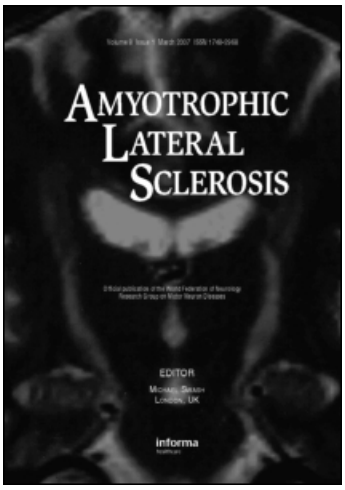

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SHORT NOTE

Further evidence that D90A-SOD1 mutation is recessively inherited in ALS patients in Italy

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Abstract
Mutations in the Cu/Zn superoxide dismutase 1 (SOD1) gene have been reported to cause adult-onset autosomal dominant amyotrophic lateral sclerosis (FALS). In sporadic cases (SALS), de novo mutations in the SOD1 gene have occasionally been observed. All the SOD1 mutations are autosomal dominantly inherited with the exception of D90A. To date, in Italy, only two sporadic ALS cases carrying the D90A mutation have been reported in a homozygous state. We investigated for the presence of this mutation in 169 unrelated ALS patients from southern Italy. The genetic analysis revealed three ALS patients (1.8%) with mild phenotype carrying the homozygous D90A mutation.

Introduction

About 3% of cases of amyotrophic lateral sclerosis (ALS), a fatal adult-onset motor neuron degeneration, are due to mutations in the Cu/Zn superoxide dismutase (SOD1) gene. All the SOD1 mutations are autosomal dominantly inherited with the exception of Asp90Ala (D90A), very common in the Scandinavian population, and Asp96Asn (D96N) which can act as recessive (1,2). Only a few cases of D90A heterozygous ALS in non-Scandinavian patients have been reported, all of them inherited as a dominant trait (3,4). To date, only two Italian sporadic ALS (SALS) cases associated with the homozygous D90A mutation, one from Tuscany and one from southern Italy, have been reported (3). The aim of this study is to investigate further the presence of the D90A mutation in ALS patients in southern Italy.

Materials and methods

One hundred and sixty-three unrelated Caucasian ALS patients (eight familial ALS and 155 sporadic cases, 84 men and 79 women; mean age 54.52 years, SD 12.14), from southern Italy were screened for D90A-SOD1 mutations in exon 4. All studied patients were diagnosed with ALS according to revised El Escorial criteria. Samples were also taken from 150 controls, matched for age, sex and geographical region. All participants gave their written informed consent, and DNA extraction and genotyping was performed by standard protocols.

Results and discussion

In our study, of all patients investigated three ALS cases (1.8%, 2 FALS and 1 SALS) showed the homozygous D90A mutation in the SOD1 gene

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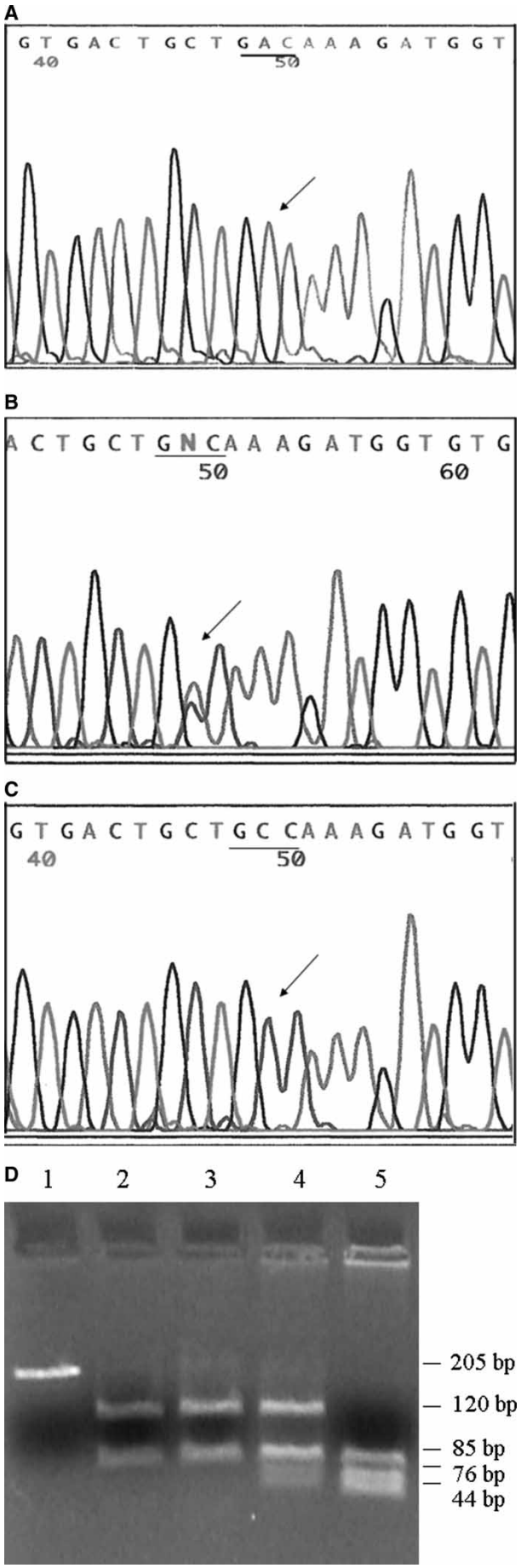

Figure 1 (*Continued*)

(Figure 1). In particular, two out of three patients shared the over-represented D90A Scandinavian haplotype (4) for three markers (D21S223, D21S63 and D21S261).

Furthermore, the screening for D90A-SOD1 mutations in more than 150 healthy subjects did not reveal any heterozygous individual. This finding is in accordance with the data of the low frequency of the D90A mutation (0.05%) previously reported elsewhere (4).

The phenotype of D90A-SOD1-ALS described in the previous studies seems to be associated with its mode of transmission because all ALS patients homozygous for the D90A showed a phenotype characterized by slow progression of the disease, mean survival of 13 years, with a predominantly lower motor neuron and lower limb form of ALS at onset of the disease. By contrast, when D90A is pathogenic in the heterozygous state, the first symptoms can occur in any territory and disease progression can be more rapid (1,4). Consistent with previous findings, our patients showed a mild phenotype (clinical description in Table I).

A previous study suggested an explanation for the recessive and the dominant inheritance of the D90A mutation, and the different expressed phenotype (4). A single ancient founder was shown for both D90A-SOD1 recessive and dominant ALS families and it was proposed that a second disease-modifying mutation arose in a more restricted region across the SOD1 gene in the recessive allele. This disease modifier could reduce the transcription of D90A SOD1 in motor neurons and, probably, in subjects carrying the recessive haplotype two copies are required to cause disease. On this basis, it is conceivable that D90A homozygotes can show prolonged survival in contrast to the dose dependent progression of disease demonstrated in mutant SOD1 transgenic mice.

In conclusion, our study gives further evidence for autosomal recessive ALS in Italian patients, confirming that the phenotypic characteristics of the homozygous D90A associated ALS closely resemble those already described in recessive D90A patients from Sweden and Finland.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Figure 1. Sequence electropherograms of the PCR products of exon 4. The arrows in the figures indicate: A) Normal sequence; B) D90A heterozygous sequence; C) D90A homozygous sequence. D) Fnu4HI digestion of the PCR product of exon 4: lane 1 undigested PCR product, lanes 2–3 normal subjects, lane 4 heterozygous unaffected subject, and lane 5 homozygous affected subject.

Table I. Clinical features of ALS patients carrying D90A SOD1-gene mutation.

Patients	Sex	FALS/ SALS	Age at onset	Site of onset	Predomiance of upper/ lower motor neurons	ALS/ FRS	NEE	NCS	Disease course
1	M	FALS	49	Weakness of distal lower limbs Compulsive laughing and crying	Lower motor neuron	16/40	f/psw in upper and lower limb muscles	Normal	Slowly progressive
2	F	FALS	68	Weakness of distal lower limbs	Lower motor neuron	20/40	f/psw in upper and lower limb muscles	Normal	Slowly progressive
3	M	SALS	32	Weakness of distal lower limbs	Lower motor neuron	25/40	f/psw in upper and lower limb muscles	Normal	Slowly progressive

FALS, familial amyotrophic lateral sclerosis; SALS, sporadic amyotrophic lateral sclerosis; ALS/FRS, ALS functional rating scale scores; NEE, needle electrode examination; f, fibrillation; psw, positive sharp wave; NCS, nerve conduction studies.

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