

TPPP/p25 amyloid seeding in multiple system atrophy: From structural self-protection toward a disease-specific biomarker

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The core pathological feature of synucleinopathies is abnormal aggregation of α -synuclein (α -syn), yet this shared pathology also creates a major diagnostic problem. Multiple system atrophy (MSA) is a rapidly progressive, fatal oligodendroglial α -synucleinopathy characterized by autonomic failure, parkinsonism, and cerebellar dysfunction. Its early clinical distinction from Parkinson's disease (PD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) remains difficult. Biomarkers indicative of neurodegeneration or α -syn pathology do not necessarily distinguish between specific disease subtypes. Therefore, a clinically meaningful biomarker for MSA should provide discriminatory information beyond general evidence of neuronal injury or synucleinopathy.¹

In the Cell article, the authors address this long-standing challenge by shifting attention from α -syn alone to tubulin polymerization-promoting protein (TPPP/p25), a microtubule-associated oligodendroglial protein enriched in glial cytoplasmic inclusions. In its physiological state, TPPP/p25 is self-protected from aggregation through intramolecular contacts between the intrinsically disordered N-terminal and C-terminal regions (NTR/CTR) and the aggregation-prone core domain (CORE). On the basis of this mechanism, the authors designed a TPPP/p25 seed amplification assay (TPPP/p25-SAA) using a minimized CORE substrate (miniCORE). The clinical analysis included cerebrospinal fluid (CSF) from 56 patients with MSA, 55 with PD, 12 with DLB, 19 with PSP, 10 with CBD, 12 with Alzheimer's disease (AD), and 58 healthy controls (222 samples in total). TPPP/p25-SAA distinguished MSA from PD with 96.4% sensitivity, 90.9% specificity, and an area under the receiver operating characteristic curve (AUC) of 0.978; against healthy controls, the corresponding values were 98.2%, 89.7%, and 0.975.² These results provide strong proof-of-concept evidence, but they should be regarded as initial diagnostic-performance estimates until the assay is reproduced prospectively in independent cohorts.

A major strength of this study is the integration of biochemical, biophysical, and structural experiments. Truncation analysis, nuclear magnetic resonance spectroscopy, cross-linking mass spectrometry, and differential scanning fluorimetry demonstrate that the aggregation propensity of TPPP/p25 resides mainly in the well-folded CORE domain rather than in the flanking disordered regions. However, conformational shielding is not the only explanation compatible with these data. Removing terminal regions also changes net charge, solubility, effective local concentration, and intermolecular access to CORE. In cells, TPPP/p25 aggregation may result from context-dependent perturbations in conformational stability and the local molecular environment, rather than from a discrete transition out of a single, uniquely shielded state. The current experiments establish conformational protection in vitro, but they do not identify which of these perturbations exposes CORE in human MSA. Furthermore, Zeng et al. identified this rare missense variant A119V in the Parkinson's Progression Markers Initiative database in a single 72-year-old male with rapid motor progression and then modeled the variant experimentally in recombinant TPPP/p25. A119V reduced thermal stability and increased susceptibility to seeded fibrillation, but the variant alone did not induce aggregation over the reported 60-hour assay; it has not been established as a recurrent MSA mutation, and no segregation, disease enrichment, or clinicopathological association has been demonstrated. A119V is therefore best interpreted as a human-observed, hypothesis-generating destabilization variant rather than a validated MSA-associated genetic driver.

Cryo-electron microscopy further shows that fibrils formed by isolated CORE, full-length wild-type TPPP/p25, and A119V TPPP/p25, share a highly similar fibril spine. This indicates that the CORE contains the dominant structural information required for amyloid propagation, provides a rational

basis for using miniCORE as an amplification substrate. Nevertheless, the structures were obtained from recombinant fibrils rather than patient-derived TPPP/p25 seeds, whose abundance, molecular form, and fibril architecture remain uncertain. These findings therefore expand the α -syn-centric model of MSA by adding TPPP/p25 as a potentially active oligodendroglial co-pathology; they do not replace that model. α -Syn remains the defining proteinopathy of MSA.³ TPPP/p25 aggregation could act as an upstream contributor, a downstream response to α -syn aggregation, a reciprocal amplifier, or a disease-associated bystander.

From a clinical translational perspective, the TPPP/p25-SAA has considerable translational potential. α -syn seed amplification assays have become powerful tools for detecting synucleinopathy, but their ability to distinguish MSA from PD remains debated.⁴ TPPP/p25-SAA should be benchmarked against the existing biomarker landscape. In a multicentre study of 47 patients with MSA, 24 with PD, and 25 healthy controls, neurofilament light chain (NfL) distinguished MSA from PD with AUCs of 0.97 in CSF and 0.90 in plasma.⁵ NfL, however, reflects neuroaxonal injury and is not specific to MSA pathology. In the same study, glial fibrillary acidic protein (GFAP) correlated with baseline clinical severity, but CSF GFAP did not distinguish MSA from PD and plasma GFAP did not differ among groups. Conversely, a 2024 eight-cohort α -syn seed amplification study reported 87% sensitivity for MSA and 77% specificity for MSA-type (type 2) seeds overall; specificity was 87% in research cohorts but fell to 68% in real-world cohorts. Thus, NfL offers accessible but pathology-nonspecific injury information, GFAP may be more useful for severity than differential diagnosis, and α -syn-SAA is pathologically anchored but assay- and cohort-dependent. TPPP/p25-SAA may add disease-enriched information, but its apparent advantage requires independent head-to-head testing rather than cross-study comparison of AUCs. TPPP/p25-SAA could provide complementary molecular information by detecting an MSA-enriched glial seeding signal. Clinical phenotype, MRI, and autonomic testing remain the entry point; α -syn-SAA can provide evidence of a synucleinopathy, while TPPP/p25-SAA may add an investigational MSA-enriched signal. Concordant positive results would increase molecular support for MSA but would still require clinical integration. Prospective studies must determine whether this matrix improves diagnostic decisions, trial enrichment, or patient outcomes beyond clinical criteria and MRI (Figure 1).

Before the clinical value and mechanistic significance of TPPP/p25-SAA can be fully established, several important questions remain to be addressed. First, the precise molecular identity of endogenous TPPP/p25 seeds in cerebrospinal fluid remains unresolved. Although immunodepletion experiments support the dependence of the assay signal on TPPP/p25, they do not establish structural equivalence between the amplified products and recombinant fibrils, nor do they exclude potential contributions from protein complexes. Moreover, the pathogenic role of TPPP/p25 aggregation in the initiation and progression of MSA has not been definitively established. TPPP/p25 aggregation may arise downstream of α -syn aggregation or may participate in a mutually reinforcing misfolding process with α -syn. Future studies should therefore determine whether TPPP/p25 aggregation acts as an independent driver, a disease amplifier, or a highly specific downstream molecular event of glial α -syn pathology. Finally, current clinical validation is restricted to CSF. Although CSF represents a biologically informative matrix for detecting seed amplification activity derived from the central nervous system, reliance on lumbar puncture may limit serial sampling and large-scale screening. Clinical translation of TPPP/p25-SAA will therefore require multicenter investigator-initiated trials (IITs) that include patients with prodromal or early-stage MSA, together with longitudinal follow-up and

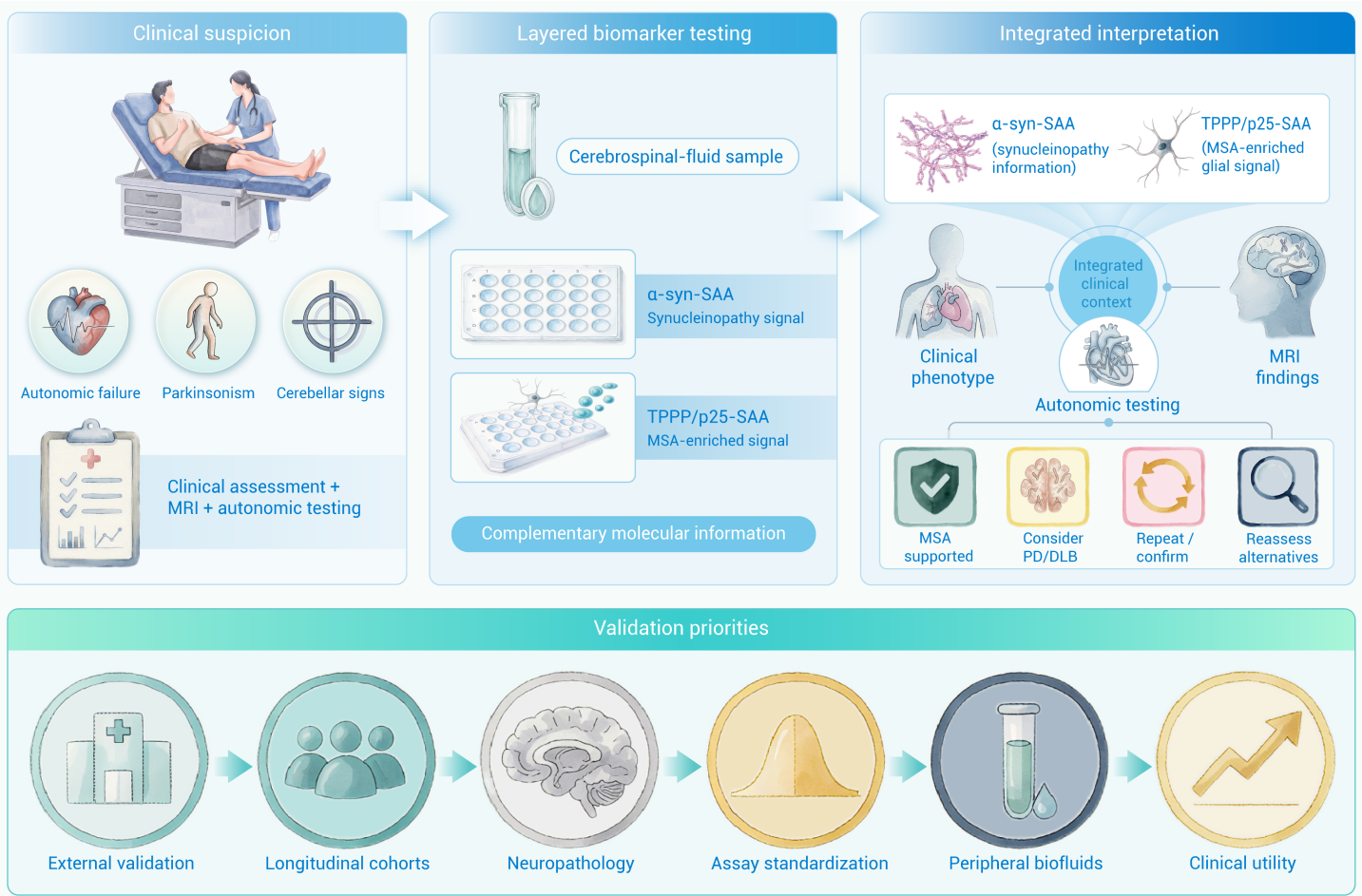


Figure 1. Proposed research framework for integrating TPPP/p25-SAA into the evaluation of suspected MSA This conceptual framework is hypothesis-generating and has not been validated for routine clinical decision-making.

neuropathological confirmation whenever feasible. Equally important, rigorous analytical standardization must be achieved before routine clinical implementation. In parallel, the assay should be further developed and validated in more readily accessible peripheral biofluids to facilitate longitudinal monitoring and broaden its potential clinical applicability.

Overall, this study provides an important mechanistic bridge from TPPP/p25 structural regulation to a candidate molecular assay. It resolves the long-standing question of whether TPPP/p25 has an intrinsic capacity to form amyloid fibrils, explains why the native protein is normally protected from aggregation, and translates this mechanistic insight into a mechanistically informed candidate diagnostic assay. TPPP/p25-SAA is a promising, mechanistically informed, MSA-enriched candidate that may complement clinical criteria, imaging, NfL, GFAP, and α -syn strain assays. Although this assay shows considerable translational promise, its ultimate clinical value will depend on independent replication, validation in larger and more representative cohorts, extension to peripheral biospecimens, and more detailed characterization of the molecular species and properties of endogenous seeds. If these challenges can be addressed, TPPP/p25 may evolve from a pathology-associated protein into an important component of future frameworks for MSA diagnosis, patient stratification, and therapeutic monitoring. More broadly, this work supports a shift in neurodegenerative disease diagnosis from symptom based classification toward mechanism-driven molecular taxonomy, a transition that may ultimately improve clinical decision-making and facilitate the development of targeted therapeutic strategies.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE MANUSCRIPT PREPARATION PROCESS

During the preparation of this work, the authors used chatgpt for English translation and paper wording polishing. The authors reviewed and edited the output as needed and take full responsibility for the content of the published

article.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.