TP53 Arg72Pro polymorphism in Turkish patients with sporadic amyotrophic lateral sclerosis

Emel Ergul, Mavi Deniz Ozel, Ali Sazci, Halil Atilla Idrisoglu

*Department of Medical Biology and Genetics, Faculty of Medicine, University of Kocaeli, Umuttepe, Kocaeli, Turkey

Department of Neurology, Faculty of Medicine, University of Istanbul, Capa, Istanbul, Turkey

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Abstract

Recently, Eve et al. (2007) reported that the expression of TP53 (NM_000546) was increased by 2.1-fold in whole spinal cord and 2.7-fold in the ventral horn of amyotrophic lateral sclerosis (ALS) patients. Based on this particular observation, we decided to evaluate whether the TP53 Arg72Pro polymorphism (rs1042522) (C215G) was implicated in the etiopathology of sporadic amyotrophic lateral sclerosis (SALS). Therefore, we genotyped 394 Turkish SALS patients and 439 matched healthy controls by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). We did not find any association between overall SALS patients with the TP53 Arg72Pro polymorphism and controls ($\chi^2 = 2.674; p = 0.263$). Consequently the TP53 Arg72Pro polymorphism was not associated with SALS.

Keywords: TP53 Arg72Pro polymorphism; Sporadic amyotrophic lateral sclerosis; Association; Turkish population

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating, progressive, adult onset neurodegenerative disorder resulting in the degeneration and death of motor neurons in the anterior horn of the spinal cord, lower brainstem, and cerebral cortex. Up to now, 3 genes have been shown to be definitely involved in ALS including SOD1, TARDBP, and FUS (Wijesekera and Leigh, 2009).

TP53 RNA levels (NM_000546) are overexpressed in patients with ALS which may lead to the pathogenesis of ALS. DNA damage involved in the pathogenesis of ALS may be caused by oxidative stress from mitochondrial or superoxide dismutase 1 dysfunction, and 8-hydroxy-2-deoxyguanosine adducts (OHdG) are elevated in postmortem central nervous system (CNS) tissue extracts from individuals with ALS. The codon 72 polymorphism (rs1042522, C215G) in TP53 gene consists of a single base pair change of either arginine or proline that seems to be involved in modulation of apoptosis (Dumont et al., 2003).

In the light of present evidence, we studied the association between TP53 Arg72Pro polymorphism and disease in sporadic amyotrophic lateral sclerosis (SALS) patients.

2. Results and discussion

Materials and methods are available as supplementary data. The TP53 Arg72Pro polymorphism was screened using polymerase chain reaction (PCR) followed by restriction digest with enzyme BstUI. Here, we showed that the TP53 Arg72Pro polymorphism was not associated with SALS in the Turkish population ($\chi^2 = 2.674; p = 0.263$) (Supplementary Table 1). Previously, TP53 expression was reported to be increased by 2.1-fold in whole spinal cord and 2.7-fold in the ventral horn of ALS patients (Eve et al., 2007). There are 2 previous studies from Turkey describing the frequencies of TP53 72Arg allele as being 63% (Buyru et al., 2007) and 66% (Kara et al., 2010). Our result was...
similar to that of Kara et al. (2010) with a frequency of 66.86% in the healthy controls.

Upon activation of TP53, this tetrameric transcription factor regulates a spectrum of genes involved in cell cycle arrest, DNA repair, apoptosis, or its own activity. TP53 protein contains 2 transcriptional activation domains AD1 and AD2: AD2 contains 5 PXXP motifs which are essential for TP53-mediated apoptosis.

DNA damage has been reported to be involved in the pathogenesis of ALS. DNA-DSBs (double strand breaks) induce phosphorylation of TP53 and stabilization mediated by ATM (ataxia telangiectasia-mutated). ATM-dependent phosphorylation of TP53 in cortical neurons has been shown in the process of DNA damage-induced in vitro within 1 hour (Martin et al., 2009).

Dumont et al. (2003) found that in cell lines containing inducible versions of alleles encoding the Pro72 and Arg72 variants, and in cells with endogenous TP53, the Arg72 variant induces apoptosis markedly better than does the Pro72 variant. Their data indicate that at least 1 source of this enhanced apoptotic potential is the greater ability of the Arg72 variant to localize to the mitochondria; this localization is accompanied by release of cytochrome c into the cytosol.

Recent studies have reported that the degeneration of motor neurons in ALS is a form of apoptotic cell death that may occur by an abnormal programmed cell death mechanism. Thus, TP53 protein levels were increased significantly \( p = 0.05 \) in ALS motor cortex and spinal cord anterior horn but not in somatosensory cortex of postmortem samples (Martin et al., 2009). Previous studies have revealed that increased levels of TP53 primarily may result from increased stability of the protein achieved through phosphorylation (Levine, 1997).

In the present study, we provide evidence that TP53 Arg72Pro polymorphism may not play a critical role in the pathology of ALS. After the onset of extensive motor neuron degeneration in ALS, the TP53 transcription factor is activated to be overexpressed in motor neurons probably due to phosphorylation.

Disclosure statement

All authors declare no actual or potential conflict of interest. Protocols were approved by the ethics committee.

Acknowledgements

All participants gave written informed consent after the study had been fully described. The University of Kocaeli Institutional Review Board approved the study. This work was done by departmental resources.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2011.05.021.

References


