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The *p.E22G* mutation in the Cu/Zn superoxide-dismutase gene predicts a long survival time
Clinical and genetic characterization of a seven-generation ALS1 Spanish pedigree

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ABSTRACT

Background: Despite the genetic heterogeneity reported in familial ALS (FALS), Cu/Zn superoxide-dismutase (*SOD1*) gene mutations are the most frequent cause of FALS, accounting for around 20% of familial cases (ALS1) and isolated sporadic cases. Some mutations are associated with a long survival time, while others are linked to a very rapid progression. Clinical–genetic characterization of ALS1 families is therefore important as it can provide information on the phenotype associated with a given mutation, the distribution of *SOD1* mutations in different ethnic groups, and can clarify the genotype–phenotype correlation in patients with *SOD1* gene mutations.
Objectives: To describe the phenotype linked to this previously reported *SOD1* gene mutation, *p.E22G* (E21G in the old nomenclature), in a large ALS1 Spanish kindred. This mutation was previously reported in a Canadian family but no clinical information was available.
Methods: Clinical characterization including gender, age at onset, site of onset and survival time was available from 15 affected members belonging to a seven-generation pedigree. The possibility of gender predominance or anticipation was also analyzed. DNA samples were available from three of the living symptomatic members. Informed consent for blood samples was obtained. We used direct sequencing to screen for *SOD1* gene mutations.
Results: An A-to-G transition at nucleotide position 65 (c.65A>G) leading to a *p.E22G* sequence change at protein level was identified in the three affected ALS patients. The phenotype was similar in all affected members in our *p.E22G* family. Initial symptoms occurred in the distal limb muscles, predominantly in the legs, and there was a mean survival time of 13.2 ± 8.6 years. The mean age at onset was 51.8 ± 10.1. The prevalence in males and females was similar, with no difference in phenotype as regards gender. The age range for onset of symptoms was between 38 and 71 years of age, although 60% of the members presented symptoms before their fiftieth birthday. The information available for five affected parent/affected offspring pairs suggested no apparent anticipation.
Conclusions: *p.E22G* is the ninth *SOD1* gene mutation reported in Spain, and the third of these to be associated with long survival (the other two being *p.G38R* — previously G37R, and *p.D77V* — previously D76V). Our results emphasize the importance of genetic and clinical characterization of ALS1 families around the world for understanding the genotype–phenotype relationships of each *SOD1* gene mutant and their relative frequency in different ethnic groups worldwide.

1. Introduction

About 10% of amyotrophic lateral sclerosis (ALS) cases are familial (FALS), and the genetics of FALS is complex. There are at least six major genes, seven minor genes, eight different loci, and an increasing number of susceptibility or modifying genes [1–29] (*). However, mutations in the gene encoding Cu/Zn superoxide dismutase (*SOD1*) account for approximately 20% of all FALS cases. FALS linked to the *SOD1* gene is designated as ALS1 (MIM 105400). There is a clear allelic heterogeneity in ALS1 — at least 128 different mutations in the *SOD1* have been described to date [30]. The *SOD1* mutations reported in ALS1 pedigrees are predominantly associated with a dominant inheritance pattern and high penetrance, despite being occasionally found in apparently sporadic or recessive cases. Although mutations in all five exons of the *SOD1* may cause ALS1, exons 4 and 5 are considered to be mutation "hot spots". D90A is considered the most common mutation worldwide. However, the most frequent mutation

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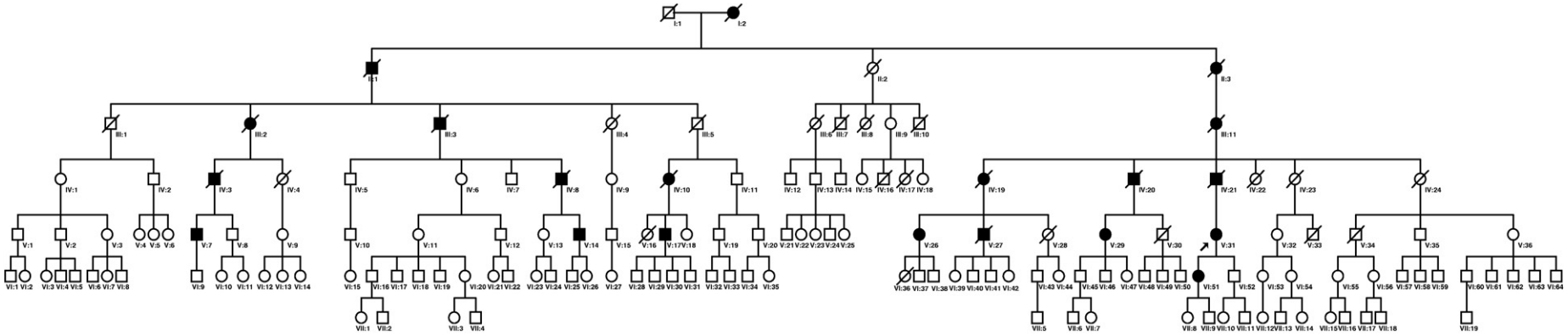

Fig. 1. Pedigree of the family studied. The proband is indicated by an arrow (VI:31). Male family members are represented by squares, females by circles, deceased members by diagonals and affected members by solid symbols.