

Protein Biomarker Clues in ALS and FTD: The Role of TDP-43 and Progranulin

Biomarker discovery and development supports neurodegenerative disease research for some of the most devastating disorders.



Neurodegenerative diseases are a group of debilitating disorders characterized by progressive degeneration of nerve cells and a range of associated clinical symptoms, including motor, cognitive, and behavioral deficits.¹ The accumulation of abnormal proteins in neurons is a key feature across many neurodegenerative disorders. The particular types of protein aggregates and their distribution across discrete neuronal populations vary between different neurodegenerative diseases and underly, in part, the clinical symptoms. Pathological protein aggregates can serve as biomarkers of disease, allowing researchers to identify and track neurodegenerative disease progression and develop novel therapeutics. For example, alpha-synuclein, amyloid-beta, and tau are some of the most widely studied for this purpose.

Among the most severe neurodegenerative disorders are amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). ALS and FTD are related to one another, sharing some of the same pathological molecular pathways, even though they are two distinct diseases. Abnormal neuronal protein accumulation in the brain occurs in both ALS and FTD, contributing to subsequent neuronal cell damage and death, as well as the associated clinical symptoms of each disease.²

ALS is characterized by progressive degeneration of motor neurons, which leads to muscle weakness that eventually affects breathing and causes death within approximately five years.³ FTD is characterized by neurodegenerative changes in brain regions that are involved in language and behavior, followed by debilitating mental, behavioral, and language deficits. ALS can occur with FTD, causing patients to deteriorate faster.

TAR DNA-Binding Protein 43 and Progranulin

TAR DNA-binding protein 43 (TDP-43) and progranulin are emerging biomarker and therapeutic targets for ALS and FTD. Aberrant deposition of TDP-43 is a hallmark feature in almost all ALS patients and approximately half of FTD patients.⁴ While mutations in the *TARDBP* gene that encodes the TDP-43 protein cause pathological changes, such mutations are not the only underlying contributor to ALS, FTD, or ALS with FTD. There is an intimate relationship between TDP-43 and progranulin, a commonly occurring nervous system protein, and the connection between them is a significant area of neurodegenerative disease research.

Many cells secrete progranulin, including central nervous system neurons and microglia. Under normal circumstances, this protein plays a role in inflammatory responses and orchestrating cellular growth, repair, protection, and survival. Researchers increasingly study progranulin to gain deeper insight into its role in neurodegenerative diseases such as ALS and FTD, among others, where decreased levels of progranulin are associated with an increase in pathological protein deposition, dysregulation of immune cells, and accumulation of waste products. For example, familial mutations in the *GRN* gene that lead to reduced progranulin production can cause an inherited form of FTD. Moreover, the severe reduction in progranulin protein production associated with *GRN* mutations is also related to FTD TDP-43 pathology, with a potential protective role for progranulin protein in mitigating neurodegeneration related to TDP-43 mutations.⁵

Pathological TDP-43 was first studied as a cerebrospinal fluid biomarker of ALS in 2008.⁶ Since then, researchers have assessed the potential of TDP-43 as a cerebrospinal fluid or blood plasma biomarker of ALS and FTD, with promising results.⁷ Progranulin is being pursued as a therapeutic target, based on research in various animal models of neurodegenerative disease that shows its protective capabilities.⁸ For example, researchers are interested in the potential of progranulin gene therapy for increasing progranulin expression and restoring normal levels of this protein to mitigate disease. To accomplish this, scientists use adeno-associated viruses for targeted delivery of *GRN* gene payloads to specific neurons in the brain.⁹ Various trials are underway in humans to test multiple potential therapeutic approaches to modulate progranulin levels in neurodegenerative disease, particularly FTD, with promising results that continue to substantiate the importance of this target.¹⁰

Tools for Biomarker Development and Therapeutic Targeting

Biomarker discovery and development for neurodegenerative disease is a burgeoning field. Discovering sensitive and specific biomarkers depends on access to reliable reagents and assays that scientists can use to reproducibly assess disease-associated biomarkers in tissues and fluids. Rigorously validated antibodies and immunoassays are essential tools for evaluating the clinical relevance of neurodegenerative disease biomarkers, especially low abundance biomarkers in blood and CSF.

Aviva's recombinant antibody development pipeline maintains rigorous quality standards that help scientists advance their biomarker and therapeutic targeting research. Aviva's repertoire of tools for studying progranulin and TDP-43 biology is expanding rapidly. This includes anti-progranulin monoclonal antibodies for use in immunocytochemistry, ELISA, and western blot, as well as off-the-shelf, semi-custom, and fully custom proteins for developing assays.

Aided by increased access to high performing reagents and assays, scientists are homing in on the role of progranulin and TDP-43 in neurodegenerative disorders and their growing potential as biomarkers for ALS and FTD diagnosis, tracking, and therapeutic targeting.¹¹⁻¹⁴ Overall, these approaches are helping scientists uncover the underlying biochemical and biomolecular pathways of neurodegenerative disease and pave the way for future translational applications.

Aviva's Custom Assay and Antibody Programs

As progranulin and TDP-43 move from emerging targets to translational biomarker programs, the limiting factor is often not scientific interest but measurement confidence. Low abundance signals in CSF and blood, multiple proteoforms, and matrix effects can make "good enough" reagents a hidden source of variability. As a result, Aviva prioritizes custom antibody discovery, development, and characterization, helping researchers generate fit for purpose binders and immunoassays, validated in relevant formats and sample types, with antibody binding kinetics measured and reported alongside performance data. The result is an approach to target specific reagent design and validation that supports reproducible data and more confident decisions as programs progress toward clinical relevance.

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