), and the *Alsin* gene, which is located at 2q33 (ALS2, MIM 205100).
- Autosomal dominant forms of amyotrophic lateral sclerosis also have been linked to 18q21 (ALS3, MIM 606640), 9q34 (ALS4, MIM 602433), and 15q15.1-q21.1 (ALS5, MIM 602099), and amyotrophic lateral sclerosis and frontotemporal dementia (MIM 105550) have been linked to 9q21–22.
- Mutations in *Dynein* are associated with motor neurone degeneration and defects in retrograde transport. This gene acts in the cellular division, trafficking, and transport of several proteins, such as SOD1.
- We report a large Brazilian Caucasian family with clinical and neurological signs compatible with the diagnosis of amyotrophic lateral sclerosis with slow progression.
- The disease seems to affect both sexes equally, with no evidence of clinical anticipation. Clinical onset occurs between age 31 and 45 years, and the cause of death is respiratory failure. Overall, 12 family members were examined personally. All patients had lower motor neurone symptoms, and five also had bulbar involvement. Electromyography, as well as muscle biopsies, showed a neurogenic pattern.
- We mapped a novel locus for autosomal dominant late onset amyotrophic lateral sclerosis/motor neurone disease (ALS/MND) variant at 20q13.33. The identification of a new gene for ALS/MND will contribute to our understanding of this intriguing disorder.

METHODS

Patients

Figure 1 shows the family pedigree. The probands–three affected sisters (IV-12, IV-13, and IV-14)–were referred to the Human Genome Research Center at the Department of Biology, University of São Paulo, with a diagnosis of motor neurone disease. Extended pedigree analysis showed 26 members were affected (10 men and 16 women); 15 of these already were deceased. Family members reported that patients III-26, IV-10, IV-12, IV-31, and IV-38 died of respiratory failure, although no postmortem confirmation of amyotrophic lateral sclerosis was done. The mean age of death was 49.8 (SD 8.1) years, and the mean age at onset was 38 (SD 6) years.

The diagnosis of amyotrophic lateral sclerosis was based on El Escorial revised criteria.[15] All studies were performed after

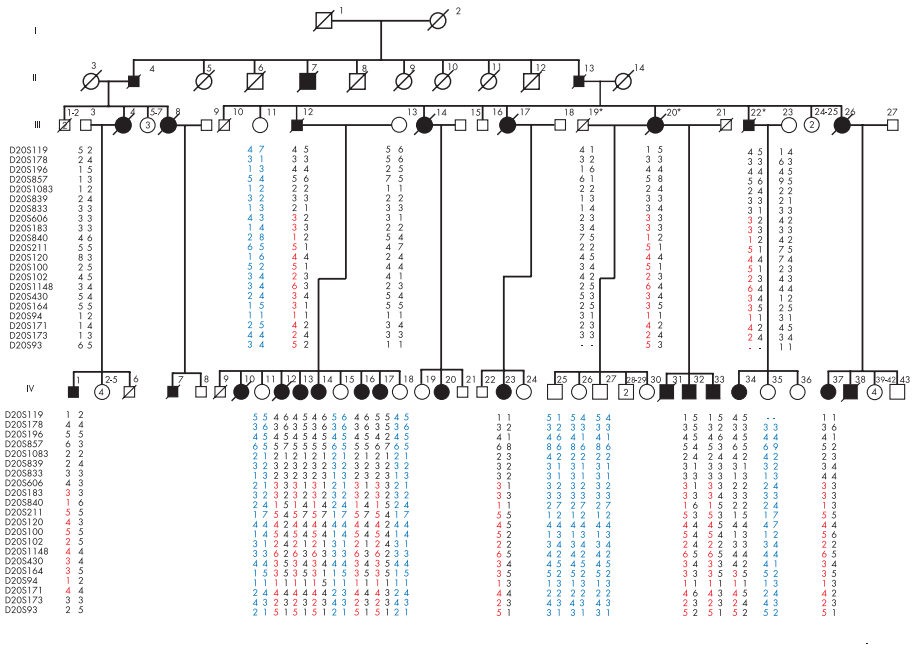

Figure 1 Family pedigree showing a candidate locus on 20q13.33. ■ man affected by disease; □ unaffected man; ● affected woman; ○ unaffected woman; / deceased; * haplotype inferred. Red text indicates haplotype shared by all patients; blue text indicates haplotype of normal siblings. Recombination events were seen in two patients (IV-1 and IV-34), which allowed placement of the candidate region between D20S430 and D20S173.

informed consent. Demographic and clinical data were taken and followed by a complete clinical and neurological examination. Serum levels of creatine kinase, magnetic resonance imaging, nerve conduction study (motor and sensory), and electromyography were performed in the standard way. Muscle biopsies were taken from the biceps of three affected patients (IV-7, IV-14, and IV-37).

We obtained DNA from the peripheral blood of 25 family members (11 affected and 14 unaffected) according to standard procedures. As the disorder has late onset, we included in the linkage analysis only affected patients, older unaffected siblings, and unrelated unaffected spouses. We performed haplotype reconstruction, on the basis of haplotype analysis of members from generation IV, for three patients (III-12, III-20, and III-22), as well as for member III-19.

Linkage analysis

We excluded all previously known loci for amyotrophic lateral sclerosis. We performed scan analysis with distant markers about 10 cM in length from the ABI Prism Linkage Mapping Set kit (version 2; Applied Biosystems, Foster City, CA, USA). Additional polymorphic markers were included in this analysis to refine the region. The PCR products were analysed in MegaBace 1000 DNA Sequencers (Amersham Biosciences, Little Chalfont, UK). The order of the markers was based on different genetic maps of the Marshfield Medical Research Foundation database and the National Center for Biotechnology Information (NCBI) database. All information about sequence tagged sites was obtained from UniSTS of NCBI and the genome database website. As the allele frequency varies according to the population, we analysed at least 30 chromosomes from normal Brazilian controls. For linkage analysis, we used the MLink program of the Fastlink package (Columbia University, New York, NY, USA) for two point analysis, and we assumed autosomal dominant inheritance with penetrance 1 until age 45 years (as the onset in all affected patients occurs before age 45 years), equal male and female recombination rates, and a gene frequency of 0.0001 for parametric analysis. Multipoint analysis was performed with SimWalk (version 2.86).[16–18]

RESULTS

Clinical features

Table 1 shows the affected family members' clinical and neurological features, as well as the results of complementary examinations.

All patients had lower motor neurone symptoms, with signs in the four limbs, and one also had upper neurone signs. Five patients (IV-23, IV-32, IV-33, IV-34, and IV-37) also had bulbar involvement. Postural tremor, one of the first symptoms to appear, was seen in eight patients, but it was stable during disease progression (IV-1, IV-16, IV-17, IV-23, IV-32, IV-33, IV-34, and IV-37).

The symptom of painful cramps was prominent, long standing, and easily obtained, and had a disabling pattern. As lower motor neurone findings confirmed by electrophysiological studies were the most conspicuous and uniform symptom in all patients, such patients first were classified as having motor neurone disease. The presence of pyramidal signs in one patient (IV-1), who could be classified as having clinically probable, laboratory supported amyotrophic lateral sclerosis, subsequently directed the investigation to the amyotrophic lateral sclerosis/motor neurone disease (AML/MND) group.

Serum creatinine kinase was normal or slightly elevated.

Electromyography in eight patients showed a neurogenic pattern compatible with motor neurone disease. Needle electromyography showed abnormal spontaneous activity such as fasciculations, fibrillations, and positive waves in the tongue and muscles of the upper and lower limbs. On effort, polyphasic and giant motor unit action potentials with reduced recruitment were seen. Sensory and motor nerve conduction studies were normal.

Analyses of muscle biopsies showed a neurogenic pattern, with groups of large and small angulated fibres and fibre type grouping.

Table 1 Clinical and neurological features of patients affected by amyotrophic lateral sclerosis and motor neurone disease

Patient	Sex	First symptoms	Age (years)			Test result				
			At first symptom	At onset of weakness	At ascertainment	Serum creatinine kinase (SU)	Findings on neurological examination	Needle electromyography	Cause of death	Age at death (years)
IV-1	Man	Cramps	31	40	42	20.0 and 23.0*	Lower motor neurone signs in lower limbs, pyramidal tract signs in upper limbs. Postural tremor	Motor neurone disease	NA	NA
IV-12	Woman	Fasciculation	40	40	49	7.0	Lower motor neurone signs in the four limbs	Motor neurone disease	Respiratory failure	49
IV-13	Woman	Fasciculation	43	43	49	19.3 and 28.0*	Lower motor neurone signs in the four limbs	Motor neurone disease	NA	NA
IV-14	Woman	Fasciculation	45	45	47	58.0 and 61.0*	Lower motor neurone signs in four limbs	Motor neurone disease	NA	NA
IV-16	Woman	Fasciculation	41	NA	44	ND	Lower motor neurone signs in four limbs† Postural tremor	ND	NA	NA
IV-17	Woman	Cramps and tremor	30	42	43	ND	Lower motor neurone signs in four limbs† Postural tremor	ND	NA	NA
IV-20	Woman	Weakness	42	42	NA	ND	Lower motor neurone signs in the four limbs†	Motor neurone disease	NA	NA
IV-23	Woman	Cramps	25	38	55	18.5	Lower motor neurone signs in the four limbs, cervical muscles, and tongue; dysarthria; and dysphagia† Postural tremor	Motor neurone disease	NA	NA
IV-32	Man	Tremor	41	46	56	25.3	Lower motor neurone signs in the four limbs and thoracic muscles and dysphagia† Postural tremor	ND	NA	NA
IV-33	Man	Tremor	44	No weakness	49	20.3	Lower motor neurone signs in the four limbs, cervico-thoracic muscles, and tongue† Postural tremor	Motor neurone disease	NA	NA
IV-34	Woman	Fatigue	37	40	45	14.0	Lower motor neurone signs in the four limbs and cervical muscles, dysarthria, and dysphagia† Postural tremor Sensory loss in left lower limb	Motor neurone disease	NA	NA
IV-37	Woman	Cramps	37	38	49	18.0	Lower motor neurone signs in the four limbs and dysphagia† Postural tremor	ND	NA	NA

NA, not applicable (patient alive); ND, not done.
* Normal values <12 SU for women and <20 SU for men.
† Signs of lower motor neurone problems: weakness, atrophy, hypotonia, hypoactive or absent reflexes, and fasciculations.

Table 2 Results of multipoint and two point LOD score analyses for informative markers at 20q13. It is considered informative if LOD >3.0.

Marker	Marker position (cM)*	LOD score								
		Multipoint	Two point at θ =							
			0	0.001	0.01	0.05	0.1	0.2	0.3	0.4
D20s1148	55.60	−6.601	−∞	0.668	2.560	3.535	3.585	2.992	2.003	0.784
D20S430	56.78	1.501	−∞	2.245	3.179	3.564	3.437	2.784	1.887	0.847
D20S164	57.69	7.450	5.704	5.694	5.604	5.196	4.664	3.524	2.268	0.923
D20S94	58.13	7.417	0.263	0.263	0.261	0.246	0.217	0.148	0.083	0.033
D20S171	58.41	7.373	6.025	6.015	5.923	5.503	4.961	3.805	2.537	1.149
D20S173	59.51	3.339	2.316	3.573	4.454	4.711	4.437	3.499	2.299	0.930
D20S93	59.55	3.339	2.665	3.921	4.802	5.055	4.775	3.821	2.590	1.139

*Inferred based on data from MapView-NCBI and Ensembl website.

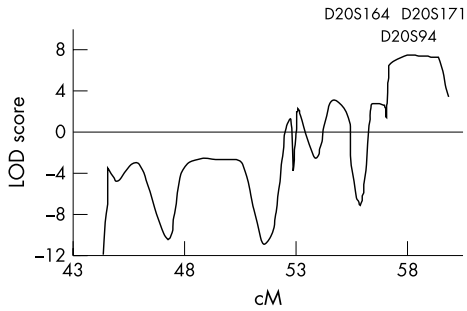

Fig 2 Multipoint LOD score analysis for 20q13 markers based on the Simwalk program. The most significant polymorphic markers are shown.

Linkage data

We detected a significant linkage at region 20q13.3 with the flanking markers D20S178, D20S196, D20S120, D20S100, D20S102, D20S171, and D20S173. Recombination events in two patients (IV-1 and IV-34), as well as the analysis of 12 additional polymorphic markers (D20S857, D20S1083, D20S839, D20S833, D20S606, D20S183, D20S840, D20S211, D20S1148, D20S430, D20S164, and D20S93), allowed us to locate the candidate gene in a region of about 2.7 Mb between the markers D20S430 and D20S173. According to NCBI MapView, this region contains 17 known genes, one pseudogene, and six predicted genes. Table 2 shows the logarithm of odds (LOD) scores. Two point LOD score analysis showed LOD scores >3 for several markers, with a maximum value of 6.02 at $\theta = 0.0$ for the marker D20S171, while multipoint analysis showed a maximum LOD score of 7.45 for the marker D20S164 (fig 2).

We are currently screening functional candidates genes in the region. Until now, the tubulin beta-1 (*TUBB-1*), cathepsin Z (*CTSZ*), and ATP synthase–epsilon subunit (*ATP5E*) genes were screened through single strand conformation polymorphism followed by direct sequencing of all amplicons, but no pathogenic mutation was identified.

DISCUSSION

We have identified a novel locus for an autosomal dominant late onset ALS/MND at 20q13.33 in a large Brazilian Caucasian family. Recently, a new amyotrophic lateral sclerosis locus was also mapped on chromosome 20.[14] This locus is located in the short arm of chromosome 20 (at 20p13), however; while ours is in the long arm.

The disease seems to affect both sexes equally, with no evidence of clinical anticipation. Clinical onset in affected patients occurs earlier than in familial amyotrophic lateral sclerosis or classic amyotrophic lateral sclerosis (mean age 38 (SD 6) years *v* 46 years and 56 years, respectively). In a previous study of Brazilian patients with sporadic amyotrophic lateral sclerosis, the mean age of onset was 52 years, although the first symptoms presented before age 40 years in 18.1% of patients.[19] The progression of the disease in patients from the present family, however, was slower than in classic amyotrophic lateral sclerosis. In addition, other signs, such as postural tremor and disabling cramps, are atypical, although postural tremor because of increased physiological tremor may be seen in patients with weakness.[20 21] On the other hand, the presence of atypical signs has prompted us to search for a differential diagnosis from other causes of motor neurone disease associated with postural tremor, such as extrapyramidal degeneration, distal hereditary motor neuropathy, adult onset spinal muscular atrophy, or even an occasional association of motor neurone disease and essential tremor.

Sporadic cases of motor neurone disease with tremor or choreiform movements, or both, have been described.[22] These patients, however, did not show the classical findings of amyotrophic lateral sclerosis–dementia–parkinsonism, which are typical of Guam complex. In these cases, autopsy studies showed degeneration in the lower motor neurones and neostriato–pallido–nigral system or in the upper and lower motor neurones, pallido–luysio–nigral system, and brainstem tegmentum.[23]

The diagnosis of distal hereditary motor neuropathy was excluded because none of our patients had pes cavus or nerve conduction abnormalities.

Many years ago, we reported a Brazilian family with seven members affected by late onset autosomal dominant spinal muscular atrophy and symptoms that overlapped with amyotrophic lateral sclerosis.[24] In this family, however, all patients showed rapid progression, with death occurring 2–3 years after onset.

We propose classifying the present family as having late onset amyotrophic lateral sclerosis/motor neurone disease with atypical signs. Recently, a family with atypical autosomal dominant amyotrophic lateral sclerosis with normal life expectancy, absence of bulbar involvement, and symmetrical distal distribution of atrophy and weakness was mapped at 9q34.[6] The authors suggested that this form and distal hereditary motor neuropathy with pyramidal signs could be the same disorder. We agree with those authors' comment that it is not easy to classify these neuromuscular conditions on the basis of clinical and neurological signs.

On the other hand, genetic findings and clinical heterogeneity with atypical findings have been common observations, and other families with this intriguing phenotype may exist. Two large Brazilian genealogies with 80 affected members with late onset (mean age 48.8 years) spinal muscular atrophy (MIM 182980) were reported several years ago.[25] Patients from these families showed slow loss of muscle strength, with progressive proximal atrophy, hypoactive or absent deep tendon reflexes, and fasciculations. It will be of interest to verify if they have the disorder we describe.

Intrafamilial clinical variability in patients who carry the same pathogenic mutation has been reported, however, for many gene related diseases, such as autosomal recessive limb girdle muscular dystrophies.[26] Furthermore, recent studies showed that modifier genes also could alter clinical phenotype. Faster progression of disease has been reported in patients with a mutation in the ciliary neurotrophic factor (*CNTF*) gene associated with the *SOD1* gene compared than in those who lack the *CNTF* mutation.[27] The authors concluded that *CNTF* is a modifier gene that could modulate the progression of the disease, but this finding was not confirmed by other investigators.[28]

On the other hand, the vascular endothelial growth factor (*VEGF*) gene is considered a risk factor for sporadic amyotrophic lateral sclerosis. Patients homozygous for –2578A/–1154A/–634G or –2578A/–1154G/–634G in the *VEGF* promoter/leader sequence were shown to be at 1.8 times greater risk of amyotrophic lateral sclerosis.[29]

Conclusion

We mapped a novel gene for an ALS/MND variant at 20q13.33 and are currently screening functional candidate genes in the region for mutations. According to the NCBI Map Viewer, the flanking markers D20S430–D20S173 span a region of about 2.7 Mb that contains 17 known genes, six predicted genes, and one pseudogene.

The *TUBB-1* gene was considered to be a strong candidate gene, because it is the major component of microtubules and, recently, alterations of the axonal transport and microtubule

Electronic database information

Database accession numbers from UniGene (NCBI)

- *TUBB1*: Hs.303023
- *CTSZ*: Hs.252549
- *ATP5E*: Hs.177530

Databases

- MapView and UniSTS of National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/)
- Center for Medical Genetics, Marshfield Medical Research Foundation database (http://www.marshfieldclinic.org/research/genetics/)
- Ensembl Genome database (www.ensembl.org)

network have been shown to be potential causes of motor neurodegeneration in amyotrophic lateral sclerosis model mice.[30] No mutation was found, however, in this gene or in the *CTSZ* or *ATP5E* genes, although the possibility of an alternative splicing or other post-transcriptional mechanism has not been ruled out yet.

Identification of the causative gene will be very important for enhancing our understanding of the underlying pathological mechanisms in this heterogeneous group of disorders and hopefully will contribute to the opening of new avenues for future therapies.

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CORRECTION

Faivre L, Cormier-Daire V, Lapierre JM, *et al*. Deletion of the *SIM1* gene (6q16.2) in a patient with a Prader-Willi-like phenotype (*J Med Genet* 2002;**39**:594–96). An erratum has been detected in the reverse primer sequence used for amplification of the intragenic microsatellite polymorphic marker of the *SIM1* gene. The sequence should read 5′-CTCTCCTGCCTGCTGATC-3′ instead of 5′-GATCAGC AGGCAGGAGAG-3′.

A novel locus for late onset amyotrophic lateral sclerosis/motor neurone disease variant at 20q13

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