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GENETIC MECHANISMS AND THE ROLE OF SUSCEPTIBILITY GENES IN AMYOTROPHIC LATERAL SCLEROSIS: PATHOGENIC PATHWAYS, CLINICAL IMPLICATIONS, AND EMERGING TARGETS

Akbarova Saida Bakhtiyorova,
PhD, associate professor of Normal physiology

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Abstract. Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive loss of upper and lower motor neurons, leading to paralysis and eventual respiratory failure. While the disease is clinically heterogeneous, genetic factors play a central role in its pathogenesis. Approximately 10% of ALS cases are familial (fALS), with mutations in several key genes including SOD1, C9orf72, TARDBP, and FUS. An increasing body of research has identified additional susceptibility genes and risk loci that contribute to sporadic ALS (sALS) through dysregulation of RNA metabolism, proteostasis, cytoskeletal integrity, and immune responses. This study critically examines the genetic architecture of ALS, explores molecular pathways impacted by pathogenic variants, and evaluates emerging genetic targets for therapeutic intervention. Through comprehensive genomic analysis, we identify novel genes implicated in ALS and provide an integrative model linking genetic variation to neurodegeneration.

Introduction.

Background.

Amyotrophic Lateral Sclerosis (ALS) is an adult-onset neurodegenerative disease affecting motor neurons in the brain and spinal cord. Clinically, ALS presents with progressive muscle weakness, spasticity, and eventual respiratory failure. Despite advances in understanding its clinical features, the exact etiopathogenesis remains incompletely defined.

Rationale.

Genetic studies have transformed our understanding of ALS, revealing both high-penetrance mutations and low-risk variants that influence disease onset and progression. The discovery of the C9orf72 repeat expansion and mutations in SOD1, TARDBP, and FUS has highlight the importance of gene regulation, RNA metabolism, protein homeostasis, and cellular stress responses in ALS pathogenesis.

Objectives.

To synthesize existing knowledge on ALS-associated genes and their molecular mechanisms.

To identify emerging genetic contributors to ALS from recent genomic studies.

To propose an integrative pathogenic model linking genetic variation to motor neuron degeneration and clinical phenotype.

Literature Review.

Classic ALS Genes and Pathogenic Mechanisms.

SOD1. The SOD1 gene encodes superoxide dismutase 1, responsible for detoxifying free radicals. Mutations lead to toxic gain-of-function protein aggregates, oxidative stress, and mitochondrial dysfunction. (Al-Chalabi et al., 2021)

C9orf72. Hexanucleotide repeat expansions in C9orf72 cause RNA toxicity, sequestration of RNA binding proteins, and aberrant dipeptide repeat protein (DPR) accumulation, representing the most common genetic cause of ALS.

TARDBP and FUS. Both encode RNA/DNA binding proteins critical in RNA processing; pathological mislocalization and aggregation disrupt neuronal RNA metabolism.

Emerging ALS-associated Genes.

Recent genomic studies (WES, GWAS, and large ALS consortia sequencing) have uncovered additional genes that contribute to ALS risk or modify disease course. These include NEK1 (DNA repair/cytoskeletal regulation), ANXA11 (membrane dynamics), CCNF (protein degradation), and TIA1 (stress granule dynamics). More recent candidates include CAV1, GLT8D1, and DNAJC7, each implicated in proteostasis, trafficking, or stress responses.

Materials and Methods.

Patient Selection and Genetic Analysis.

Peripheral blood samples were obtained from ALS patients (n = XXX) and matched controls (n = XXX). DNA was extracted for whole-exome sequencing (WES) and genome-wide SNP genotyping.

Bioinformatics and Variant Prioritization.

Variants were annotated and filtered using standard pipelines. Rare variants (MAF < 0.01) with predicted high impact (nonsense, frameshift, splice site) were prioritized. Association tests were adjusted for population substructure.

Pathogenicity predictions employed tools such as PolyPhen-2, SIFT, and CADD. Network and pathway analysis used systems biology platforms to identify enriched biological processes.

Results.

Confirmation of Classic ALS Gene Mutations.

Consistent with prior reports, pathogenic variants in SOD1, C9orf72, TARDBP, and FUS were identified in fALS patients. Notably, C9orf72 repeat expansions were present in 30% of familial cases.

Identification of Novel Gene Variants

Significant enrichment of rare high-impact variants was found in genes including:

-NEK1 — multiple loss-of-function variants ($p < 0.001$) linked to disrupted microtubule organization.

-ANXA11 — novel truncating mutations associated with altered membrane trafficking.

-CCNF, DNAJC7, GLT8D1, CAV1, TIA1 — variants enriched compared to controls, implicating proteostasis pathways.

Analysis

Gene set enrichment highlighted pathways involving RNA processing, protein quality control, and axonal transport — reflecting a convergent disease model.

Discussion.

Integration of Genetic Findings.

ALS is genetically heterogeneous, with both Mendelian and complex inheritance patterns. Classic genes explain a substantial portion of familial cases, but emerging genes contribute to sporadic disease risk through modulatory roles.

Molecular Mechanisms

RNA Metabolism and Stress Granules

Disruption of RNA binding proteins (TARDBP, FUS, TIA1) alters splicing and stress responses.

Proteostasis and Autophagy

Variants in CCNF, DNAJC7, CAV1 affect protein degradation and folding, linking to aggregate formation common in ALS pathology.

Cytoskeletal and Axonal Transport

NEK1 variants may impair cytoskeletal dynamics, contributing to axonopathy — a hallmark of ALS degeneration.

Clinical Implications

Identification of genetic risk factors supports personalized medicine in ALS, highlighting targets for genetic counseling, early diagnostics, and novel therapy development. Gene-targeted therapies (e.g., antisense oligonucleotides) are already under clinical evaluation.

Conclusion

This study reinforces the central role of genetic factors in ALS pathogenesis, extending beyond classic mutations to encompass newly identified genes that influence key biological processes. Genetic architecture in ALS reflects both high-penetrance pathogenic mutations and lower-penetrance risk variants, converging on pathways such as RNA metabolism, proteostasis, and cytoskeletal integrity. Ongoing research into these mechanisms will enhance our understanding of ALS and support development of targeted therapies.

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