Dear Editor,

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two devastating neurodegenerative diseases that have a significant overlap in clinical and pathological features (1). ALS is a progressive motor neuron disease that leads to muscle weakness, atrophy, and eventually paralysis, while FTD is a form of dementia that primarily affects the frontal and temporal lobes of the brain, leading to changes in behavior, personality, and language. In recent years, there has been growing evidence of an association between ALS and FTD, with many cases exhibiting features of both diseases. This paper will discuss the recent advances in our understanding of the link between ALS and FTD, including their clinical and pathological features, genetic factors, and potential treatments (2).

Clinical Features

ALS and FTD are both characterized by a wide range of clinical features, making it difficult to distinguish them from each other in some cases. In ALS, the most common symptoms are muscle weakness, wasting, and fasciculation, which typically begin in the limbs and then progress to involve other parts of the body. In contrast, FTD is characterized by changes in behavior, personality, and language, with patients often exhibiting apathy, disinhibition, and loss of empathy. However, there is significant overlap between the two diseases, with some ALS patients exhibiting cognitive and behavioral deficits, and some FTD patients exhibiting motor symptoms (3, 4).

The overlap between ALS and FTD has led to the recognition of a new clinical entity known as ALS-FTD or ALS with cognitive and behavioral impairment (ALS-CBI). ALS-CBI is characterized by the co-ocurrence of ALS and FTD symptoms, with patients exhibiting both motor and cognitive deficits. This clinical entity has been associated with specific genetic mutations, which will be discussed later in this paper (5).

Pathological Features

The pathological features of ALS and FTD are also highly interrelated, with many cases exhibiting features of both diseases. In ALS, the primary pathological feature is the degeneration of motor neurons in the brain and spinal cord, leading to muscle weakness and atrophy. In contrast, FTD is characterized by the degeneration of neurons in the frontal and temporal lobes of the brain, leading to changes in behavior, personality, and language (6).

However, recent studies have shown that many ALS patients also exhibit degeneration of the frontal and temporal lobes, which is a hallmark of FTD. In addition, many FTD patients also exhibit degeneration of the motor neurons, which is a hallmark of ALS. This overlap in pathological features has led to the recognition of a new pathological entity known as TDP-43 proteinopathy, which is characterized by the accumulation of abnormal TDP-43 protein in the brain and spinal cord. TDP-43 proteinopathy has been identified in both ALS and FTD patients, suggesting that they may share a common underlying pathology (7).

Genetic Factors

The link between ALS and FTD is further supported by the identification of specific genetic mutations that are associated
with both diseases. The most common genetic mutation associated with ALS is C9ORF72, which is also associated with FTD. In fact, the C9ORF72 mutation is the most common genetic cause of both ALS and FTD, accounting for up to 40% of familial cases and 7% of sporadic cases (4).

Other genetic mutations associated with both ALS and FTD include TARDBP and FUS, which are genes involved in RNA processing and transport. Mutations in these genes have been found in both ALS and FTD patients, further supporting the idea that they share a common underlying pathology.

**Potential Treatments**

The link between ALS and FTD has important implications for the development of potential treatments for these diseases. Many drugs that have been developed for ALS have also shown promise in treating FTD, and vice versa. For example, riluzole, which is the only FDA-approved drug for ALS, has been shown to reduce cognitive and behavioral deficits in FTD patients (2).

Other potential treatments for ALS and FTD include gene therapy, stem cell therapy, and immunotherapy. Gene therapy involves the delivery of normal genes to replace or supplement defective genes, while stem cell therapy involves the transplantation of stem cells to replace damaged cells. Immunotherapy involves the use of antibodies to target specific proteins that are involved in the development of ALS and FTD (5).

**Conclusion**

In conclusion, recent advances in our understanding of the link between ALS and FTD have revealed a complex interplay between these two devastating neurodegenerative diseases. ALS and FTD share many clinical, pathological, and genetic features, suggesting that they may share a common underlying pathology. The recognition of ALS-CBI as a distinct clinical entity has important implications for the diagnosis and treatment of patients with both ALS and FTD symptoms. Future research is needed to further elucidate the link between ALS and FTD and to develop effective treatments for these diseases.

**Keywords:** Amyotrophic lateral sclerosis, frontotemporal dementia, association, TDP-43

**References**