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Genetics of Amyotrophic Lateral Sclerosis: A Review

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder with a poor prognosis that affects both upper motor neurons (UMN) and lower motor neurons (LMN). Currently, 126 candidate genes associated with familial and sporadic ALS have been identified. The exact pathogenesis mechanisms associated with ALS remains unknown however, several underlying ALS pathogenesis resulting in motor neuron degeneration have been identified including superoxide metabolism, RNA metabolism, autophagy, endoplasmic reticulum (ER) stress and the unfolded protein response (UPR), cell division, axonal transport, D-amino acid degradation and apoptosis. Here, we present a comprehensive review the genetics of ALS, in particular, the most commonly mutated ALS-related genes which may provide insightful information to understand their involvement in ALS.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal neurodegenerative disease without effective treatments. It is also the most common adult-onset motor neuron disorder. The disease is characterised by the loss of upper motor neurons in motor cortex and lower motor neurons in the brainstem and spinal cord, that results in progressive paralysis and death due to respiratory failure, within three years of onset of the first symptoms (1). ALS affects people worldwide and although the exact incidence is unknown, ALS incidence across the European populations is fairly uniform, with a median incidence rate is 2.08 per 100 000 persons per year and a median prevalence rate of 5.40 per 100 000 persons per year (2). In sporadic ALS (SALS), the incidence is higher in men (3.0 per 100 000 person-years) than in women (2.4 per 100 000 person-years), however, in familial ALS (FALS) the incidence in men and women is similar (3). The disease usually occurs after 40 years of age, between 47 to 63 years of age and incidence of ALS diminishes rapidly after the age of 80 (3). Limb-onset ALS, is identified by the coexistence of upper motor neuron (UMN) and lower motor