The Changing ALS Disease Landscape

Research into the causes of amyotrophic lateral sclerosis (ALS) is the most significant factor in the changing disease landscape, according to Nicholas Maragakis, MD, a neurologist and Director of the Center for ALS Specialty Care at Johns Hopkins Medicine.

Currently, more than 40 genes are thought to cause or increase the risk of developing ALS. Four genes — **C9orf72, SOD1, TARDBP, and FUS** — may account for up to 70% of people with familial ALS, also called inherited ALS. While about 10% of ALS cases are familial (90% are sporadic), knowing the underlying cause in some cases has opened doors to new therapeutic approaches.

“Even though the total number of patients affected by familial ALS is a subset, the identification of those genes has allowed for potential targeting of gene therapies for those patients,” says Dr. Maragakis. “Based on the results of the data from toferson [Qalsody], which is now an approved drug for SOD1-mediated ALS, I hope that other gene-targeted therapies will follow in the footsteps and also be successful.”

Challenges remain because of the broad and sometimes unknown causes of ALS. “One of the frustrations we still have is that there is not a single unifying pathway or genetic etiology for ALS,” says Dr. Maragakis. “However, encouragingly, we've seen a lot of research input from academia as well as pharma buy-in to investigate several different probable ALS-relevant cascades.”

These include various genes, including **UNC13A** and **STMN2**, that affect TAR DNA binding protein 43 (TDP-43), a primary component of abnormal protein deposits observed in the brains of many ALS patients. “Its influence on the genesis of disease is an exciting topic with a lot to be discovered in its relationship to ALS, as well as frontotemporal dementia and other diseases like Alzheimer’s. So, I think TDP-43-mediated downstream cascades are going to be particularly relevant,” Dr. Maragakis says.

He also points to growing interest in several other ALS-relevant cascades that are not necessarily associated with familial ALS.

As this work advances, Dr. Maragakis sees the National ALS Registry playing a role in increasing access to research studies, clinical trials, and new therapies. “A centralized process that can allow patients equal access to care and identification of factors that may influence their care is a good thing,” he says.

Nicholas Maragakis, MD
Director of the Center for ALS Specialty Care at Johns Hopkins Medicine

Resources

- Find information for patients and researchers on the National ALS Registry.
- Find a disease overview and resources on MDA’s Amyotrophic Lateral Sclerosis (ALS) webpage.
- Share MDA’s ALS Fact Sheet with patients and families.
- Download MDA’s ALS Impact Sheet to see how MDA supports families living with ALS.