



From Population Genetics to Precision Medicine: The Evolving Role of Epidemiological Research in Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) remains one of the most complex neurodegenerative disorders, characterized by progressive motor neuron degeneration and significant clinical heterogeneity. While remarkable advances in genetics have transformed our understanding of disease mechanisms, most ALS cases cannot be explained by genetics alone. Increasing evidence supports a multifactorial model in which genetic susceptibility and environmental exposures interact to influence disease risk and progression. This evolving perspective highlights the continuing importance of epidemiological research in the era of precision medicine.

The discovery of pathogenic variants in genes such as SOD1, C9orf72, TARDBP, and FUS has reshaped ALS research and opened new avenues for targeted therapies. Gene-specific treatments, particularly for SOD1-associated ALS, demonstrate the promise of precision medicine. However, approximately 90% of ALS cases are sporadic, indicating that additional factors contribute to disease development.

Population-based genetic studies have shown that the distribution of ALS-associated variants differs considerably among populations because of founder effects and regional genetic diversity. Consequently, studying geographically distinct populations not only improves diagnostic accuracy and genetic counselling but also enhances our understanding of disease

mechanisms. Moreover, epidemiological investigations provide the complementary perspective. Although environmental risk factors such as smoking, occupational exposures, pesticides, and heavy metals have been associated with ALS, their individual contributions remain modest and often inconsistent across studies. Rather than acting independently, these exposures are likely to influence disease development in genetically susceptible individuals.

The future of ALS research lies in integrating these complementary approaches. Advances in whole-genome sequencing, multi-omics technologies, and biomarker discovery are generating unprecedented insights into disease biology. At the same time, national disease registries, electronic health records, wearable technologies, and artificial intelligence are improving epidemiological research through more comprehensive and longitudinal data collection. Together, these resources will facilitate the identification of gene-environment interactions and improve patient stratification for clinical trials.

Ultimately, precision medicine extends beyond identifying pathogenic variants. It requires understanding how genetics, environment, lifestyle, and population characteristics collectively shape disease risk and progression. Population-based studies therefore remain fundamental to translating molecular discoveries into meaningful clinical practice.

As ALS research continues to evolve, integrating genetics with epidemiology will be essential for improving early diagnosis, refining risk prediction, and developing personalized therapeutic strategies. Rather than competing disciplines, genetics and epidemiology represent complementary pillars that together will advance our understanding of ALS and ultimately improve patient care.