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The molecular and genetic view of tauopathies: From structural polymorphism to systemic neurodegeneration

Taupatilere moleküler ve genetik bakış: Yapısal polimorfizmden sistemik nörodejenerasyona

Esra Demir Ünal[1], Selim Selçuk Çomoğlu[2]

[1]Department of Neurology, Ankara Yıldırım Beyazıt University Medical Faculty, Ankara, Türkiye
[2]Department of Neurology, University of Health Sciences Gülhane Medical Faulty, Ankara Etlik City Hospital, Ankara, Türkiye

ABSTRACT

Tauopathies constitute a broad group of clinically heterogeneous neurodegenerative disorders, including Alzheimer's disease, progressive supranuclear palsy, and Pick's disease, characterized by abnormal metabolism, misfolding, and intracellular aggregation of the microtubule-associated protein tau. These diseases are defined by disruptions in alternative splicing of the tau protein, toxic post-translational modifications such as hyperphosphorylation and acetylation, and the "prion-like" spread of pathological tau seeds across anatomically connected regions. Recent cryogenic electron microscopy studies have demonstrated that each tauopathy has a unique filament-folding structure, elucidating the molecular basis of phenotypic variation among diseases. The aim of this review is to provide a holistic perspective by synthesizing recent developments in the molecular and genetic architecture of tauopathies, particularly newly discovered genetic risk loci and cellular proteostasis mechanisms. In this context, detailing the process from the physiological functions of the tau protein to its pathological transformation aims to analytically evaluate the diagnostic value of fluid biomarkers and current data on next-generation clinical-stage therapeutic strategies, such as monoclonal antibodies and antisense oligonucleotides.

Keywords: Fluid biomarkers, neurodegeneration, prion-like propagation, tau protein, tauopathies

ÖZ

Taupatiler, mikrotübül ilişkili protein tau'nun anormal metabolizması, yanlış katlanması ve hücre içi agregasyonu ile karakterize edilen, Alzheimer hastalığı, progresif supranükleer palsi ve Pick hastalığı gibi klinik olarak heterojen nörodejeneratif bozuklukları kapsayan geniş bir gruptur. Bu hastalıklar, tau proteininin alternatif splicing süreçlerindeki bozulmalar, hiperfosforilasyon ve asetilasyon gibi toksik post-translasyonel modifikasyonlar ve patolojik tau birikimlerinin anatomik olarak bağlantılı bölgeler boyunca "prion benzeri" yayılımı ile tanımlanır. Son yıllardaki kriyojenik elektron mikroskopisi çalışmaları her bir taupatinin kendine özgü bir filament katlanma yapısına sahip olduğunu kanıtlayarak, hastalıklar arasındaki fenotipik varyasyonun moleküler temelini aydınlatmıştır. Bu derlemenin amacı, taupatilerin moleküler ve genetik mimarisindeki güncel gelişmeleri, özellikle yeni keşfedilen genetik risk lokuslarını ve hücresel proteostaz mekanizmalarını sentezleyerek bütünsel bir perspektif sunmaktır. Bu kapsamda, tau proteininin fizyolojik fonksiyonlarından patolojik dönüşümüne kadar olan sürecin detaylandırılması; sıvı biyobelirteçlerin tanısal değerinin ve monoklonal antikorlar ile antisense oligonükleotidler gibi klinik aşamadaki yeni nesil terapötik stratejilerin güncel verilerinin analitik bir yaklaşımla değerlendirilmesi hedeflenmektedir.

Anahtar sözcükler: Sıvı biyobelirteçler, nörodejenerasyon, prion-benzeri yayılım, tau proteini, taupatiler

Tauopathies include neurodegenerative syndromes that begin with disruption of the 3R/4R isoform balance arising from microtubule-associated protein tau (MAPT)-derived alternative exon splicing, liquid-liquid phase separation (LLPS) triggered by multiple post-translational modifications (PTMs) such as Ser/Thr hyperphosphorylation, lysine-targeted acetylation, truncation, and ubiquitination, progressing toward paired helical filament (PHF) and straight filament (SF) formation; they show filament fold heterogeneity and intercellular propagation of pathological tau seeds via prion-like "seeding" mechanisms along anatomical neural networks.[1-4] High-penetrance missense and splicing mutations within MAPT are associated with familial frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) phenotypes, and interactions between the MAPT H1 haplotype and genome-wide association study

Corresponding author: Esra Demir Ünal, MD. Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, 06010 Çankaya, Ankara, Türkiye.
E-mail: esrademirunal@aybu.edu.tr | Doi: 10.5606/phhb.dergisi.2026.66

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(GWAS)-derived loci contribute to the pathogenesis of 4R-tauopathy via pathways including vesicular trafficking, endoplasmic reticulum stress response, and oligodendrocyte function.[5-10] Proteostasis components, kinase/phosphatase imbalance, and seeding capability, determined by filament conformation, shape both intracellular aggregation kinetics and intercellular propagation potential, while PTMs-specific proteomic profiles provide potential biomarkers for subtype differentiation.[7,11] Within this framework, the aim of this review is to synthesize the molecular processes from the physiological functions of tau protein to pathological transformation; isoform/PTM-based filament conformations; prion-like seeding and intercellular propagation mechanisms; and the functional effects of MAPT mutations and novel GWAS loci; and additionally, to analytically evaluate the diagnostic value of fluid biomarkers such as cerebrospinal fluid (CSF)/plasma p-tau217/p-tau181 and neurofilament light chain (NfL), as well as the molecular rationale of clinical-stage molecular therapeutic strategies, including second-generation tau-positron emission tomography (PET) tracers, monoclonal antibodies, antisense oligonucleotides (ASOs), and proteolysis-targeting chimera (PROTAC)-based degradation, and clarify research and clinical priorities.

STRUCTURAL PERSPECTIVE ON TAU PROTEIN

Tau protein belongs to the intrinsically disordered protein family, which helps maintain axonal stability in neurons of the central nervous system.[12] Synthesized from the MAPT gene, this protein lacks a thermodynamically stable tertiary structure, thereby conferring extraordinary flexibility in interacting with diverse ligands. Encoded by the MAPT gene on chromosome 17q21.31, this protein physiologically promotes microtubule (MT) polymerization and stabilizes MTs.[13] In a healthy adult neuron, tau binds to and dissociates from the MT surface on nanosecond timescales; this dynamic kiss-and-run process allows motor proteins (kinesin and dynein) to transport cargo along the axon, as shown in Figure 1.[14]

Research in 2025-2026 has demonstrated that tau extends beyond classical MT functions. High-resolution mass spectrometry data show that tau stabilizes pericentromeric heterochromatin structures within the nucleus.[15-17] Intracellular tau concentration is normally maintained in the range of 1.5-2.2 μM; disruption of this homeostatic balance alters cytosolic viscosity, leading to a "molecular crowding" effect and nucleation events that constitute the initial kinetic basis of pathological aggregation.[11]

Isoform dynamics and physiological roles

Tau isoform dynamics play a central role in the MT-based regulation of neuronal morphology and function. Variants derived from MAPT transcripts, 0N/1N/2N and 3R/4R, exhibit distinct expression profiles across neuronal subregions, and this heterogeneous expression helps explain selective vulnerability in the hippocampus, entorhinal cortex, and certain subcortical nuclei.[15] Isoforms differ in biophysical properties, MT-binding affinity, stabilization capacity, and aggregation potential. For example, deficiency or overexpression of 4R isoforms directly affects MT dynamics, impairing axoplasmic transport; this disrupts synaptic vesicle trafficking, mitochondrial relocation, and ultimately synaptic homeostasis.[16] Beyond genetic regulation, age-related changes in ribonucleic acid (RNA)-binding protein expression and epigenetic modulation can shift isoform ratios by altering splicing regulation. Clinically, the molecular differences largely determine the distinct neuropathological and clinical presentations of 3R-dominant and 4R-dominant pathologies; therefore, therapeutic interventions must evaluate isoform-specific effect profiles.[17]

MAPT gene architecture and alternative splicing dynamics

The MAPT gene has a complex genomic architecture consisting of 16 exons, and alternative splicing of exons 2, 3, and particularly exon 10 in the adult human brain gives rise to six principal tau isoforms, distinguished by 0N/1N/2N and 3R/4R. In the healthy adult brain, the 3R:4R ratio is balanced at approximately 1:1, and molecular events that disrupt this balance define the specific pathological signatures of primary tauopathies.[18] Inclusion of exon 10 produces 4R isoforms, which tend to bind MTs more strongly; this binding advantage, in addition to MT stabilization, increases tau's intracellular exposure time and thus the likelihood of PTMs, predisposing to proteostasis imbalance.[18,19] Age- and cellular energy-stress-dependent changes in spliceosome components and SR-family splicing factor expression have been observed; for example, mitochondrial complex I inhibitors induce serine/arginine-rich splicing factor 2 (SRSF2) and related factors, increasing exon 10 inclusion and contributing to the emergence of 4R-dominant phenotypes. This finding highlights that cellular metabolic state can directly modulate MAPT splicing dynamics.[20]

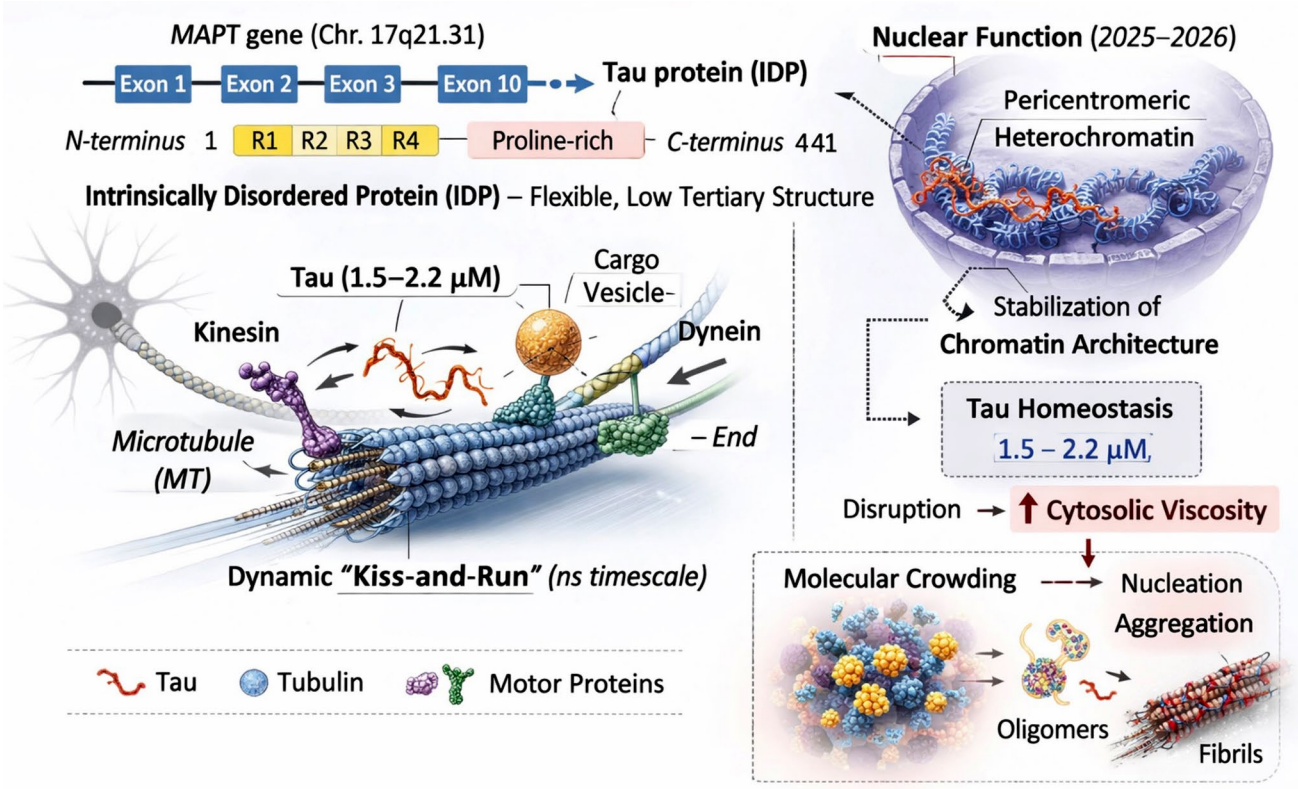

Figure 1. Structural perspective of tau protein in neurons. Tau protein, an IDP encoded by the MAPT gene on Chr 17q21.31, dynamically binds to MTs to stabilize axonal transport mediated by motor proteins kinesin and dynein. In addition to canonical MT functions, tau localizes to the nucleus where it stabilizes pericentromeric heterochromatin, as shown by high-resolution structural analyses. Physiological intracellular tau concentrations (1.5-2.2 µM) maintain cytosolic homeostasis; perturbations lead to molecular crowding, nucleation events, and initial tau fibril aggregation, representing the kinetic basis of tauopathy formation. Key structural elements, dynamic interactions, and aggregation pathways are highlighted in this schematic.

IDP, intrinsically disordered protein, MAPT, microtubule-associated protein tau; Chr, chromosome; MT, microtubules.

This figure was partially created with the assistance of artificial intelligence.

POST-TRANSLATIONAL MODIFICATIONS AND TAU PATHOBIOLOGY

The pathological aggregation journey of tau goes beyond the classical nucleation model, beginning instead with LLPS processes; the presence of RNA and RNA-binding proteins facilitates tau forming membraneless condensates even at physiological concentrations, and within this microenvironment, tau concentration increases dramatically relative to the surroundings, creating a kinetic landscape favorable for oligomerization and fibrillization. Moreover, the LLPS phase can undergo a rapid "liquid→solid" transition under oxidative stress and specific PTMs (e.g., certain p-tau epitopes and acetylations), thereby producing irreversible fibrils. Therefore, LLPS represents an early and targetable window for therapeutic intervention.[21,22] Additionally, the structural heterogeneity of tau aggregates is explained by distinct 'folds' resolved by cryogenic electron microscopy (cryo-EM); each tauopathy exhibits a unique protofilament core folding pattern, affecting both *in vivo* imaging ligand binding and conformation-specific antibody recognition; thus, molecular fold differences are an essential factor in disease-specific diagnostics and therapeutic strategies.[18,21] Tau's intercellular propagation is defined by "prion-like" seeding mechanisms: aggregate seeds are released, taken up by neighboring cells via exosomes/extracellular vesicles and receptors, and re-establish conformational information, thereby determining regional progression; this process is supported by both *in vivo* model data and clinico-anatomical progression correlations in humans.[23] Furthermore, tau pathology is linked to disruption of the spliceosome: pathological tau-splicing component interactions can impair pre-messenger RNA (mRNA) processing, leading to "cryptic" splicing events and a global collapse of transcriptomic integrity; this provides a novel

molecular mechanism for neuronal dysfunction and degeneration, highlighting the spliceosome itself as a therapeutic target.[24] Tau's cellular localization exceeds its classical role as an axonal structural stabilizer; its dendritic and postsynaptic functions, modulating N-methyl-D-aspartate receptor activity via Fyn kinase and regulating synaptic homeostasis, are critical. In pathological states, tau mislocalization in dendrites leads to GluN2B-mediated excitotoxicity and synaptic dysfunction, directly linking this mechanism to learning and memory deficits.[25] Recently, tau-mitochondria interactions have been detailed: pathological p-tau forms interact with voltage-dependent anion channel 1 (VDAC1) and mitochondrial dynamics proteins, disrupting the electron transport chain, the balance between mitofusion and mitofission, and mitophagy. Conversely, manipulation of VDAC1 levels (e.g., partial reduction) in model systems attenuates tau-associated mitochondrial toxicity, showing neuroprotective effects; this underscores the therapeutic potential of the tau-mitochondria axis.[26] This integrated molecular perspective combines MAPT splicing, PTM 'signatures,' LLPS kinetics, spliceosome homeostasis, glial contributions, and mitochondrial interactions into a single pathobiological network, strongly supporting the need for subtype-specific biomarker development and fold- and cell-type-specific therapeutic strategies, as shown in Table 1.

Molecular determinants of liquid-liquid phase separation and aggregation kinetics

The pathological aggregation of tau protein is initiated not by the classical "nucleation and elongation" model that dominated for decades but

Table 1. Integrated molecular perspective of tau pathobiology and neurodegeneration

Author	Molecular mechanism	Molecular pathophysiology
Wegmann et al.[20] Ambadipudi et al.[27]	Liquid–liquid phase separation	Formation of protein-rich, membraneless condensates through multivalent interactions; increases local tau concentration and facilitates tau nucleation.
Ash et al.[21] Kanaan et al.[28]	Liquid-to-solid phase transition	Stress-induced maturation of tau condensates into pathological oligomers and fibrillar assemblies, promoted by disease-associated post-translational modifications.
Shi et al.[1] Fitzpatrick et al.[4]	Structural fold polymorphism	Disease-specific tau filament folds determine molecular identity of tauopathies; distinct protofilament architectures define clinicopathological phenotypes.
Rauch et al.[23] Jucker & Walker[51]	Prion-like seeding and propagation	Misfolded tau spreads between neurons through receptor-mediated uptake mechanisms including LRP1-dependent internalization and trans-synaptic propagation.
Hsieh et al.[24]	Spliceosome disruption	Pathological tau interaction with U1 snRNP induces cryptic RNA splicing abnormalities and widespread transcriptomic instability.
Hoover et al.[25]	Dendritic mislocalization	Abnormal redistribution of tau to dendritic spines causes synaptic dysfunction through altered glutamatergic signaling independent of neuronal death.
Vijayan et al.[26]	Mitochondrial dysfunction axis	Tau-associated mitochondrial abnormalities involving VDAC1 regulation, mitochondrial dynamics, and bioenergetic impairment contribute to neuronal vulnerability.
Kovacs[55] Reid et al.[56]	Cell-type-specific glial tauopathy	Astrocytic and oligodendroglial tau accumulation disrupts metabolic support, inflammatory regulation, and myelin homeostasis.
Seidler et al.[47] Kunach et al.[48]	Conformational epitope dynamics	Cryo-EM and ligand-binding studies reveal structure-dependent tau epitopes relevant for PET imaging and therapeutic targeting.
Wesseling et al.[17] Arakhamia et al.[60]	Tau post-translational modification landscape	Disease-specific phosphorylation and PTM patterns generate heterogeneous tau strains and influence aggregation properties.
Goedert[22] Savastano et al.[36]	Tau condensate remodeling and microtubule dysfunction	Pathological phosphorylation alters tau condensate properties and compromises physiological microtubule assembly.

LRP1, Low-Density Lipoprotein Receptor-Related Protein 1; U1 snRNP, U1 Small Nuclear Ribonucleoprotein Particle; RNA, ribonucleic acid; VDAC1, Voltage-Dependent Anion Channel 1; Cryo-EM, Cryogenic Electron Microscopy; PET, positron emission tomography; PTM, post-translational modification.

by the recently characterized LLPS mechanism.[27] Tau's intrinsically disordered structure, high content of charged residues, and conformational flexibility make it highly sensitive to electrostatic changes in the cellular microenvironment; interactions with RNA, heparan sulfate proteoglycans, and other polyanionic molecules lead tau to separate from the soluble monomeric pool, undergoing phase separation and forming liquid-like condensates.[27-31] Within these condensates, tau concentration increases by approximately 100-200-fold compared to the surrounding cytoplasm, thereby permitting protein-protein interactions that are kinetically inaccessible under normal conditions.[27,32]

In vivo imaging and advanced biophysical studies show that tau droplets formed by LLPS are initially highly dynamic, fluid, and reversible; however, oxidative stress, mitochondrial dysfunction, and especially hyperphosphorylation of tau reduce molecular mobility within droplets, triggering a "liquid-to-solid" transition.[28] This transformation progresses over hours to days under cellular stress, resulting in irreversible oligomer formation and fibril nucleation, as supported by experimental evidence.[28,32,33]

The PTM profile of tau within LLPS droplets is a key determinant of aggregation kinetics; in particular, conformers bearing the p-tau231 epitope in phase-separated environments accelerate the liquid-to-solid transition by approximately threefold, initiating pathological aggregation early and aggressively.[27,34-36] The electrostatic properties of the microtubule-binding region and their modifications (phosphorylation/acetylation) strongly influence droplet stability and nucleation probability.[30,36] These data suggest that the irreversible toxicity threshold in tauopathies occurs not at mature fibril formation but during the early concentration phase initiated by LLPS; consequently, pharmacological or biological interventions targeting LLPS present a broader and more efficacious therapeutic window than approaches applied after fibril formation.[37-40]

FILAMENT CONFORMATIONS: CRYO-EM DATA AND CLINICO-PATHOLOGICAL IMPLICATIONS

Advances in cryo-EM have enabled atomic-level resolution of tau filaments, initiating a paradigm shift in molecular classification of tauopathies. The PHF and SFs in Alzheimer's disease (AD) were initially resolved in high-resolution studies, revealing that PHF/SF cores exhibit a defined C-shaped protofilament architecture.[41] Subsequent studies confirmed that filaments from Pick's disease (PiD), chronic traumatic encephalopathy, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) each possess distinct and discernible "tau folds"; for example, PiD exhibits a wider J-shaped fold, whereas PSP/CBD shows more rigid, multi-layered motifs corresponding to isoform composition and PTM profile.[42-44]

This morphological diversity has direct clinical implications: conformational epitopes and hydrophobic pockets on filament surfaces determine small-molecule binding as well as monoclonal antibody or PET ligand interactions; thus, a lack of *in vivo* signal does not necessarily indicate the absence of pathology, but rather commonly reflects an inability to access the target fold.[45,46] Laboratory studies have also shown that recombinant tau can be converted to disease-specific filaments under appropriate conditions and cofactors, allowing *in vitro* models to closely resemble patient-derived filaments; this confirms the key role of PTMs and cofactors (RNA, polyanions, inorganic ions, etc.) in filament folding.[47,48] The Cryo-EM studies also defined atomic-level PET ligand binding modes; for instance, the second-generation ligand MK-6240 binds PHF cores in a single binding mode, interacting with specific amino acid residues and providing structural information essential for ligand optimization and fold-specific therapeutic design.[49] Collectively, structural studies that integrate disease-specific folds, PTM profiles, and cofactor presence provide guidance for the rational design of fold-specific small molecules, antibodies, or PROTAC approaches.[46,47,50]

INTERCELLULAR PROPAGATION AND SEEDING MECHANISMS

One central mechanism explaining the anatomical and temporal progression of tauopathies is the transfer of misfolded tau conformers with seeding activity to neighboring cells, converting endogenous tau into pathological conformations. In this prion-like model, release, extracellular stability, uptake, and intracellular reconstruction are sequential, interconnected processes; exosomes, free oligomeric forms, and receptor-mediated endocytosis play key roles in this axis.[51,52] Cellular and animal studies have shown that specific surface receptors, particularly low-density lipoprotein receptor-related protein 1, are key to neuronal uptake of extracellular tau, providing potential targets for modulating interneuronal propagation.[53] Experimental data also indicate

that different tau "strains" exhibit varying tropism and toxicity, with certain conformers preferentially accumulating in specific cell types or neuroanatomical network nodes, underpinning the molecular basis of clinical heterogeneity.[51,54] Integration with recent brain connectome studies shows that tau propagation correlates not only with physical proximity but also with functional network connectivity; highly connected hub regions may exhibit faster or earlier pathological accumulation of tau.[53,55] Physiological states also modulate this propagation: activation of the glymphatic system during non-rapid eye movement sleep facilitates extracellular tau clearance, whereas chronic sleep deprivation markedly accelerates tau seed dissemination, supported by clinical and imaging evidence.[56] This integrated molecular-cellular-network perspective directs strategic therapeutic targeting and provides a rationale for combination approaches, including immunotherapeutic/neutralizing strategies, receptor blockade, or inhibition of exosome biogenesis.

CELL-TYPE-SPECIFIC PATHOLOGY: NEURONS AND GLIA

Historically, tauopathies were classified as primary neuronal degeneration disorders, but accumulating neuropathological and molecular data over the last decade indicate that tau accumulation in glial cells plays a central role in defining the phenotypes of primary tauopathies. Tufted astrocytes in PSP, characteristic astrocytic plaques in corticobasal degeneration, and argyrophilic grain disease's twisted argyrophilic inclusions demonstrate that glial tau pathology is not merely an accompanying phenomenon but represents disease-specific pathognomonic signatures.[55,56] The morphology and immunochemical properties of these glial inclusions differ markedly from those of neuronal tau aggregates; moreover, evidence increasingly supports the notion that glial cell-type-specific filament conformations can form, potentially influencing disease course.[57,58] Single-cell and spatial omics analyses show that tau accumulation in oligodendrocytes can permanently suppress transcriptional networks required for myelin homeostasis and repair, providing a molecular basis for white matter degeneration and axonal conduction deficits observed in 4R-tauopathy phenotypes.[58,59] Astrocytic tau burden not only disrupts cellular metabolism but also contributes to blood-brain barrier impairment and chronic local inflammation, pathologically reprogramming the neuronal microenvironment.[55,56,60] These data strongly indicate that future therapeutic methods should not be limited to targeting neuronal tau but should also include cell-type-specific approaches to address dysfunction in astrocytes and oligodendrocytes.

GENETIC ARCHITECTURE: MAPT MUTATIONS, HAPLOTYPES, AND GWAS FINDINGS

From a genetic perspective, the etiopathogenesis of tauopathies involves both high-penetrance familial phenotypes and risk modulation in sporadic cases, thereby providing a quantitative, pathway-integrated framework. Large-scale GWAS have repeatedly identified strong signals around MAPT in PSP, CBD, and clinically defined tauopathies, as well as non-MAPT loci such as STX6, EIF2AK3, MOBP, and BIN1; for instance, Höglinger et al.[61] reported genome-wide significance at STX6, EIF2AK3, and MOBP loci in a staged PSP GWAS (Stage-1: 1,114 PSP cases *vs.* 3,247 controls; Stage-2: 1,051 cases *vs.* 3,560 controls), and two independent MAPT signals increased PSP risk. The CBD GWAS similarly identified shared risk loci with PSP; CBD samples (small but well-characterized pathologically) showed common risk signals.[62,63] Meta-analyses in AD revealed tau-associated genetic signatures alongside amyloid, immune, and lipid pathways, indicating that AD risk is shaped by both the cumulative effects of numerous low-impact variants and interactions among several high-impact loci.[64]

The MAPT-focused studies demonstrated that the H1/H2 inversion and H1 sub-haplotypes strongly modulate PSP/CBD risk; reported odds ratios for H1d, H1g, and H1o were approximately 1.86, 3.64, and 2.60, respectively, and were associated with both risk and tau pathology severity.[63] In familial forms, pathogenic MAPT variants are associated with high-penetrance FTDP-17 phenotypes, and functional and structural studies explain how these mutations disrupt exon 10 splicing, isoform ratios (3R/4R), and aggregation kinetics at atomic/conceptual levels; current datasets report > 100 MAPT variants, whose phenotypic effects influence isoform balance and emergence of specific filament folds.[65,66]

Individual GWAS loci generally have modest effects, but cumulative effects captured by polygenic risk scores (PRS) show substantial explanatory power at clinical and biomarker levels; pathology-confirmed series applying PRS reported AUC ≈ 80-84%, and recent cell-weighted PRS approaches reveal associations between neuron/astro/oligodendrocyte/

microglia-specific genetic loads and β-amyloid and tau biomarkers, demonstrating PRS utility not only for risk prediction but also for cell-specific pathogenesis modeling.[67,68] Quantitatively, large AD meta-analyses and PRS studies indicate that single-nucleotide polymorphism-based narrow-sense heritability estimates vary by study and diagnostic criteria, ranging from 25-40% in clinically diagnosed cohorts and higher in pathology- or CSF-confirmed cohorts, reflecting strong influences of age, case definition, and the APOE region.[68]

Ultimately, the genetic architecture of tauopathies is controlled by a combination of a few high-impact mutations and many low-impact variants; modern translational approaches overlay GWAS-derived lead loci with expression quantitative trait locus, single-cell expression, epigenomic, and PTM/proteomic data to functionally validate which risk alleles disrupt which pathways in specific cell types. This quantitative-genetic framework provides a foundation for individualized diagnostics and fold- or isoform-specific ASO or antibody selection in clinical strategies, as shown in Table 2.

GLIAL CONTRIBUTIONS, EPIGENETIC CHANGES, AND CELL TYPE-SPECIFIC PATHOLOGY

Recent research has established glial contributions and epigenetic reprogramming as central mechanisms in the pathogenesis of tauopathy. Astrocytes and oligodendrocytes are recognized as active participants that can accelerate or modulate neurodegeneration, rather than serving solely as passive targets of tau accumulation.[69-72] Epigenetic alterations in oligodendrocytes suppress gene networks essential for myelin homeostasis, thereby disrupting white matter integrity and impairing axonal conduction, thereby accelerating neurodegeneration.[70,71] Microglial activation exerts a dual effect: early, regulated activation facilitates the clearance of pathological tau, whereas chronic, excessive activation increases

Table 2. Genetic architecture and epigenetic determinants of tauopathies

Author	Genetic factor/mechanism	Pathophysiological impact
Höglinger et al.[61]	Non-MAPT GWAS risk loci (STX6, EIF2AK3, MOBP)	Common genetic variants influence PSP susceptibility through regulation of protein trafficking, cellular stress pathways, and tau biology.
Heckman et al.[63]	MAPT H1 Sub-haplotypes (H1d, H1g, H1o)	MAPT haplotype variation modifies PSP risk and correlates with pathological tau burden.
Hutton et al.[6] Strang et al.[65]	Pathogenic MAPT mutations	Exon 10 splicing abnormalities alter 3R/4R tau isoform balance and cause familial FTDP-17 tauopathies.
Bruch et al.[19]	SRSF2-Mediated 4R tau regulation	Mitochondrial complex I dysfunction increases SRSF2 expression, promoting exon 10 inclusion and 4R tau accumulation.
Leonenko et al.[67] Baker et al.[68]	Polygenic risk architecture	Aggregate effects of common variants contribute to Alzheimer disease susceptibility and explain part of disease heritability.
Frost et al.[76]	Tau-induced chromatin remodeling	Pathological tau promotes global chromatin relaxation and transcriptional dysregulation.
Levine et al.[78] Nativio et al.[79]	Epigenetic aging signatures	Altered DNA methylation patterns associate with accelerated neuronal aging and Alzheimer pathology.
Selenica et al.[81] Salta et al.[82]	microRNA-132 and HDAC6 dysregulation	Loss of regulatory miRNAs and altered tau acetylation impair tau clearance mechanisms.
Grubman et al.[70] Miyoshi et al.[71]	Single-cell transcriptomic remodeling	Cell-specific transcriptional changes reveal altered neuronal and glial networks in Alzheimer disease.
Desikan et al.[58] Kunkle et al.[64]	Alzheimer genetic risk architecture	Genome-wide variants affecting amyloid, tau, immune, and lipid pathways contribute to disease susceptibility.

MAPT, microtubule-associated protein tau; GWAS, genome-wide association study; STX6, Syntaxin 6; EIF2AK3, eukaryotic translation initiation factor 2 alpha kinase 3; MOBP, myelin-associated oligodendrocyte basic protein; PSP, progressive supranuclear palsy; 3R/4R tau, three-repeat/four-repeat tau isoforms; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; SRSF2, serine and arginine rich splicing factor 2; DNA, deoxyribonucleic acid; miRNA, microRNA; RNA, ribonucleic acid; HDAC6, histone deacetylase 6.

proinflammatory cytokine release and fosters a neurotoxic environment.[73-75] This duality highlights the increasing focus on glial-targeted therapies and the necessity for cell-type-specific interventions.

Tau accumulation influences not only cytoplasmic aggregation but also chromatin organization within neuronal nuclei. Pathological tau induces heterochromatin decondensation, destabilizing genomic integrity and resulting in widespread transcriptional dysregulation.[76] Epigenomic analyses indicate that brain tissue from tauopathies exhibits an advanced "epigenetic age" profile, independent of chronological age, as evidenced by deoxyribonucleic acid (DNA) methylation patterns.[77,78] Studies have documented accelerated epigenetic aging of approximately 15-20 years in tauopathic neurons. Histone deacetylase enzymes, particularly histone deacetylase 6 and sirtuin 1, play central roles in tauopathies. Dysregulation of these enzymes alters tau acetylation, disrupts cellular stress responses, and impairs neuronal survival.[79,80] Furthermore, neuroprotective microRNAs such as miR-132, which regulate tau synthesis, are markedly reduced in tauopathies, eliminating negative feedback on tau expression.[81] Collectively, these findings support the conceptualization of tau pathology as both protein aggregation and persistent dysregulation of gene expression.

MOLECULAR SUBTYPES AND PERSONALIZED CLASSIFICATION

The clinical and pathological heterogeneity of tauopathies has rendered the traditional "single-type AD" paradigm obsolete, prompting the adoption of classification systems based on molecularly defined subtypes. The precision-tau classification, introduced in 2026, stratifies patients into four principal molecular subtypes by integrating CSF p-tau/t-tau ratios, spatial distribution patterns from tau-PET imaging, and individual genetic risk profiles.[82] This methodology emphasizes not only the quantity of tau but also its biochemical properties and propagation dynamics, resulting in a more nuanced definition of disease. Notably, the "rapidly progressive tauopathies" subgroup shows an approximately fivefold increase in tau fragmentation relative to classical cases, a finding strongly associated with aggressive clinical progression. This molecular classification is also essential for guiding therapeutic strategies: ASO-based approaches targeting exon-10 splicing achieve greater biological and clinical efficacy in patients with predominant 4R-tau strains, while conformation-specific monoclonal antibodies are more effective in Alzheimer-type tauopathies with mixed 3R/4R tau.[83,84] These findings underscore the necessity for personalized therapeutic strategies in tauopathies.

Fluid and imaging biomarkers: Diagnosis and monitoring

Recent advances in diagnostics and monitoring integrate second-generation tau-PET ligands with fluid biomarkers, including plasma p-tau217, p-tau181, total tau, and NfL.[85-88] Plasma p-tau217 demonstrates high sensitivity and specificity for distinguishing AD, establishing it as a key clinical tool. However, the development of plasma biomarkers specific to primary 4R-tauopathies is ongoing. The p-tau multi-panel approach enables simultaneous measurement of p-tau217, p-tau205, and NfL from a single blood sample, thereby improving diagnostic accuracy and monitoring of neuronal degeneration.[84] Second-generation tau-PET ligands, such as MK-6240 and PI-2620, offer enhanced signal specificity by minimizing off-target binding.[82] Artificial intelligence-assisted PET analysis can accurately predict tau propagation, providing a robust endpoint for clinical trials.

THERAPEUTIC APPROACHES AND PRECISION MEDICINE PERSPECTIVE

Suppression of tau production and inhibition of propagation: ASO and immunotherapy

Current tau-targeted therapies primarily employ two strategies: suppression of pathological tau production and inhibition of intercellular propagation of tau seeds. ASO technologies address the molecular basis of disease by targeting MAPT mRNA to suppress tau protein translation, thereby reducing both physiological and pathological tau levels. Studies involving BIIB080 (IONIS-MAPTRx) have demonstrated over 50% reduction in tau synthesis, as evidenced by decreased CSF p-tau and total tau levels.[89,90] Phase 2 clinical results from late 2025 indicate that ASO therapy slows cognitive decline, providing the first robust evidence that early tau suppression can modify disease progression.[91]

Immunotherapeutic strategies are designed to block intercellular tau propagation. Monoclonal antibodies bind extracellular tau species, thereby preventing transsynaptic spread. Bepranemab (UCB0107) and Tilavonemab (ABBV-8E12) are prominent candidates that bind specific tau epitopes

with high affinity.[92,93] A significant challenge remains the blood-brain barrier's low permeability. The development of transferrin receptor-mediated brain-shuttle technologies, currently in phase 3, has increased central nervous system delivery of monoclonal antibodies by 8-10-fold and substantially reduced target tau load.[94]

Structure-based precision medicine: Fold-specific drugs and PROTAC technology

Atomic-resolution structural data obtained through cryo-EM have facilitated the development of next-generation therapies that directly address the molecular heterogeneity of tauopathies. Fold-specific drug design selectively targets the three-dimensional filament folding unique to each tauopathy.[95] This strategy inhibits pathological aggregates while preserving normal tau functions, thereby reducing the off-target toxicity observed with earlier inhibitors. Proteolysis-targeting chimeras represent a significant advancement, directing pathological tau proteins to the ubiquitin-proteasome system for degradation via E3 ligases.[96] Early human and advanced preclinical studies conducted between 2025 and 2026 demonstrate that orally bioavailable tau-PROTAC molecules can rapidly reduce total tau load in the brain and suppress neurodegeneration.[97]

Clinical experiences with tau-targeted therapies have demonstrated that the primary reason for failure was intervention at inappropriate disease stages and suboptimal patient selection. Retrospective analyses reveal that most interventions were initiated at advanced stages, when irreversible neuronal loss had already occurred. The current paradigm emphasizes the importance of initiating treatment in the preclinical phase, 10-15 years before symptom onset.[98] Furthermore, evidence indicates that amyloid plaque clearance alone does not result in clinical improvement, as tau pathology is independent of amyloid and self-sustaining.[99] Systematic reviews and meta-analyses published in 2025–2026 indicate that combination therapies that combine anti-amyloid and anti-tau agents significantly improve cognitive performance compared with monotherapies.[100] In the coming years, precision medicine approaches have the potential to enable treatments optimized based on an individual's tau strain, molecular subtype, and genetic risk profile; clustered regularly interspaced short palindromic repeat-based gene editing could permanently target familial MAPT mutations; and biomarker-guided screening programs could detect tau pathology before clinical symptoms emerge, transforming tauopathies from "untreatable" diseases into manageable chronic conditions.[101]

In conclusion, this review establishes that it is no longer scientifically valid to regard tauopathies as classical, homogeneous, late-diagnosed neurodegenerative diseases. Accumulating evidence from structural biology, genomics, epigenomics, multi-omics, and advanced imaging over the past decade demonstrates that tau pathology is a highly heterogeneous process, driven by isoform balance, conformational strain and fold diversity, PTM, LLPS, and cell-type-specific (neuronal and glial) biology. The MAPT genetic architecture, GWAS-defined polygenic risk networks, and epigenetic reprogramming elucidate how tau aggregation becomes a self-propagating pathology at the protein, cellular, and network levels. This molecular diversity underlies variations in clinical phenotypes and treatment responses, highlighting the need to replace the "one target-one therapy" paradigm with precision medicine guided by molecular subtypes. Next-generation strategies, including ASOs, conformation-specific immunotherapies, fold-targeted small molecules, and PROTACs, when combined with early and biomarker-based patient selection, represent the first interventions capable of genuinely modifying the natural course of tauopathies. Ultimately, tauopathies are redefined as manageable chronic neurodegenerative disorders, characterized by early diagnosis, genetic risk stratification, and molecularly guided combination therapies.

Author Contributions

E.D.U., S.S.Ç.: Concept and design, critical review; S.S.Ç.: Supervision, data collection and processing, analysis and interpretation, literature search; E.D.U.: Writing.

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