Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Pathological Insights into Neurodegenerative Diseases: Exploring Biomarkers and Diagnostic Innovations

Maram Mohammad Ahmad Basaad [1], Mssawed Ahmed Darrag [2], Sami Sand Al Otibi [3], Badreah Salman Aldhafeeri [4], Fayez Saleem Aldhafeeri [5], Mohammed Ibrahim Zuayr [6], Assaf Dwai Ghazi Alotibi [7], Amal Salman Alyahya [8], Muteb Hasir Hassani [9], Mariam Abdullah Alghamdi [10], Bidoor Sabr Al Anezi [11], Enas Abdu Yahya Yahya [12], Abdulkhalq Abdullah Alasmari [13], Yousef Obaid Wasel Alhejaili [14], Noramahmoud Ramdan [15]

[1] KSA, Ministry of Health, East Jeddah hospital
[2] KSA, Ministry of Health, abu arish hospital
[3] KSA, Ministry of Health, Ruwaydat Al-Ared General Hospital
[4] KSA, Ministry of Health, PHC ALBALDIYA Hafar AlBatin
[5] KSA, Ministry of Health, Central Blood Bank Hafar AlBatin
[6] KSA, Ministry of Health, King Fahad specialty hospital
[7] KSA, Ministry of Health, Dawadmi General Hospital
[8] KSA, Ministry of Health, King Fahd General Hospital in Jeddah
[9] KSA, Ministry of Health, King Fahd Central Hospital .jazan
[10] KSA, Ministry of Health, DIRIYAH HOSPITAL
[11] KSA, Ministry of Health, Sharg almohmadih cintr care.. Hafar Al-Batin
[12] KSA, Ministry of Health, PHC ALNJAMEAH JIZAN
[13] KSA, Ministry of Health, mohayel Genenral hospital
[14] KSA, Ministry of Health, Al Salam Waqf Hospital in Medina
[15] Ministry of Health, Abo El Reesh Children hospital

Abstract

Background: Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases, pose significant health challenges globally due to their chronic, progressive nature and severe impact on neurological function. Despite advances in symptom management, treatments remain insufficient in addressing underlying disease mechanisms. Molecular genetics has enabled critical insights into the molecular underpinnings of these diseases, with an emphasis on genetic mutations and biomarkers.

Aim: This article explores the genetic factors and biomarkers associated with neurodegenerative diseases, focusing on the role of amyloid-β, tau, and α-synuclein proteins. The aim is to examine how these proteins contribute to disease pathogenesis and how genetic research can lead to novel diagnostic and therapeutic innovations.

Methods: The review integrates research findings from molecular genetics, clinical studies, and recent advancements in neurodegenerative disease research. It examines the genetic variations and mutations in key genes, such as APP, PSEN1, and PSEN2, and their effects on disease onset and progression. The article also discusses biomarkers and diagnostic approaches, including genetic screening and protein identification.

Results: Key findings highlight the genetic underpinnings of Alzheimer's disease, particularly mutations in the APP, PSEN1, and PSEN2 genes. Variants like A673T and A673V show distinct effects on amyloid aggregation and neurodegeneration. Additionally, APOE's role in Alzheimer's pathogenesis is explored, emphasizing the differential effects of its isoforms on amyloid deposition and cognitive function. The article also underscores the importance of biomarkers in early diagnosis and personalized treatment strategies.

Conclusion: The research affirms that neurodegenerative diseases are heavily influenced by genetic factors, with specific mutations playing a pivotal role in their pathogenesis. Advancements in molecular genetics and biomarkers hold promise for developing targeted diagnostic tools and therapies. However, more research is needed to fully understand the complexity of these diseases and their treatment.

Keywords: neurodegenerative diseases, Alzheimer's disease, amyloid-β, tau proteins, genetic mutations, biomarkers, diagnostics, molecular genetics..

1. Introduction

Recent studies emphasize neurodegenerative illnesses as a primary contributor to disability and mortality globally. Progress in molecular genetics has accelerated significantly owing to technological advancements, an enhanced comprehension of disease causes, and evolving viewpoints on gene editing and its prospective benefits. The notion of genes is not a recent development of the 20th century. Aristotle postulated the existence of genetic components, proposing that maternal characteristics were encoded in menstrual blood, whereas paternal attributes were included in semen. Hippocrates proposed a theory that Charles Darwin subsequently aligned with his notion of "pangenesis" [1]. Substantial scientific advancements transpired centuries thereafter. The initial discovery occurred when Czech scientist Johann Gregor Mendel presented the concepts of

*Corresponding author e-mail: Mmbasaad@moh.gov.sa , (Maram Mohammad Ahmad Basaad).
Receive Date: 22 November 2024, Revise Date: 08 December 2024, Accept Date: 09 December 2024
DOI: 10.21608/ejchem.2024.338414.10854

"recessive, discrete, and dominant factors" via his hybridization studies on peas. Wilhelm von Waldeyer subsequently coined the term “Chromosomen,” expanding upon Theodor Boveri’s notion of “Chromatinelemente” [3]. In 1962, Francis Crick and James D. Watson were awarded the Nobel Prize in Physiology or Medicine for elucidating the molecular structure of nucleic acids. This pivotal finding clarified both molecular genetics and the fundamental aspects of life, encompassing DNA, RNA, and protein production. It further demonstrated that small nucleotide misalignments could interfere with protein synthesis, hence contributing to disease etiology.

Neurodegenerative diseases comprise a range of chronic and progressive conditions marked by protein deposits or misfoldings, leading to metabolic changes, functional deficits, and neuronal death in the brain and spinal cord. Although existing treatments can alleviate symptom progression and enhance illness management, they do not adequately address the fundamental reasons. Molecular genetics is essential for elucidating the mechanisms underlying these illnesses, facilitating the discovery of genes involved in their pathogenesis and promoting the advancement of more effective therapeutics [5]. Furthermore, molecular genetics has been essential in identifying certain proteins—namely amyloid-β, tau, α-synuclein, and prion proteins—that cluster within cells and trigger neurodegenerative diseases [4,6]. Every neurodegenerative illness has unique pathogenic processes and clinical manifestations. The most common illnesses, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and amyotrophic lateral sclerosis, are associated with particular hereditary variables. A common characteristic of these disorders is the accumulation of proteins, which modifies the physical and chemical properties of neurons, ultimately resulting in cellular malfunction and degeneration [4,7].

Alzheimer’s Disease (AD)

Alzheimer’s disease (AD) is the most prevalent neurodegenerative disorder, accounting for approximately 70% of all dementia cases [7]. The condition was first documented in 1901 by Alois Alzheimer, who observed a 51-year-old woman exhibiting symptoms such as sleep disturbances, memory deficits, and increasing disorientation. Post-mortem analysis revealed the presence of neurofibrillary tangles, composed of hyperphosphorylated tau proteins, and neuritic plaques, formed by aggregated beta-amyloid peptides. These findings led Alzheimer to conclude that the disease results from the accumulation of these pathological structures [8]. According to Gatz et al., environmental factors can influence the likelihood of developing AD in individuals with genetic predispositions [9]. For over three decades, the amyloid cascade hypothesis dominated the understanding of AD pathophysiology, focusing on beta-amyloid formation. However, recent research emphasizes the involvement of additional systems, such as the glymphatic system and receptor for advanced glycation end products (RAGE), offering a more comprehensive perspective on the disease's complexity [10].

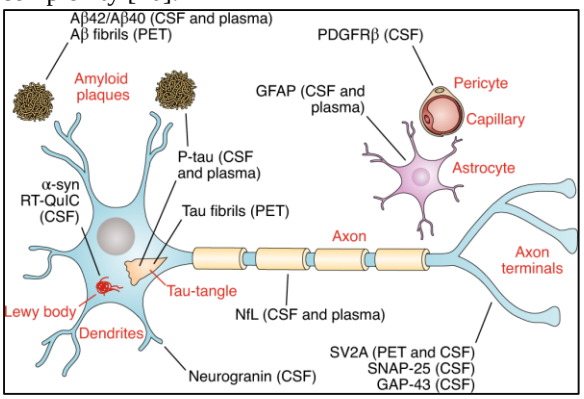

Figure 1: Markers of Neurodegenerative Disorders.

Amyloid Precursor Protein (APP)

The genetic basis of Alzheimer's disease (AD) mainly includes mutations in the amyloid precursor protein (APP) gene, linked to autosomal dominant inheritance and early-onset AD. APP is processed by two separate pathways: the amyloidogenic route and the non-amyloidogenic pathway. In the latter case, APP is cleaved by alpha and gamma secretases [13]. The amyloidogenic route, in contrast, entails cleavage by beta and gamma secretases, resulting in the production of beta-amyloid peptides such as Aβ38, Aβ40, and Aβ42, with Aβ42 exhibiting the lowest solubility and highest propensity for aggregation [14,15].

The APP gene, situated on chromosome 21, is significantly associated with the heightened risk of early-onset Alzheimer's disease in individuals with trisomy 21. In 2012, a study by Jonsson et al. revealed the Icelandic A673T variant (rs63750847), which diminishes the aggregation and generation of Aβ40 and Aβ42 by approximately 40%, consequently reducing the risk of Alzheimer's disease and age-related cognitive decline [17,18]. Subsequent research in 2014, encompassing 2,641 Chinese people, discovered no evidence of this mutation within the study group, indicating community-specific genetic variability [19]. A 2015 study with 3,487 Danish respondents revealed the mutation in only one individual (0.014%), in contrast to its prevalence of 0.43% in Nordic populations [20]. The A673V mutation, linked to early-onset Alzheimer's disease in homozygous individuals, displays a unique clinical pattern. In contrast to other familial variants of Alzheimer's disease, which predominantly affect amyloid deposits in the striatum, this mutation largely impacts the cerebellum [21,22].

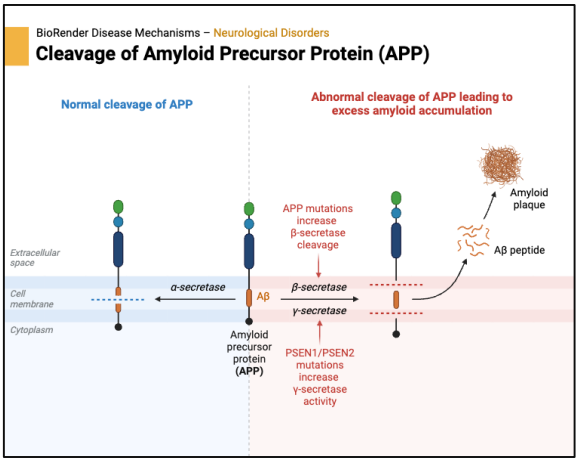

Figure 2: Amyloid Precursor Protein.

Mutations in the APP gene, particularly the E693 series in exon 17, may either increase susceptibility to or confer protection against Alzheimer's disease. Significant mutations comprise E693Q (Dutch), E693del (Osaka), E693K (Italian), and E693G (Arctic), each of which modifies the 22nd amino acid of Aβ to create E22 variations. The E693Q mutation results in the E22Q peptide, linked to hereditary cerebral hemorrhage with amyloidosis (HCHWA-D), which is marked by recurrent strokes and dementia caused by amyloid deposition in cerebral artery walls, resulting in cerebral amyloid angiopathy [23-25]. The E693del mutation produces the E22Δ peptide, which intensifies endoplasmic reticulum stress and stimulates glial fibrillary acidic protein (GFAP) expression, hence associating the mutation with glymphatic system impairment [26,27]. Although E22Δ generates less amyloid deposits, these deposits exhibit greater resistance to proteolysis, as demonstrated in a 2008 study [28]. McKnelly et al. conducted additional investigation demonstrating that E22 peptides disrupt cell membranes, with cytotoxicity escalating in relation to their positive charge. Among these peptides, E22Δ (two positive charges) exhibits the lowest cytotoxicity, whereas E22K (four positive charges) from the Italian mutation demonstrates the worst detrimental effect on cellular integrity [29].

Presenilin1:

Presenilin1, an integral component of the γ-secretase complex, is encoded by the PSEN1 gene, located on chromosome 14q24.3 [34]. Variations in the nucleotide sequence of this gene account for approximately 70–80% of autosomal dominant Alzheimer's disease cases [35,36]. Mutations in PSEN1 disrupt γ-secretase activity, favoring the production of Aβ42 over Aβ40, leading to the pathological accumulation of Aβ42 [37]. However, some researchers suggest that increased amyloid production alone may not fully explain the link between presenilin mutations and Alzheimer's disease, with alternative theories implicating roles in memory, learning, and neuronal survival, as evidenced by mouse studies [38]. Specific mutations on exon 4 of the PSEN1 gene, such as A79V, M84V, and L85P, demonstrate varying effects. A79V is a dominant mutation that raises the Aβ42-to-Aβ40 ratio by suppressing Aβ40 production [39,40], while M84V leads to multiple atrophies, including temporal, frontal, cerebellar, and cortical, by increasing Aβ42 levels [42,43]. Another mutation, L85P, enhances the Aβ42-to-Aβ40 ratio and also increases Aβ43 production, with pathological aggregations observed in the basal ganglia and cortex [44,45]. Additionally, the Int4del mutation (L113_l114insT), located in the splice region following exon 4, generates aberrant transcripts, including one encoding a PSEN1 protein with an extra threonine. This mutation alters amyloid production by reducing Aβ40 and Aβ38 levels while increasing the Aβ42-to-Aβ40 ratio [46–48]. Mutations in other exons also contribute to Alzheimer's pathology. The M139V mutation on exon 5 increases Aβ42 and Aβ43 levels while reducing Aβ40, Aβ38, and Aβ37, though clinical and morphological changes are subtle [49,50]. Similarly, the S212Y mutation on exon 7 is neuropathologically consistent with typical Alzheimer's disease, characterized by neurofibrillary tangles and neuritic plaques [51]. Furthermore, the A434C mutation is associated with amyloid and plaque deposits in the neocortex, hippocampus, and amygdala, accompanied by gliosis. This mutation alters the γ-secretase interaction, resulting in elevated Aβ42 production [52,53].

Presenilin2:

Presenilin2, also part of the γ-secretase complex, is encoded by the PSEN2 gene, which is located on chromosome 1q42.13 and contains 12 exons [53]. While mutations in presenilin genes are often linked to early-onset Alzheimer's disease, not all PSEN2 variations cause AD. For example, the K82fs mutation on exon 5, identified in a Belgian patient with frontotemporal dementia, reduces presenilin2 levels in the hippocampus and frontal cortex, and is associated with Pick's disease rather than Alzheimer's [54]. Another notable mutation, c.*71C>A, occurs on exon 13 in the untranslated region (3'UTR) and interferes with miR-183-5p binding, inhibiting its suppressive function. This mutation is linked to a higher Aβ42-to-Aβ40 ratio and hippocampal atrophy, making it relevant for Alzheimer's diagnostics [55,56]. The M239V mutation, discovered in 1995 on exon 8, has been definitively associated with early-onset Alzheimer's disease. Autopsies of affected individuals reveal hallmark beta-amyloid deposits and tau neurofibrillary tangles [57].

Apolipoprotein E

Early-onset Alzheimer's disease (AD) accounts for about 1–2% of all AD cases, although the majority of documented genetic occurrences are linked to mutations in APOE (apolipoprotein E). This glycoprotein, consisting of 299 amino acids, is primarily produced in the central nervous system (CNS) by diverse glial cells, such as microglia,

astrocytes, choroid plexus cells, mural vascular cells, and neurons damaged by stress. APOE is highly expressed in both central and peripheral regions; nevertheless, the blood-brain barrier (BBB) maintains the separation of these pools. Comprehending the functions of these distinct pools is essential for investigating Alzheimer's disease pathogenesis and recognizing treatment prospects. APOE is predominantly synthesized in the liver, where it aids in the redistribution and metabolism of lipids, including triglycerides, cholesterol, cholesteryl esters, and phospholipids, through lipoprotein particles. APOE isoforms exhibit varying affinities for these particles: APOE4 is more associated with triglyceride-rich lipoproteins, whereas APOE2 and APOE3 favor high-density lipoproteins (HDLs) [59].

APOE-mediated lipid transport is essential for central nervous system repair and development. For example, APOE3 facilitates neurite outgrowth more efficiently than APOE4, highlighting its dominance in astrocytes. APOE4 is associated with structural abnormalities in neurons, reduced expression of synaptic proteins, and compromised glutamatergic signaling essential for neuronal plasticity and network integrity. The effects of APOE differ by cell type, as it is expressed under various conditions by astrocytes, microglia, oligodendrocytes, and pericytes. To comprehend APOE's impact in the brain, it is crucial to examine its structure, lipidation status, and metabolic characteristics across distinct cell types [60]. Research underscores the crucial function of APOE in Alzheimer's disease through its interaction with amyloid-beta (Aβ) protein. APOE co-deposits with Aβ in amyloid plaques, directly influencing the risk of Alzheimer's disease. Research using mice indicates that the deletion of APOE modifies Aβ plaque shape, highlighting its significance in fibrillization and amyloid accumulation. The isoform-specific effects of APOE on amyloid pathology are well-established: APOE4 enhances Aβ aggregation and deposition relative to APOE3, whereas APOE2 correlates with delayed deposition, reduced pathology, and cognitive protection [61]. Moreover, APOE4 stabilizes soluble cytotoxic Aβ fragments and promotes fibrillogenesis, accelerating amyloid disease. This interaction presents a possible therapeutic target in the initial stages of amyloid disease progression [62,63]. APOE facilitates Aβ elimination via receptor-mediated pathways and proteolytic degradation. Neuronal LRP1 receptors promote the uptake of Aβ/APOE complexes; however, APOE4 carriers demonstrate compromised clearance due to diminished complex stability. Furthermore, APOE4 is inferior to APOE2 and APOE3 in proteolytic degradation, resulting in diminished Aβ clearance overall [64].

APOE and Tau

Neurofibrillary tangles (NFTs), defined by hyperphosphorylated tau clumps, are a hallmark of Alzheimer's disease pathogenesis. Research indicates that APOE4 carriers exhibit elevated tau phosphorylation rates compared to individuals with APOE2 or APOE3, especially in the presence of Aβ oligomers. PET imaging of APOE4 carriers reveals increased tau accumulation regardless of the presence of amyloid plaques. Moreover, APOE4 has demonstrated a greater efficacy in promoting tau phosphorylation and neuronal mortality compared to APOE3 in induced pluripotent stem cell cultures. Animal models validate these findings, revealing elevated total and phosphorylated tau levels in APOE4 carriers, which intensify tau-related neurotoxicity through microglial activation [65]. Notably, the elimination of astrocytic APOE4 mitigates tau-related synaptic degeneration and the production of disease-associated genes, providing a safeguard against microglial phagocytosis. APOE2 has been associated with heightened tau aggregation via the development of tau/APOE complexes, potentially attributable to non-lipidated APOE2 [66]. Genome-wide association studies indicate that APOE2 reduces Alzheimer's disease risk by influencing protein phosphatase 2A (PP2A), a crucial tau phosphatase, in contrast to the harmful effects of APOE4 [67]. Moreover, APOE isoforms affect tauopathies beyond Alzheimer's disease, encompassing frontotemporal dementia and chronic traumatic encephalopathy. APOE4 carriers with FTD exhibit earlier onset of tau pathology and more significant cognitive deterioration than non-APOE4 carriers. Mechanistically, APOE interacts with tau areas implicated in NFT production, exhibiting isoform-specific effects. APOE3 exhibits a greater tau-binding affinity, whereas the diminished binding of APOE4 is associated with heightened GSK3-mediated tau hyperphosphorylation and the production of neurofibrillary tangles. Current research seeks to clarify these pathways to enhance understanding of APOE's involvement in tau etiology and to formulate focused treatment methods.

APOE and Neuroinflammation

Recent studies emphasize neuroinflammation as a crucial element in dementia, with APOE significantly influencing inflammatory mechanisms. APOE plays a role in the etiology of Alzheimer’s disease (AD) through many routes that intersect with neuroinflammatory processes. Microglia, the brain's immune cells, aggregate around amyloid plaques and engage in their clearance while coordinating inflammatory responses. Investigations utilizing APOE-deficient mice demonstrate less microglial activation in reaction to amyloid accumulation, signifying the essential role of APOE in facilitating appropriate microglial activation. Moreover, disease-associated microglia (DAM) or microglial neurodegenerative (MGnD) phenotypes regularly exhibit APOE as a regulatory factor. APOE isoforms differentially affect microglial activity; APOE3 provokes more vigorous microglial responses to

amyloid-beta (Aβ) compared to APOE4. This differentiation pertains to the interaction between APOE and Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), with binding affinity contingent upon the APOE isoform and lipidation status. The diminished affinity and lipidation state of APOE4 may hinder homeostatic microglial responses, hence exacerbating its attenuated anti-inflammatory function. Moreover, APOE regulates systemic inflammatory indicators such as C-reactive protein (CRP). APOE4 carriers demonstrate diminished cerebrospinal fluid (CSF) CRP levels while exhibiting elevated serum CRP levels, which correlates with a higher prevalence of Alzheimer's disease (AD). Longitudinal studies indicate that APOE, rather than CRP, primarily affects cognitive decline, implying that APOE4 carriers have atypical immunological responses associated with neurodegeneration. These findings highlight the therapeutic potential of targeting APOE-mediated inflammatory pathways in Alzheimer's disease.

Important APOE Mutations Involved in AD Onset

c.-488C>A: This mutation, located in the APOE promoter region, disrupts binding sites for the transcription factor EGR1, potentially affecting APOE regulation. Its biological significance remains unclear but is linked to the HuD protein functional domain, which regulates neuronal-like cells.

c.-24+38G>A: Identified in Southern Chinese individuals, this rare mutation is most prevalent among East Asians. Its frequency in the global population is 0.00033, with higher detection in East Asian populations, though its role in AD pathogenesis requires further exploration.

c.-24+288G>A: This variant is more common in individuals of East Asian ancestry, with a frequency of 0.015 in East Asian populations compared to 0.00016 globally. Its presence in AD and mild cognitive impairment (MCI) cases suggests a possible but unconfirmed link to neurodegenerative processes.

c.-23-377A>G: This mutation appears more frequently in East Asian individuals and is associated with AD, MCI, and healthy controls. Its global prevalence is 0.00073, but it exhibits significantly higher incidence in East Asian populations.

A18T: This mutation, found in APOE's signal peptide, disrupts secretory efficiency, potentially impairing APOE function. Detected in Southern Chinese individuals, its association with AD and MCI suggests clinical relevance, particularly in East Asian populations. These findings highlight APOE's genetic complexity and its isoform- and mutation-specific contributions to AD onset and progression, warranting further investigation into its therapeutic potential.

Microtubule-Associated Protein Tau and Its Role in Neurodegeneration

The discovery that mutations in the microtubule-associated protein tau (MAPT) gene cause frontotemporal dementia with parkinsonism linked to chromosome 17 (FTLD-17) underscored the critical role of tau dysfunction in neurodegeneration. Unlike Alzheimer's disease (AD), where Aβ plays a prominent role, tau pathology alone can drive neurodegeneration, broadening its relevance to various central nervous system disorders, including Pick's disease, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and argyrophilic grain disease. This highlights tau as a potential therapeutic target not only for AD but for numerous tauopathies.

Tau Isoforms and Post-Translational Modifications

The human brain expresses six isoforms of tau, generated via alternative splicing of the MAPT gene on chromosome 17q21. These isoforms differ based on the inclusion of zero, one, or two N-terminal inserts (0N, 1N, 2N) and the presence of three or four microtubule-binding repeats (3R or 4R). Healthy brains maintain a balance between 3R and 4R tau. However, in tauopathies such as FTLD-17, mutations near exon 10 skew this ratio, favoring 4R tau, which interacts more strongly with microtubules and contributes to pathological aggregation. Tau undergoes various post-translational modifications (PTMs) that regulate its function and stability. Among these, phosphorylation is the most extensively studied and is particularly relevant in neurodegenerative diseases. While tau is normally phosphorylated at 2–3 residues, hyperphosphorylation, involving up to 9–10 residues, is a hallmark of AD and related tauopathies. This modification reduces tau's affinity for microtubules, impairs degradation pathways, and promotes the formation of neurofibrillary tangles (NFTs). Other PTMs, such as glycosylation, ubiquitination, nitration, and oxidation, further contribute to tau dysfunction.

Mechanisms of Tau Hyperphosphorylation

Hyperphosphorylation of tau results from an imbalance between tau kinases (e.g., GSK-3β, CDK5, PKA, MAPK) and phosphatases (primarily PP2A). This imbalance may be driven by factors such as Aβ toxicity, impaired glucose metabolism, inflammation, and infections. Hyperphosphorylated tau not only aggregates into NFTs but also disrupts cytoskeletal integrity, leading to neuronal dysfunction and cell death. Immunocytochemical studies have revealed that hyperphosphorylated tau accumulates in neurons before NFT formation, suggesting that it is an early pathological event in AD.

Conformational Changes and Pathological Aggregation

Tau undergoes conformational changes in diseased brains, making it more susceptible to phosphorylation and aggregation. Monoclonal antibody studies have demonstrated these conformational changes in both AD patients and transgenic mouse models overexpressing human tau. In FTLD-17, certain tau mutations directly enhance its phosphorylation by brain kinases. However, in AD, hyperphosphorylation likely arises from broader

dysregulation of phosphorylation-dephosphorylation processes, affecting other neuronal proteins, including tubulin and neurofilaments.

Therapeutic Implications

Given its central role in neurodegeneration, tau represents a promising therapeutic target. Strategies to restore kinase-phosphatase balance, prevent tau aggregation, or enhance its clearance are being explored. Understanding the pathways governing tau PTMs may lead to novel interventions for AD and related tauopathies, offering hope for conditions with limited treatment options.

Important MAPT Mutations Involved in AD Onset

MAPT IVS10+12 C>T

This mutation, discovered in the Kumamoto pedigree—a Japanese family with frontotemporal dementia—presents with parkinsonism and dementia typically manifesting in the fifth decade of life, with an average onset age of 53 years and a seven-year illness duration. Affected individuals exhibited elevated exon 10 tau transcripts and 4R tau isoforms, with aggregates in neurons and glial cells. The hyperphosphorylated 4R tau formed twisted ribbon-like filaments. Yasuda et al. [84] and Takamatsu et al. [85] provided neuropathological insights, confirming tau's role in neurodegeneration through exon 10 involvement.

MAPT A152T

The A152T variant is associated with an increased risk of dementia with Lewy bodies (DLB) but not Parkinson's disease (PD). This mutation affects tau's ability to bind microtubules, leading to impaired assembly and stability. Patients display abnormal tau accumulation, with diverse neuropathologies such as Lewy body pathology and prominent neuronal loss with tau deposition in subcortical regions. Mutant tau shows a higher propensity for oligomer formation and greater vulnerability to proteolysis. Studies using iPSCs confirm increased tau pathology in A152T carriers [86][87][88].

MAPT K257T

Autopsy analysis revealed Pick's disease, a subtype of frontotemporal dementia (FTD), characterized by severe frontotemporal atrophy, particularly in the temporal lobes. Involved regions showed numerous tau-positive Pick bodies, with diffuse hyperphosphorylated tau detected in cell bodies. Recombinant tau protein with the K257T mutation displayed reduced capacity to facilitate microtubule assembly [89].

MAPT L266V

Kobayashi et al. [90] reported a case of severe frontotemporal atrophy with Pick-like pathology, including prominent atrophy in the frontal, temporal cortices, and caudate nucleus. Extensive tau-positive inclusions were found in neurons and astrocytes throughout the cortical layers and brainstem. Another case reported by Hogg et al. [91] also demonstrated significant atrophy and tau-positive inclusions, with findings across various brain regions. This mutation alters exon 10 splicing, leading to higher levels of 4R tau and decreased microtubule assembly efficiency, with 3R tau isoforms more likely to assemble than their 4R counterparts.

Conclusion:

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases, continue to present considerable challenges in terms of diagnosis and treatment. These conditions are primarily characterized by the gradual loss of neuronal function due to protein misfolding and accumulation. Research into the genetic basis of these diseases has advanced considerably, providing essential insights into their pathophysiology. The role of genetic mutations in genes such as amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) is crucial in understanding the onset and progression of Alzheimer's disease (AD). Mutations in these genes, along with the interaction of specific proteins like amyloid-β and tau, contribute to the formation of neurofibrillary tangles and amyloid plaques, hallmarks of AD. The discovery of genetic variations, such as the Icelandic A673T and A673V mutations, has provided valuable data on how these mutations influence the aggregation and toxicity of amyloid-β peptides. Notably, these mutations appear to reduce the risk of AD and age-related cognitive decline by altering the amyloid aggregation process. Furthermore, mutations in the PSEN1 gene, which disrupt γ-secretase activity, lead to the preferential accumulation of the toxic amyloid-β42, further compounding the neurodegenerative process. These insights not only deepen our understanding of the disease but also open new avenues for potential therapeutic interventions that could target the underlying genetic causes of AD. Moreover, the role of apolipoprotein E (APOE), particularly the APOE4 allele, has been well-documented in increasing the risk of Alzheimer's disease by promoting amyloid plaque formation. APOE4's effect on amyloid aggregation and neuronal damage underscores its importance as a biomarker in Alzheimer's diagnostics. However, research suggests that APOE isoforms interact differently with amyloid, and the protective effects of APOE2 highlight the potential for developing interventions that could mimic these protective mechanisms. The potential for using biomarkers in the early detection of neurodegenerative diseases cannot be overstated. Advances in molecular diagnostics, including genetic screening and protein identification, hold the promise of enabling early intervention before irreversible damage occurs. Furthermore, understanding the genetic underpinnings of neurodegenerative diseases paves the way for personalized treatment approaches, targeting specific mutations and protein deposits. In conclusion, while

significant progress has been made in unraveling the genetic and molecular mechanisms underlying neurodegenerative diseases, further research is essential. Understanding how genetic mutations contribute to disease progression will be critical in developing more effective therapies and improving early diagnosis. As molecular genetics continues to evolve, it is expected that future research will not only identify novel biomarkers but also lead to breakthroughs in gene-editing technologies and personalized medicine, offering hope for better management and potential cures for these devastating conditions.

References:

1. Berry, R.M. The genetic revolution and the physician's duty of confidentiality: The role of the old Hippocratic virtues in the regulation of the new genetic intimacy. *BMJ* **1997**, *18*, 401–441.
2. De Castro, M. Johann Gregor Mendel: Paragon of experimental science. *Mol. Genet. Genom. Med.* **2016**, *4*, 3–8.
3. Saceleanu, V.M.; Mohan, A.G.; Covache-Busuioc, R.A.; Costin, H.P.; Ciurea, A.V. Wilhelm von Waldeyer: Important Steps in Neural Theory, Anatomy and Citology. *Brain Sci.* **2022**, *12*, 224.
4. Kovacs, G.G. Concepts and classification of neurodegenerative diseases. In *Handbook of Clinical Neurology*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 301–307.
5. Brettschneider, J.; Del Tredici, K.; Lee, V.M.-Y.; Trojanowski, J.Q. Spreading of pathology in neurodegenerative diseases: A focus on human studies. *Nat. Rev. Neurosci.* **2015**, *16*, 109–120.
6. Guo, J.L.; Lee, V.M.Y. Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases. *Nat. Med.* **2014**, *20*, 130–138.
7. Castellani, R.J.; Rolston, R.K.; Smith, M.A. Alzheimer Disease. *Disease-a-Month* **2010**, *56*, 484–546.
8. Ciurea, V.A.; Covache-Busuioc, R.-A.; Mohan, A.G.; Costin, H.P.; Voicu, V.; Academy, B.R. Alzheimer's disease: 120 years of research and progress. *J. Med. Life* **2023**, *16*, 173–177.
9. Gatz, M.; Reynolds, C.A.; Fratiglioni, L.; Johansson, B.; Mortimer, J.A.; Berg, S.; Fiske, A.; Pedersen, N.L. Role of Genes and Environments for Explaining Alzheimer Disease. *Arch. Gen. Psychiatry* **2006**, *63*, 168–174.
10. An, F.; Zhao, R.; Xuan, X.; Xuan, T.; Zhang, G.; Wei, C. Calycosin ameliorates advanced glycation end product-induced neurodegenerative changes in cellular and rat models of diabetes-related Alzheimer's disease. *Chem. Interact.* **2022**, *368*, 110206.
11. Van Cauwenberghe, C.; Van Broeckhoven, C.; Sleegers, K. The genetic landscape of Alzheimer disease: Clinical implications and perspectives. *Anesth. Analg.* **2016**, *18*, 421–430.
12. Roberts, S.; Ripellino, J.; Ingalls, K.; Robakis, N.; Felsenstein, K. Non-amyloidogenic cleavage of the beta-amyloid precursor protein by an integral membrane metalloendopeptidase. *J. Biol. Chem.* **1994**, *269*, 3111–3116.
13. Gao, C.-X.; Wu, Q.; Sun, J.-X.; Song, X.-H.; Wang, J.; Xiong, C.-Q.; Teng, F.-X. Blocking beta 2-adrenergic receptor inhibits dendrite ramification in a mouse model of Alzheimer's disease. *Neural Regen. Res.* **2017**, *12*, 1499–1506.
14. Okochi, M.; Tagami, S.; Yanagida, K.; Takami, M.; Kodama, T.S.; Mori, K.; Nakayama, T.; Ihara, Y.; Takeda, M. γ-Secretase Modulators and Presenilin 1 Mutants Act Differently on Presenilin/γ-Secretase Function to Cleave Aβ42 and Aβ43. *Cell Rep.* **2013**, *3*, 42–51.
15. Hampel, H.; Hu, Y.; Hardy, J.; Blennow, K.; Chen, C.; Perry, G.; Kim, S.H.; Villemagne, V.L.; Aisen, P.; Vendruscolo, M.; et al. The amyloid-β pathway in Alzheimer's disease: A plain language summary. *Neurodegener. Dis. Manag.* **2023**, *13*, 141–201.
16. Tosh, J.L.; Rhymes, E.R.; Mumford, P.; Whittaker, H.T.; Pulford, L.J.; Noy, S.J.; Cleverley, K.; Strydom, A.; Fisher, E.M.C.; Wiseman, F.K.; et al. Genetic dissection of down syndrome-associated alterations in APP/amyloid-β biology using mouse models. *Sci. Rep.* **2021**, *11*, 5736.
17. Jonsson, T.; Atwal, J.K.; Steinberg, S.; Snaedal, J.; Jonsson, P.V.; Bjornsson, S.; Stefansson, H.; Sulem, P.; Gudbjartsson, D.F.; Maloney, J.; et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature* **2012**, *488*, 96–99.
18. Benilova, I.; Gallardo, R.; Ungureanu, A.-A.; Cano, V.C.; Snellinx, A.; Ramakers, M.; Bartic, C.; Rousseau, F.; Schymkowitz, J.; De Strooper, B. The Alzheimer Disease Protective Mutation A2T Modulates Kinetic and Thermodynamic Properties of Amyloid-β (Aβ) Aggregation. *J. Biol. Chem.* **2014**, *289*, 30977–30989.
19. Liu, Y.-W.; He, Y.-H.; Zhang, Y.-X.; Cai, W.-W.; Yang, L.-Q.; Xu, L.-Y.; Kong, Q.-P. Absence of A673T variant in APP gene indicates an alternative protective mechanism contributing to longevity in Chinese individuals. *Neurobiol. Aging* **2014**, *35*, 935.e11–935.e12.
20. Mengel-From, J.; Jeune, B.; Pentti, T.; McGue, M.; Christensen, K.; Christiansen, L. The APP A673T frequency differs between Nordic countries. *Neurobiol. Aging* **2015**, *36*, 2909.e1–2909.e4.
21. Giaccone, G.; Morbin, M.; Moda, F.; Botta, M.; Mazzoleni, G.; Uggetti, A.; Catania, M.; Moro, M.L.; Redaelli, V.; Spagnoli, A.; et al. Neuropathology of the recessive A673V APP mutation: Alzheimer disease with distinctive features. *Acta Neuropathol.* **2010**, *120*, 803–812.

22. Villemagne, V.L.; Ataka, S.; Mizuno, T.; Brooks, W.S.; Wada, Y.; Kondo, M.; Jones, G.; Watanabe, Y.; Mulligan, R.S.; Nakagawa, M.; et al. High Striatal Amyloid β-Peptide Deposition Across Different Autosomal Alzheimer Disease Mutation Types. *Arch. Neurol.* **2009**, *66*, 1537–1544.
23. Readhead, B.; Haure-Mirande, J.-V.; Zhang, B.; Haroutunian, V.; Gandy, S.; Schadt, E.E.; Dudley, J.T.; Ehrlich, M.E. Molecular systems evaluation of oligomerogenic APPE693Q and fibrillogenic APPKM670/671NL/PSEN1Δexon9 mouse models identifies shared features with human Alzheimer's brain molecular pathology. *Mol. Psychiatry* **2016**, *21*, 1099–1111.
24. Natté, R.; Maat-Schieman, M.L.C.; Haan, J.; Bornebroek, M.; Roos, R.A.; Van Duinen, S.G. Dementia in hereditary cerebral hemorrhage with amyloidosis-Dutch type is associated with cerebral amyloid angiopathy but is independent of plaques and neurofibrillary tangles. *Ann. Neurol.* **2001**, *50*, 765–772.
25. Nishitsuji, K.; Tomiyama, T.; Ishibashi, K.; Kametani, F.; Ozawa, K.; Okada, R.; Maat-Schieman, M.L.; Roos, R.A.; Iwai, K.; Mori, H. Cerebral vascular accumulation of Dutch-type Aβ42, but not wild-type Aβ42, in hereditary cerebral hemorrhage with amyloidosis, Dutch type. *J. Neurosci. Res.* **2007**, *85*, 2917–2923.
26. Uddin, M.S.; Tewari, D.; Sharma, G.; Kabir, M.T.; Barreto, G.E.; Bin-Jumah, M.N.; Perveen, A.; Abdel-Daim, M.M.; Ashraf, G.M. Molecular Mechanisms of ER Stress and UPR in the Pathogenesis of Alzheimer's Disease. *Mol. Neurobiol.* **2020**, *57*, 2902–2919.
27. Alberdi, E.; Wyssenbach, A.; Alberdi, M.; Sánchez-Gómez, M.V.; Cavaliere, F.; Rodríguez, J.J.; Verkhratsky, A.; Matute, C. Ca^{2+}-dependent endoplasmic reticulum stress correlates with astrogliosis in oligomeric amyloid β-treated astrocytes and in a model of Alzheimer's disease. *Aging Cell* **2013**, *12*, 292–302.
28. Tomiyama, T.; Nagata, T.; Shimada, H.; Teraoka, R.; Fukushima, A.; Kanemitsu, H.; Takuma, H.; Kuwano, R.; Imagawa, M.; Ataka, S.; et al. A new amyloid β variant favoring oligomerization in Alzheimer's-type dementia. *Ann. Neurol.* **2008**, *63*, 377–387.
29. McKnelly, K.J.; Kreutzer, A.G.; Howitz, W.J.; Haduong, K.; Yoo, S.; Hart, C.; Nowick, J.S. Effects of Familial Alzheimer's Disease Mutations on the Assembly of a β-Hairpin Peptide Derived from $Aβ_{16–36}$. *Biochemistry* **2022**, *61*, 446–454.
30. Paik, Y.K.; Chang, D.J.; Reardon, C.A.; Walker, M.D.; Taxman, E.; Taylor, J.M. Identification and characterization of transcriptional regulatory regions associated with expression of the human apolipoprotein E gene. *J. Biol. Chem.* **1988**, *263*, 13340–13349.
31. Maloney, B.; Ge, Y.-W.; Alley, G.M.; Lahiri, D.K. Important differences between human and mouse APOE gene promoters: Limitation of mouse APOE model in studying Alzheimer's disease. *J. Neurochem.* **2007**, *103*, 1237–1257.
32. Yee, A.; Tsui, N.B.; Kwan, R.Y.; Leung, A.Y.; Lai, C.K.; Chung, T.; Lau, J.Y.; Fok, M.; Dai, D.L.; Lau, L.-T. Apolipoprotein E Gene Revisited: Contribution of Rare Variants to Alzheimer's Disease Susceptibility in Southern Chinese. *Curr. Alzheimer Res.* **2021**, *18*, 67–79.
33. Zhou, Y.; Mägi, R.; Milani, L.; Lauschke, V.M. Global genetic diversity of human apolipoproteins and effects on cardiovascular disease risk. *J. Lipid Res.* **2018**, *59*, 1987–2000.
34. Saunders, A.M. Gene identification in Alzheimer's disease. *Pharmacogenomics* **2001**, *2*, 239–249.
35. Theuns, J.; Del-Favero, J.; Dermaut, B.; van Duijn, C.M.; Backhovens, H.; Broeck, M.V.D.; Serneels, S.; Corsmit, E.; Van Broeckhoven, C.; Cruts, M. Genetic variability in the regulatory region of presenilin 1 associated with risk for Alzheimer's disease and variable expression. *Hum. Mol. Genet.* **2000**, *9*, 325–331.
36. Cruts, M.; Theuns, J.; Van Broeckhoven, C. Locus-specific mutation databases for neurodegenerative brain diseases. *Hum. Mutat.* **2012**, *33*, 1340–1344.
37. Sun, L.; Zhou, R.; Yang, G.; Shi, Y. Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of Aβ42 and Aβ40 peptides by γ-secretase. *Proc. Natl. Acad. Sci. USA* **2016**, *114*, E476–E485.
38. Wines-Samuelson, M.; Schulte, E.C.; Smith, M.J.; Aoki, C.; Liu, X.; Kelleher, R.J.; Shen, J. Characterization of Age-Dependent and Progressive Cortical Neuronal Degeneration in Presenilin Conditional Mutant Mice. *PLoS ONE* **2010**, *5*, e10195.
39. Kauwe, J.S.K.; Jacquart, S.; Chakraverty, S.; Wang, J.; Mayo, K.; Fagan, A.M.; Holtzman, D.M.; Morris, J.C.; Goate, A.M. Extreme cerebrospinal fluid amyloid β levels identify family with late-onset Alzheimer's disease presenilin 1 mutation. *Ann. Neurol.* **2007**, *61*, 446–453.
40. Kumar-Singh, S.; Theuns, J.; Van Broeck, B.; Pirici, D.; Vennekens, K.; Corsmit, E.; Cruts, M.; Dermaut, B.; Wang, R.; Van Broeckhoven, C. Mean age-of-onset of familial alzheimer disease caused by presenilin mutations correlates with both increased Aβ42 and decreased Aβ40. *Hum. Mutat.* **2006**, *27*, 686–695.
41. Koriath, C.; Kenny, J.; Adamson, G.; Druyeh, R.; Taylor, W.; Beck, J.; Quinn, L.; Mok, T.H.; Dimitriadis, A.; Norsworthy, P.; et al. Predictors for a dementia gene mutation based on gene-panel next-generation sequencing of a large dementia

referral series. *Mol. Psychiatry* **2020**, *25*, 3399–3412.
42. Gallo, M.; Frangipane, F.; Cupidi, C.; De Bartolo, M.; Turone, S.; Ferrari, C.; Nacmias, B.; Grimaldi, G.; Laganà, V.; Colao, R.; et al. The novel PSEN1 M84V mutation associated to frontal dysexecutive syndrome, spastic paraparesis, and cerebellar atrophy in a dominant Alzheimer's disease family. *Neurobiol. Aging* **2017**, *56*, 213.e7–213.e12.
43. Hsu, S.; Gordon, B.A.; Hornbeck, R.; Norton, J.B.; Levitch, D.; Louden, A.; Ziegemeier, E.; Laforce, R., Jr.; Chhatwal, J.; Day, G.S.; et al. Discovery and validation of autosomal dominant Alzheimer's disease mutations. *Alzheimers Res. Ther.* **2018**, *10*, 67.
44. Kakuda, N.; Takami, M.; Okochi, M.; Kasuga, K.; Ihara, Y.; Ikeuchi, T. Switched Aβ43 generation in familial Alzheimer's disease with presenilin 1 mutation. *Transl. Psychiatry* **2021**, *11*, 558.]
45. López-García, S.; Jiménez-Bonilla, J.; Delgado, A.L.; Balaguer, P.O.; Ceberio, J.I.; Marraco, I.B.; Rodríguez, E.R.; Sánchez-Juan, P. A Rare PSEN1 (Leu85Pro) Mutation Causing Alzheimer's Disease in a 29-Year-Old Woman Presenting as Corticobasal Syndrome. *J. Alzheimers Dis.* **2019**, *70*, 655–658.
46. Arber, C.; Llerena, C.V.; Toombs, J.; Pocock, J.M.; Ryan, N.S.; Fox, N.C.; Zetterberg, H.; Hardy, J.; Wray, S. Amyloid precursor protein processing in human neurons with an allelic series of the PSEN1 intron 4 deletion mutation and total presenilin-1 knockout. *Brain Commun.* **2019**, *1*, fcz024.
47. De Jonghe, C.; Cruts, M.; Rogaeva, E.A.; Tysoe, C.; Singleton, A.; Vanderstichele, H.; Meschino, W.; Dermaut, B.; Vanderhoeven, I.; Backhovens, H.; et al. Aberrant Splicing in the Presenilin-1 Intron 4 Mutation Causes Presenile Alzheimer's Disease by Increased A 42 Secretion. *Hum. Mol. Genet.* **1999**, *8*, 1529–1540.
48. Szaruga-Bracke, M.; Veugelen, S.; Benurwar, M.; Lismont, S.; Sepulveda-Falla, D.; Lleo, A.; Ryan, N.S.; Lashley, T.; Fox, N.; Murayama, S.; et al. Qualitative changes in human γ-secretase underlie familial Alzheimer's disease. *J. Exp. Med.* **2015**, *212*, 2003–2013.
49. Fox, N.C.; Kennedy, A.M.; Harvey, R.J.; Lantos, P.L.; Roques, P.K.; Collinge, J.; Hardy, J.; Hutton, M.; Stevens, J.M.; Warrington, E.K.; et al. Clinicopathological features of familial Alzheimer's disease associated with the M139V mutation in the presenilin 1 gene. Pedigree but not mutation specific age at onset provides evidence for a further genetic factor. *Brain* **1997**, *120*, 491–501.
50. Chávez-Gutiérrez, L.; Bammens, L.; Benilova, I.; Vandersteen, A.; Benurwar, M.; Borgers, M.; Lismont, S.; Zhou, L.; Van Cleynenbreugel, S.; Esselmann, H.; et al. The mechanism of γ-Secretase dysfunction in familial Alzheimer disease. *EMBO J.* **2012**, *31*, 2261–2274.
51. Ringman, J.M.; Gylys, K.H.; Medina, L.D.; Fox, M.; Kepe, V.; Flores, D.L.; Apostolova, L.G.; Barrio, J.R.; Small, G.; Silverman, D.H.; et al. Biochemical, neuropathological, and neuroimaging characteristics of early-onset Alzheimer's disease due to a novel PSEN1 mutation. *Neurosci. Lett.* **2011**, *487*, 287–292.
52. Devi, G.; Fotiou, A.; Jyrinji, D.; Tycko, B.; DeArmand, S.; Rogaeva, E.; Song, Y.-Q.; Medieros, H.; Liang, Y.; Orlacchio, A.; et al. Novel presenilin 1 mutations associated with early onset of dementia in a family with both early-onset and late-onset Alzheimer disease. *Arch. Neurol.* **2000**, *57*, 1454–1457.
53. Levy-Lahad, E.; Wasco, W.; Poorkaj, P.; Romano, D.M.; Oshima, J.; Pettingell, W.H.; Yu, C.E.; Jondro, P.D.; Schmidt, S.D.; Wang, K.; et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* **1995**, *269*, 973–977.
54. Perrone, F.; Cacace, R.; Van Mossevelde, S.; Bossche, T.V.D.; De Deyn, P.P.; Cras, P.; Engelborghs, S.; van der Zee, J.; Van Broeckhoven, C. Genetic screening in early-onset dementia patients with unclear phenotype: Relevance for clinical diagnosis. *Neurobiol. Aging* **2018**, *69*, 292.e7–292.e14.
55. Jia, L.; Fu, Y.; Shen, L.; Zhang, H.; Zhu, M.; Qiu, Q.; Wang, Q.; Yan, X.; Kong, C.; Hao, J.; et al. *PSEN1*, *PSEN2*, and *APP* mutations in 404 Chinese pedigrees with familial Alzheimer's disease. *Alzheimers Dement.* **2020**, *16*, 178–191.
56. Pang, Y.; Li, T.; Wang, Q.; Qin, W.; Li, Y.; Wei, Y.; Jia, L. A Rare Variation in the 3′ Untranslated Region of the Presenilin 2 Gene Is Linked to Alzheimer's Disease. *Mol. Neurobiol.* **2021**, *58*, 4337–4347.
57. Wallon, D.; Rousseau, S.; Rovelet-Lecrux, A.; Quillard-Muraine, M.; Guyant-Maréchal, L.; Martinaud, O.; Pariente, J.; Puel, M.; Rollin-Sillaire, A.; Pasquier, F.; et al. The French Series of Autosomal Dominant Early Onset Alzheimer's Disease Cases: Mutation Spectrum and Cerebrospinal Fluid Biomarkers. *J. Alzheimers Dis.* **2012**, *30*, 847–856.
58. Marcon, G.; Giaccone, G.; Cupidi, C.; Balestrieri, M.; Beltrami, C.A.; Finato, N.; Bergonzi, P.; Sorbi, S.; Bugiani, O.; Tagliavini, F. Neuropathological and Clinical Phenotype of an Italian Alzheimer Family with M239V Mutation of Presenilin 2 Gene. *J. Neuropathol. Exp. Neurol.* **2004**, *63*, 199–209.
59. Huang, Y.; Weisgraber, K.H.; Mucke, L.; Mahley, R.W. Apolipoprotein E: Diversity of Cellular Origins, Structural and Biophysical Properties, and Effects in Alzheimer's Disease. *J. Mol. Neurosci.* **2004**, *23*, 189–204.

60. Liu, C.-C.; Kanekiyo, T.; Xu, H.; Bu, G. Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nat. Rev. Neurol.* **2013**, *9*, 106–118.
61. Kara, E.; Marks, J.D.; Fan, Z.; Klickstein, J.A.; Roe, A.D.; Krogh, K.A.; Wegmann, S.; Maesako, M.; Luo, C.C.; Mylvaganam, R.; et al. Isoform- and cell type-specific structure of apolipoprotein E lipoparticles as revealed by a novel Forster resonance energy transfer assay. *J. Biol. Chem.* **2017**, *292*, 14720–14729.
62. Lin, Y.-T.; Seo, J.; Gao, F.; Feldman, H.M.; Wen, H.-L.; Penney, J.; Cam, H.P.; Gjoneska, E.; Raja, W.K.; Cheng, J.; et al. APOE4 Causes Widespread Molecular and Cellular Alterations Associated with Alzheimer's Disease Phenotypes in Human iPSC-Derived Brain Cell Types. *Neuron* **2018**, *98*, 1141–1154.e7.
63. Kang, S.S.; Ebbert, M.T.W.; Baker, K.E.; Cook, C.; Wang, X.; Sens, J.P.; Kocher, J.-P.; Petrucelli, L.; Fryer, J.D. Microglial translational profiling reveals a convergent APOE pathway from aging, amyloid, and tau. *J. Exp. Med.* **2018**, *215*, 2235–2245.
64. Mathys, H.; Davila-Velderrain, J.; Peng, Z.; Gao, F.; Mohammadi, S.; Young, J.Z.; Menon, M.; He, L.; Abdurrob, F.; Jiang, X.; et al. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature* **2019**, *570*, 332–337.
65. Therriault, J.; Benedet, A.L.; Pascoal, T.A.; Mathotaarachchi, S.; Chamoun, M.; Savard, M.; Thomas, E.; Kang, M.S.; Lussier, F.; Tissot, C.; et al. Association of Apolipoprotein E ε4 With Medial Temporal Tau Independent of Amyloid-β. *JAMA Neurol.* **2020**, *77*, 470–479.
66. Shi, Y.; Alzheimer's Disease Neuroimaging Initiative; Yamada, K.; Liddelow, S.A.; Smith, S.T.; Zhao, L.; Luo, W.; Tsai, R.M.; Spina, S.; Grinberg, L.T.; et al. ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature* **2017**, *549*, 523–527.
67. Harris, F.M.; Brecht, W.J.; Xu, Q.; Mahley, R.W.; Huang, Y. Increased tau Phosphorylation in Apolipoprotein E4 Transgenic Mice Is Associated with Activation of Extracellular Signal-regulated Kinase. *J. Biol. Chem.* **2004**, *279*, 44795–44801.
68. Wadhwani, A.R.; Affaneh, A.; Van Gulden, S.; Kessler, J.A. Neuronal apolipoprotein E4 increases cell death and phosphorylated tau release in alzheimer disease. *Ann. Neurol.* **2019**, *85*, 726–739.
69. Gibb, G.M.; Pearce, J.; Betts, J.C.; Lovestone, S.; Hoffmann, M.M.; Maerz, W.; Blackstock, W.P.; Anderton, B.H. Differential effects of apolipoprotein E isoforms on phosphorylation at specific sites on tau by glycogen synthase kinase-3β identified by nano-electrospray mass spectrometry. *FEBS Lett.* **2000**, *485*, 99–103.
70. Park, J.-S.; Ji-Seon, P.; Sang-Wook, K.; Kang, M.-J.; Kang, S.-W.; Kim, D.-H.; Yoon, S.-Y. Disease-Associated Mutations of TREM2 Alter the Processing of N-Linked Oligosaccharides in the Golgi Apparatus. *Traffic* **2015**, *16*, 510–518.
71. Saceleanu, V.M.; Covache-Busuioc, R.-A.; Costin, H.-P.; Glavan, L.-A.; Ciurea, A.V. An Important Step in Neuroscience: Camillo Golgi and His Discoveries. *Cells* **2022**, *11*, 4112.
72. Ulrich, J.D.; Ulland, T.K.; Mahan, T.E.; Nyström, S.; Nilsson, K.P.; Song, W.M.; Zhou, Y.; Reinartz, M.; Choi, S.; Jiang, H.; et al. ApoE facilitates the microglial response to amyloid plaque pathology. *J. Exp. Med.* **2018**, *215*, 1047–1058.
73. Keren-Shaul, H.; Spinrad, A.; Weiner, A.; Matcovitch-Natan, O.; Dvir-Szternfeld, R.; Ulland, T.K.; David, E.; Baruch, K.; Lara-Astaiso, D.; Toth, B.; et al. A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. *Cell* **2017**, *169*, 1276–1290.e17.
74. Hutton, M.; Lendon, C.L.; Rizzu, P.; Baker, M.; Froelich, S.; Houlden, H.; Pickering-Brown, S.; Chakraverty, S.; Isaacs, A.; Grover, A.; et al. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **1998**, *393*, 702–705.
75. Spillantini, M.G.; Bird, T.D.; Ghetti, B. Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17: A New Group of Tauopathies. *Brain Pathol.* **2006**, *8*, 387–402.
76. Poorkaj, P.; Bird, T.D.; Wijsman, E.; Nemens, E.; Garruto, R.M.; Anderson, L.; Andreadis, A.; Wiederholt, W.C.; Raskind, M.; Schellenberg, G.D. Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann. Neurol.* **1998**, *43*, 815–825.
77. Goedert, M.; Spillantini, M.G.; Jakes, R.; Rutherford, D.; Crowther, R.A. Multiple isoforms of human microtubule-associated protein tau: Sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron* **1989**, *3*, 519–526.
78. Baudier, J.; Cole, R. D Interactions between the microtubule-associated tau proteins and S100b regulate tau phosphorylation by the Ca2+/calmodulin-dependent protein kinase II. *J. Biol. Chem.* **1988**, *263*, 5876–5883
79. Drewes, G.; Ebneth, A.; Preuss, U.; Mandelkow, E.-M.; Mandelkow, E. MARK, a Novel Family of Protein Kinases That Phosphorylate Microtubule-Associated Proteins and Trigger Microtubule Disruption. *Cell* **1997**, *89*, 297–308.
80. Drewes, G.; Lichtenberg-Kraag, B.; Döring, F.; Mandelkow, E.; Biernat, J.; Goris, J.; Dorée, M.; Mandelkow, E. Mitogen activated protein (MAP) kinase transforms tau protein into an Alzheimer-like state. *EMBO J.* **1992**, *11*, 2131–2138.

81. Bancher, C.; Brunner, C.; Lassmann, H.; Budka, H.; Jellinger, K.; Wiche, G.; Seitelberger, F.; Grundke-Iqbal, I.; Iqbal, K.; Wisniewski, H. Accumulation of abnormally phosphorylated τ precedes the formation of neurofibrillary tangles in Alzheimer's disease. *Brain Res.* **1989**, *477*, 90–99.
82. Davies, P.; Vincent, I.J. On the role of tau phosphorylation in the formation of PHF. *Neurobiol. Aging* **1995**, *16*, 420–422
83. Wang, J.-Z.; Wu, Q.; Smith, A.; Grundke-Iqbal, I.; Iqbal, K. τ is phosphorylated by GSK-3 at several sites found in Alzheimer disease and its biological activity markedly inhibited only after it is prephosphorylated by A-kinase. *FEBS Lett.* **1998**, *436*, 28–34.
84. Yasuda, M.; Takamatsu, J.; D'Souza, I.; Crowther, R.A.; Kawamata, T.; Hasegawa, M.; Hasegawa, H.; Spillantini, M.G.; Tanimukai, S.; Poorkaj, P.; et al. A novel mutation at position +12 in the intron following exon 10 of the tau gene in familial frontotemporal dementia (FTD-Kumamoto). *Ann. Neurol.* **2000**, *47*, 422–429.
85. Takamatsu, J.; Kondo, A.; Ikegami, K.; Kimura, T.; Fujii, H.; Mitsuyama, Y.; Hashizume, Y. Selective Expression of Ser 199/202 Phosphorylated Tau in a Case of Frontotemporal Dementia. *Dement. Geriatr. Cogn. Disord.* **1998**, *9*, 82–89.
86. Labbé, C.; Ogaki, K.; Lorenzo-Betancor, O.; Soto-Ortolaza, A.I.; Walton, R.L.; Rayaprolu, S.; Fujioka, S.; Murray, M.E.; Heckman, M.G.; Puschmann, A.; et al. Role for the microtubule-associated protein tau variant p.A152T in risk of α-synucleinopathies. *Neurology* **2015**, *85*, 1680–1686.
87. Jin, S.C.; Pastor, P.; Cooper, B.; Cervantes, S.; Benitez, B.A.; Razquin, C.; Goate, A.; Cruchaga, C.; Ibero-American Alzheimer Disease Genetics Group Researchers. Pooled-DNA sequencing identifies novel causative variants in PSEN1, GRN and MAPT in a clinical early-onset and familial Alzheimer's disease Ibero-American cohort. *Alzheimers Res. Ther.* **2012**, *4*, 34.
88. Coppola, G.; Chinnathambi, S.; Lee, J.J.; Dombroski, B.A.; Baker, M.C.; Soto-Ortolaza, A.I.; Lee, S.E.; Klein, E.; Huang, A.Y.; Sears, R.; et al. Evidence for a role of the rare p.A152T variant in MAPT in increasing the risk for FTD-spectrum and Alzheimer's diseases. *Hum. Mol. Genet.* **2012**, *21*, 3500–3512.
89. Rizzini, C.; Goedert, M.; Hodges, J.R.; Smith, M.J.; Jakes, R.; Hills, R.; Xuereb, J.H.; Crowther, R.A.; Spillantini, M.G. *Tau* Gene Mutation K257T Causes a Tauopathy Similar to Pick's Disease. *J. Neuropathol. Exp. Neurol.* **2000**, *59*, 990–1001.
90. Kobayashi, T.; Ota, S.; Tanaka, K.; Ito, Y.; Hasegawa, M.; Umeda, Y.; Motoi, Y.; Takanashi, M.; Yasuhara, M.; Anno, M.; et al. A novel L266V mutation of the tau gene causes frontotemporal dementia with a unique tau pathology. *Ann. Neurol.* **2003**, *53*, 133–137.
91. Hogg, M.; Grujic, Z.M.; Baker, M.; Demirci, S.; Guillozet, A.L.; Sweet, A.P.; Herzog, L.L.; Weintraub, S.; Mesulam, M.-M.; LaPointe, N.E.; et al. The L266V tau mutation is associated with frontotemporal dementia and Pick-like 3R and 4R tauopathy. *Acta Neuropathol.* **2003**, *106*, 323–336.