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The Pathological Role of Loss-Function of FUS-NLS Mutation in Juvenile ALS Cannot be Ignored

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ABSTRACT

Abbreviations: JALS: Juvenile Amyotrophic Lateral Sclerosis; FUS: Fused in Sarcoma; PRLD: Prion-Like Domain; NLS: Nuclear Localization Signal; CTD: C-Terminal Domain

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Juvenile amyotrophic lateral sclerosis (JALS) is a degenerative neurological disease that occurs before the age of 25, involves upper and lower motor neurons and progresses progressively, with earlier onset, more rapid progression, and severe symptoms than classical ALS. So far, there is no effective treatment for JALS. The pathogenesis of JALS is still unknown and involves genetic, environmental, and biological factors. With the development of gene sequencing technology genetic factors are still dominate pathogenesis. JALS pathogenic gene spectrum is different from the classical ALS. Fused in sarcoma (FUS), which accounts for less than 1% of the causative mutation in classical ALS, is more than 60% of JALS, especially sporadic JALS [1,2]. However, its pathological mechanism is still controversial. Loss of function and Gain toxicity are the two main hypotheses used to explain the neurone death induced by FUS-NLS mutations. Based on our reading and understanding, we emphasize more that loss function cannot be ignored. FUS is a radiosensitive DNA/RNA binding protein composed of 526 amino acids encoded by the FUS gene containing 15 exons. FUS shuttles between nucleus and cytoplasm and is distributed in axons, dendrites, and dendritic spines of neurons, which is closely related to normal function maintenance and plasticity of neurons.

It consists of seven domains, including a prion-like domain (PRLD) located at the N-terminal, three intrinsically disordered Arg-gly-rich domains (RGGs), one RNA recognition motif (RRM), and one RNA-binding zinc finger (ZNF) and a C-terminal nuclear localization signal (NLS) [1]. There are more than 50 ALS-associated FUS mutations, of which approximately 40 are located in nuclear localization sequences (NLS) [1]. Current research focus on Gain toxicity hypotheses to explain the neurone death induced by FUS-NLS mutations [3,4]. FUS entry into the nucleus is mediated by binding of its NLS sequence to the nuclear entry receptor TNPO1 (transportin-1, TNPO1) [5]. Deletion of NLS fragments and mutations in sequences can lead to FUS entry barrier and abnormal aggregation of cytoplasmic proteins [6]. In cytoplasm, TNPO1 also regulates Liquid-liquid phase separation, LLPS of FUS. FUS-NLS mutations disturb the liquid-liquid phase separation equilibrium, which is one of the mechanisms leading to abnormal cytoplasmic aggregation [6,7]. However, the exudation nucleus of FUS is independent of exudation receptor XPO1 (Exportin1,XPO1), which is considered to be exudation through passive diffusion, and the binding of newly synthesized mRNA to FUS can limit its exudation [8].

It was found that the abnormal protein sequence after FUSR503fs (C. 1509-1510delag) mutation site can increase the retention of FUSR503fs in the nucleus [9]. Nucleotide sequences of FUS (low-Complexity Domains) [10] are anchored in the C-terminal domain (CTD) of RNA polymerase II (RNAPII) [11] and regulate the transcription of 2/3 of genes related to synaptic activity by preventing hyperphosphorylation of Ser2 of RNAPII [12]. FUS mutations, even in the nucleus, can affect the transcriptional activity of RNAPII and lead to some changes in biological functions [13]. Overexpression of nuclear FUS, rather than endogenous FUS knockdown, has been shown to cause neuron death, suggesting that FUS acquired nuclear toxicity plays an important role in the pathogenesis of ALS [14]. It can also bind to an active transcription region located downstream of the gene PolyA signaling, preferentially binding proteins involved in transcriptional regulation to participate in RNA level regulation [15]. In addition, FUS can inhibit viral replication, sarcoma cell proliferation, and related RNA and protein expression [16]. FUS can bind to RNAPII in the nucleus to regulate the transcriptional activity of various transcription factors [17,18]. FUS-NLS mutations lead to abnormal axon distribution and dysfunction of key NLS-binding protein factors such as SMN (Survival Motor Neuron) [19] and reduced area of nerve endplate [20]. Therefore, functional loss of FUS-NLS cannot be ignored in the pathogenesis of JALS, and we hope that more relevant studies will be carried out.

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