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**MOLECULAR GENETIC APPROACHES IN THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS**

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Amyotrophic lateral sclerosis is a complex and fatal neurological disorder whose underlying mechanisms are not fully understood, and there are no effective treatments available to slow or stop its progression. However, recent progress in ALS genomics has connected specific genes with observable characteristics, leading to the development of innovative therapeutic strategies and providing researchers with

valuable tools like genetically modified rodent models that mimic ALS pathology. These animal models have proven to be highly valuable for advancing translational research in ALS. Since the identification of the Cu/Zn superoxide dismutase (SOD1) gene mutation in 1993 as the first genetic anomaly in amyotrophic lateral sclerosis (ALS), more than 50 genes have been linked to either causing or modifying ALS and ALS/frontotemporal dementia (FTD) spectrum disease. The most common mutations occur in C9orf72, SOD1, TAR DNA binding protein 43 (TARDBP), and fused in sarcoma (FUS) genes. Over the past three decades, extensive global efforts have been made to uncover the biological pathways responsible for these gene mutations in ALS/FTD pathogenesis. Consequently, gene therapy strategies aimed at suppressing the toxic effects of these etiologic genes have been widely explored. These strategies include: (i) targeting abnormal transcribed RNA with microRNA or antisense oligonucleotides (ASOs) to remove or inhibit them, (ii) using RNA interference (RNAi) to degrade abnormal mRNA, (iii) reducing or inhibiting mutant proteins (e.g., using antibodies against misfolded proteins), and (iv) editing DNA genomes using techniques like clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein (CRISPR/Cas). The promising outcomes from these investigations have resulted in the implementation of some of these strategies in ALS clinical trials, particularly for genes like C9orf72 and SOD1. This shows an overview of advances in gene therapy for ALS/FTD, with a focus on genes such as C9orf72, SOD1, TARDBP, and FUS.

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