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Brief communication

Identification of a novel missense (C7W) mutation of *SOD1* in a large familial amyotrophic lateral sclerosis pedigree

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ABSTRACT

Mutations of Cu-Zn superoxide dismutase (*SOD1*) have rarely been identified in Chinese patients with amyotrophic lateral sclerosis (ALS). We recently initiated a program to screen mutations of *SOD1*, *TARDBP*, and *C9orf72* genes, the most commonly mutated genes in ALS patients in Western countries, in Chinese ALS patients. In this study, we report a novel missense *SOD1* mutation with a substitution of tryptophan for cysteine at the seventh amino acid (p.C7W, traditionally named p.C6W) based on HUGO Gene Nomenclature in a familial ALS pedigree. We also found that the activities of *SOD1* were significantly decreased in the C7W patient and the carriers of the family, compared with the *SOD1* activities of normal family members. Compared with reported C7G and C7S patients, analysis of phenotype revealed relatively mild disease phenotypes in C7W patients, which is correlated with less deteriorated alteration in protein structure. Like those of many other familial ALS families, variable clinical phenotypes in the C7W intrafamily suggest that potential genetic modifiers may contribute to this disease.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the degeneration of motor neurons in the brain, brainstem, and spinal cord, resulting in fatal paralysis (OMIM. 105400). The prevalence of ALS is about 3–8:100,000. Most cases of ALS are sporadic, but approximately 5% of ALS cases are familial (FALS) (Byrne et al., 2011). The mean age of onset is 46 years in FALS with mean duration about 2–5 years (Traynor et al., 1999). Cu-Zn superoxide dismutase gene (*SOD1*) mutations on chromosome 21q22.1 account for 13.6% of FALS and 0.7% of sporadic ALS based on multiple large population studies (Chio et al., 2008). Cases of FALS caused by mutations in the *SOD1* gene usually display autosomal dominant inheritance but occasionally display autosomal recessive inheritance as well (Andersen et al., 1995). To date, >150 missense mutations in all 5 exons of *SOD1* have been reported (http://alsod.iop.kcl.ac.uk/) (Tortelli et al., 2013).

Compared with the base Chinese population of 1.3 billion, all known FALS-causative gene mutations including *SOD1* mutation reported in Chinese FALS are rare. With >10,000 daily outpatient visits to our hospital, we found a trend of increasing ALS patients in our neurologic department. Therefore, we recently initiated an ALS research program to collect and screen ALS patients using candidate genes as well as whole-exome sequencing. Given that FALS is extremely heterogeneous and almost half of patients have unknown etiology, we first screened 3 candidate genes (i.e., *SOD1*, *TARDBP*, and *C9orf72*) and then applied whole-exome sequencing in house for the remaining patients without mutations in the candidate genes (Wu et al., 2012). Here we report the identification of a novel mutation of the *SOD1* gene in 1 of 3 FALS pedigrees we collected.

2. Case report

This study was approved by the ethics committee of the Beijing Institute of Life Science, Chinese Academy of Science. Informed consent was obtained from all human subjects or their parents.

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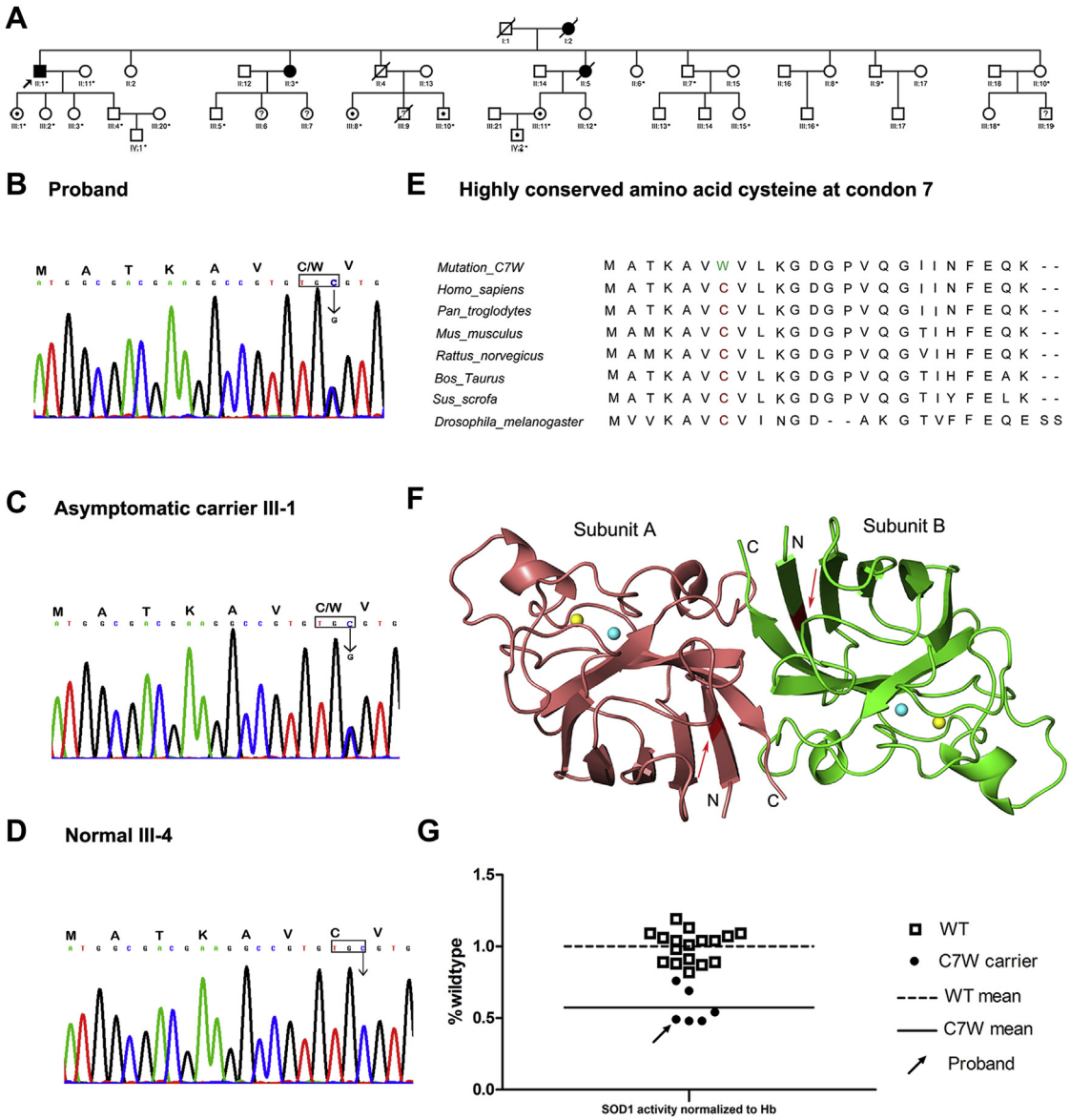

Fig. 1. A novel C7W missense mutation in the Cu-Zn superoxide dismutase gene (*SOD1*) identified in a Chinese familial amyotrophic lateral sclerosis (ALS) family. (A) Pedigree of the family with ALS. Males are represented by squares, females by circles, deceased by diagonals, and affected members by filled symbols. Asterisks (*) indicate that available DNA was used for Sanger sequencing. A black circle in a square or circle indicates an asymptomatic carrier. A ? in a square or circle indicates an unknown mutant. The proband (II-1) is indicated by an arrow. (B) A missense mutation C7W of *SOD1* is identified by Sanger sequencing in the proband with heterozygous C/G at nucleotide 21 in exon 1. (C) A missense mutation C7W of *SOD1* is also identified in the asymptomatic III-11 with heterozygous C/G at nucleotide 21 in exon 1. (D) Sanger sequence of the C7-containing region from the normal control (III-4). (E) Multiple sequence alignment of *SOD1* shows that cysteine at codon 7 is highly conserved among species. (F) C7W mutation and *SOD1* structure. The location of C7W in red is indicated by red arrows. The monomer subunit A is colored in deep salmon and the subunit B is in green. *N*- and *C*-terminal regions of each monomer are marked. The metal atoms in the active site are shown in spheres with copper in sky blue and zinc in yellow. (G) *SOD1* activity is normalized to hemoglobin (Hb). The average level of *SOD1* activity in C7W carriers is 57.5% (± 12.2 SD) of the wild-type (WT) controls.

The patients, originated from a Chinese Han pedigree in Northern China (Fig. 1A), had a mean age of onset of 67 years (range: 53–74), approximately 15.8 years later than previously reported C7 mutations of FALS. The mean duration for deceased patients in this pedigree was 1.92 years (range: 1.83–2.0; Table1). In December 2011, the 74-year-old proband began to complain of progressive weakness and atrophy of the right lower extremity. In the following 6 months, weakness and atrophy spread to the left lower extremity, and then 1 year after the onset, he became wheelchair-bound and developed slight dysarthria. Neurologic examination revealed diffuse atrophy and fasciculation in the lower extremities and dorsal muscles. Strength in muscles of the lower extremities was Medical Research Council grade 0–2 (Great Lakes ALS Study Group, 2003). Decreased muscle tone, disappearance of deep tendon reflexes, and bilaterally indifferent plantar response in the lower extremities were detected in the proband. No cognitive impairment was observed. Electromyography (EMG) showed active denervation discharges in the muscles of lower limbs and paraspinal muscles. A diagnosis of clinically suspected ALS, based on El Escorial criteria (Brooks, 1994), was made. Patient II-3 was a 72-year-old woman currently living and bedridden with ALS with disease duration of 3.83 years. The onset site was also in the lower extremities, then spreading to her bulbar and arms. Neurologic examination showed reduced strength in all 4 extremities (Medical Research Council grade 0–2) with profound amyotrophia. Increased muscle tone, brisk deep tendon, and bilaterally