Alzheimer’s disease background

What is Alzheimer’s disease (AD)?

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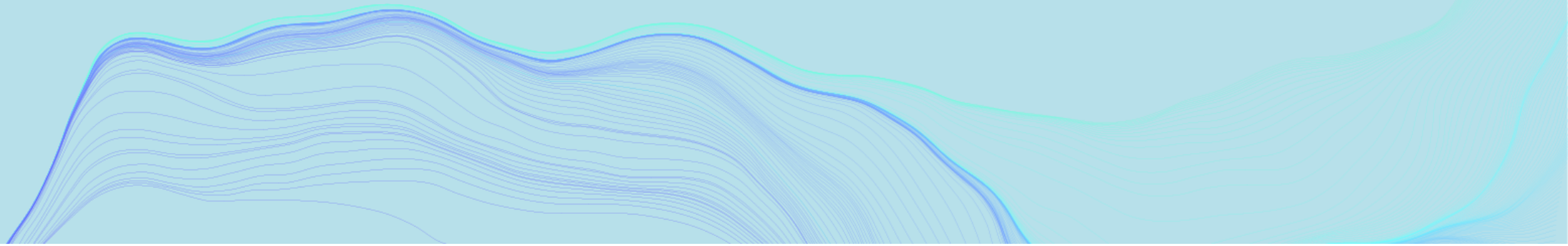
Contents

What is Alzheimer’s disease (AD)?



Eisai hhc human health care

Alzheimer’s disease

AD is a **multifactorial and heterogeneous neurodegenerative disorder**,[1] which has become an increasing public health issue[2]

AD is the most common cause of dementia, and is estimated to account for 60–80% of dementia cases[3]

AD is a **leading cause of disability and morbidity in the elderly**[3]

- The long duration of illness contributes significantly to the public health impact because much of that time is spent in a state of disability and dependence[3]

Various mechanisms have been proposed over the years to describe the pathogenic events that lead to the development of AD,[1] all of which suggest that the **presence of Aβ and tau, synaptic failure, and neuronal dysfunction are common features of AD** and play a pivotal role in cognitive dysfunction[1,4]

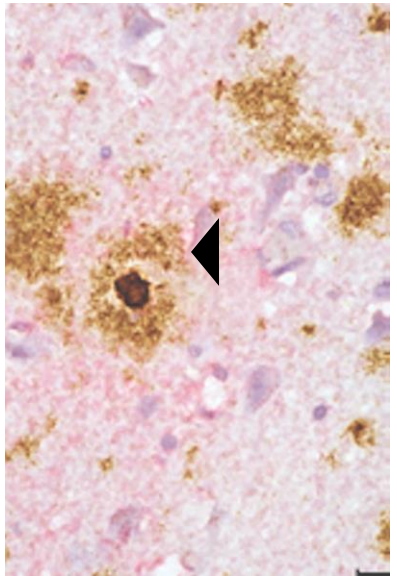
Aβ, amyloid beta; AD, Alzheimer's disease

1. Kazim SF, Iqbal K. Mol Neurodegener 2016;11:50; 2. Niu H, et al. Neurologia 2017;32:523–532; 3. Alzheimer’s Association. Alzheimers Dement. 2023;19(4):1598–1695; 4. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189

Key pathological features of Alzheimer's disease

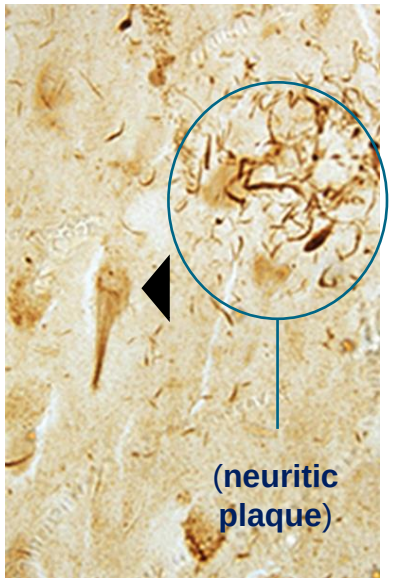
- The neuropathological features of AD include **amyloid plaques** containing **dystrophic neurites, NFTs** (aggregates of phosphorylated-tau protein), neuritic plaques, vascular amyloidosis, glial responses, and **synaptic and neuronal loss**[1,2]
- Aβ plaques build-up primarily before the onset of cognitive deficits;[2,3] while NFTs, neuron loss, and particularly synaptic loss, parallel the progression of cognitive decline[2]
- Aβ plaques and NFTs are the most characteristic of AD. Therefore, the criteria for the pathological diagnosis of AD rely on their amount and/or distribution[2]
- However, synaptic and neuronal loss, plasticity changes, and the presence of soluble oligomeric forms of Aβ, likely contribute to a decline in cognition that occurs over decades[2]
- Neuroinflammation (eg gliosis) may also play an important role in the neurodegenerative process (ie in response to CNS injury)[4]

Aβ[4]



Arrow signifies an Aβ plaque

Tau[5]



Arrow signifies an NFT

Left hand image used with permission from Mathur R, et al. PLoS One 2015;10:e0118463 (CC-BY 4.0. https://creativecommons.org/licenses/by/4.0/)
Right hand image used with permission from Day RJ, et al. PLoS One 2015;10:e0132637 (CC-BY 4.0. https://creativecommons.org/licenses/by/4.0/)

Aβ, amyloid beta; AD, Alzheimer's disease; CNS, central nervous system; NFT, neurofibrillary tangle

1. Sweeney MD, et al. Alzheimers Dement 2019;15(1):158-167; 2. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189; 3. Bateman RJ, et al. N Engl J Med 2012;367:795–804; 4. Mathur R, et al. PLoS One 2015;10:e0118463;
5. Day RJ, et al. PLoS One 2015;10:e0132637

Amyloid plaques and neurofibrillary tangles are key hallmarks of Alzheimer's disease

The neuropathologic hallmarks of AD include features such as:

- Amyloid plaques and cerebral amyloid angiopathy
- NFTs
- Glial responses
- Synaptic and neuronal loss[1]

In the AD continuum:

- Aβ plaques and tau NFT accumulation are the earliest changes
- Inflammation, synaptic degeneration, and neuronal loss occur
- Neurodegeneration and level of tau correlate with clinical symptoms[1–5]

Aβ, amyloid beta; AD, Alzheimer's disease; NFT, neurofibrillary tangle

1. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189; 2. Jack CR, et al. Alzheimers Dement 2018;14:535–562; 3. Bateman RJ, et al. N Engl J Med 2012;367:795–804; 4. Bennett AD, et al. Arch Neurol 2004;61:378–384; 5. Horie K, et al. Brain 2021;3:515–527

Conformational evolution of Aβ and the affected cell types in brain

Aβ is a hallmark of AD pathophysiology[1]

- Aβ exists and evolves through different conformational states, through nucleation and aggregation[2]
- Both preclinical and clinical data provide evidence that soluble oligomers and protofibrils are central toxic species involved in AD pathogenesis, disrupting synaptic function and directly causing neuronal toxicity[2]
- In animal models, the levels of protofibrils in the brain are correlated with spatial learning deficits[3]

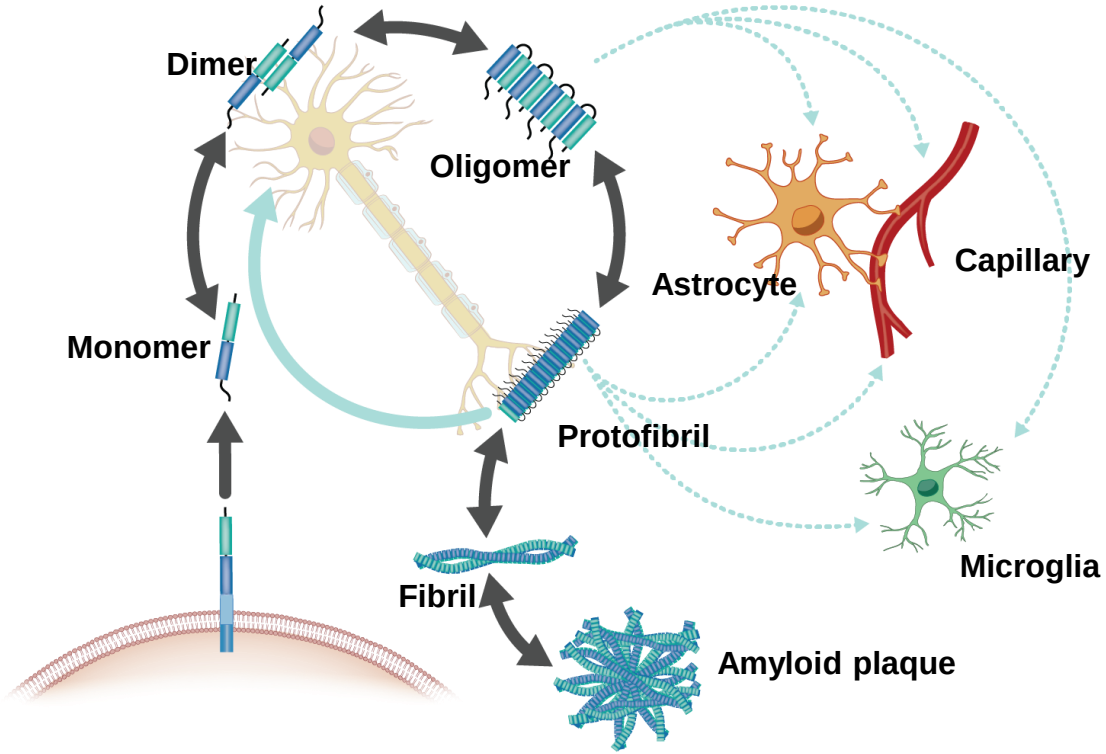


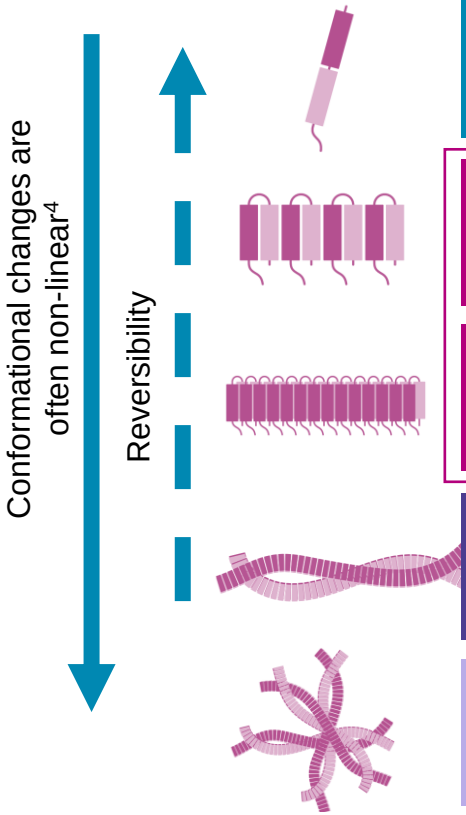
Figure used with permission from Hampel H, et al. Mol Psychiatry 2021;26:5481-5503 (CC-BY 4.0 https://creativecommons.org/licenses/by/4.0/)

AD, Alzheimer's disease

1. Walsh DM, et al. J Biol Chem. 1997;272:22364-22372.; 2. Paranjape GS, et al. ACS Chem Neurosci. 2012;3:302-311.; 3. Lord A, et al. FEBS J. 2009;276:995-1006.

Aβ evolves through different conformational states

Aβ evolves through different conformational states, through nucleation and aggregation.[1] Aβ species exist in dynamic equilibrium as soluble monomers, oligomers and protofibrils, as well insoluble fibrils that accumulate in amyloid plaques.[2,3]



Monomers	Low-molecular-weight Aβ monomeric proteins that undergo conformational shifts, facilitating aggregation and formation of solid fibrils[4]
Oligomers	Small, low-molecular-weight soluble aggregate structures comprising of several monomers. This species represents a prominent intermediate state in the amyloid aggregation pathway[5]
Protofibrils	High-molecular-weight soluble aggregate structures consists of several cross-β protofilaments held together by weak side-chain interactions. These structures are defined as curvilinear. This species represents a soluble fibril intermediate[5–7]
Fibrils	A class of linear mature protein and peptide assembly comprising of multiple protofibrils. Typically, irreversible (some amyloid aggregation is reversible)[5,7]
Plaque	Consist of entangled amyloid fibril bundles[5]

The soluble intermediate aggregated species of Aβ, termed oligomers and protofibrils, are believed to be key pathogenic forms responsible for neurotoxicity[1]

Aβ, amyloid beta

1. Paranjape GS, et al. ACS Chem Neurosci. 2012;3:302-311; 2. Lau HHC, et al. Acta Neuropathol 2021;142(1):17–39; 3. Hampel H, et al. Mol Psychiatry 2021;26(10):5481–5031; 4. Wells C, et al. Int J Biol Macromol. 2021;181:582–60; 5. Michaels T, et al. Nat Rev Phys. 2023;5: 379–397; 6. Ono K & Tsuji M. Int J Mol Sci 2020;21(3):952; 7. Khurana R , et al. Biophys J 2003;85:1135–1144

Pathological changes associated with Aβ deposition

In AD, Aβ accumulates into intermediate soluble oligomers and insoluble amyloid fibrils, which are the main **constituent of amyloid plaques** (mainly Aβ42) and **cerebral amyloid angiopathy** (primarily Aβ40)[1]

Progressive Aβ deposition is followed by surrounding neuritic and glial cytopathology in brain regions serving cognition, including memory[4]

Accumulation of Aβ could potentially act as a trigger of other downstream processes, in particular tau aggregation, which mediate neurodegeneration[2,3]

Aβ deposition is also responsible for microglia activation, contributes to the enhancement of the inflammatory response by NF-κB stimulation, and regulates the ERK and MAPK pathways[5]

Aβ, amyloid beta; AD, Alzheimer's disease; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B

1. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189; 2. Musiek ES, Holtzman DM. Nat Neurosci 2015;18:800–806; 3. Hardy J, Selkoe DJ. Science 2002;297:353–356; 4. Selkoe DJ, Hardy J. EMBO Mol Med 2016;8:595–608; 5. Ridolfi E, et al. Clin Dev Immunol 2013;2013:939786

Topographic distribution of Aβ plaques within the brain

- Amyloid plaques are abundant in the cortex of patients with AD and are commonly classified as **diffuse** or **dense-core** plaques based on their morphology and staining[1]
- **Aβ plaques accumulate mainly in the isocortex**[1]
  - The allocortex, basal ganglia, relevant nuclei of the brainstem, and the cerebellum are also associated with amyloid deposition but to a much lesser extent, and at a later stage than the associative isocortex[1]
- The spatiotemporal pattern of progression for amyloid deposition is far less predictable than NFTs[1]
- Reactive astrocytes and activated microglial cells are commonly associated with dense-core amyloid plaques, indicating that Aβ is a major trigger for the proliferation and activation of these cells[2]
  - Astrocyte and microglial proliferation and activation both occur in the early stages of AD[2,3]
  - When stimulated by Aβ, reactive astrocytes in the cerebral cortex may produce neurotoxic chemokines and cytokines, which likely contributes to the development of cognitive decline in AD[2]

Aβ, amyloid beta; AD, Alzheimer's disease; MCI, mild cognitive impairment; NFT, neurofibrillary tangle

1. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189; 2. Vehmas AK, et al. Neurobiol Aging 2003;24:321–331; 3. Rodriguez-Vieitez E, el al. Brain 2016;139(Pt 3):922–936

The role of tau in Alzheimer's disease pathology

Tau is a brain-specific, axon-enriched, microtubule-associated protein (**t-tau**)[1] and is generated by neurons[1]

Under normal physiologic conditions, tau phosphorylation is regulated by a balance between tau kinase and phosphatase activities[2]

Disruption of this equilibrium is thought to lead to an accumulation of abnormal **p-tau**, which causes tau to aggregate and form **NFTs**[2]

Changes in levels of t-tau and p-tau can occur years before the onset of AD dementia[3]

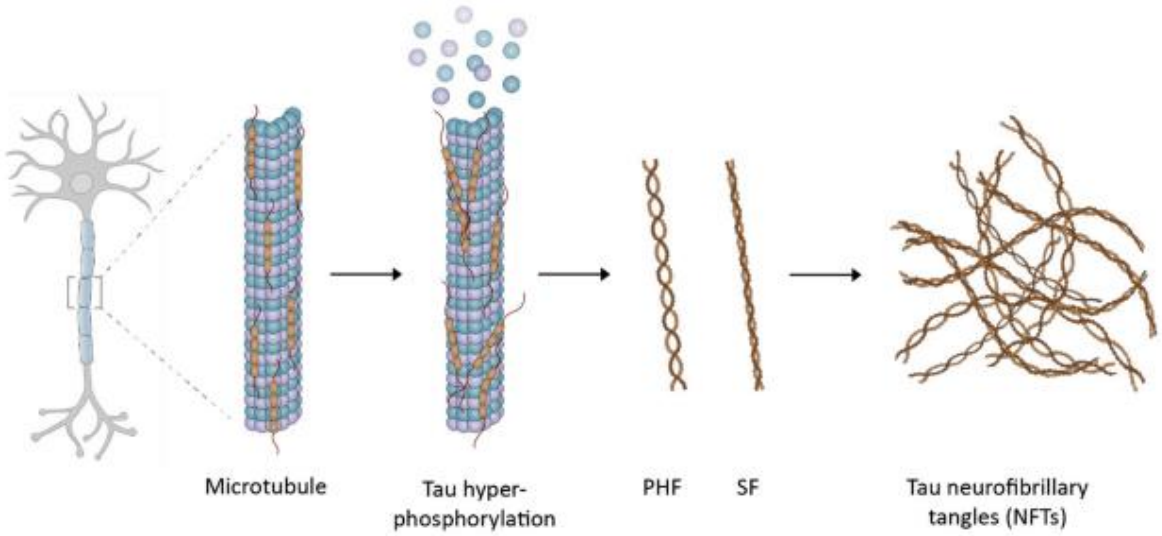
Increases in CSF t-tau can reflect neuronal degeneration, while the level of **p-tau has been shown to correlate with the NFT load within the brain** (higher CSF p-tau levels = higher NFT load)[4,5]

AD, Alzheimer's disease; NFT, neurofibrillary tangle; p-tau, phosphorylated-tau; t-tau, total-tau

1. Buèe L, et al. Brain Res Brain Res Rev 2000;33:95–130; 2. Martin L, et al. Ageing Res Rev 2013;12:39–49; 3. Bateman RJ, et al. NEJM 2012;367:795-804; 4. Blennow K, et al. Alzheimers Dement 2015;11:58–69;
5. Blennow K. Neurol Ther 2017;6:S15–S24

The formation of NFTs

- Tau is the major constituent of NFTs in AD[1]
- In patients with AD, three forms of tau aggregates exist:[2]
  - NFTs in neuronal somata
  - Neuropil threads in neuronal dendrites
  - Neuritic plaques
- NFTs also occur in other neurodegenerative disorders termed **tauopathies** (but not typically in the presence of Aβ), eg FTD with Parkinsonism, Pick's disease, and progressive supranuclear palsy[3]



Tau proteins self-aggregate to form paired helical filaments and tightly wrapped straight filaments, which then leads to the formation of NFTs

Image used with permission from Jie CVML, et al. Pharmaceuticals (Basel). 2021;14:110 (CC-BY 4.0. https://creativecommons.org/licenses/by/4.0/)

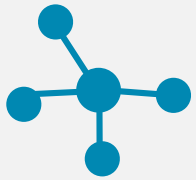
Aβ, amyloid beta; AD, Alzheimer's disease; FTD, frontotemporal dementia; NFT, neurofibrillary tangle

1. Wegmann S, et al. EMBO J 2018;37:e98049; 2. Lim S, et al. Comput Struct Biotechnol J 2014;12:7–13; 3. Gendron TF, Petrucelli L. Mol Neurodegener 2009;4:13

The role of TDP-43 in Alzheimer’s disease: Aβ-independent pathway

TDP-43 has been found to coexist with tau-positive NFTs within the same neuron in patients with AD[1]

Expression of TDP-43 **increases proinflammatory cytokine expression** in the brain (eg IL-6, TNF-α)[3]



Tau may trigger deposition of TDP-43 in selectively vulnerable neuronal populations[2]

According to FTLD/ALS research, TDP-43 may also contribute to mitochondrial dysfunction and **neuronal dysfunction**; however, these functions need further demonstration in AD models[3]

TDP-43 can be detected in serum and CSF; however, further investigation is required to identify whether TDP-43 could be used as a diagnostic biomarker for AD[3]

Aβ, amyloid beta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; FTLD, frontotemperal lobar degeneration; IL, interleukin; NFT, neurofibrillary tangle; TDP-43, transactive response DNA binding protein; TNF, tumor necrosis factor

1. Higashi S, et al. Brain Res 2007;1184:284–294; 2. Amador-Ortiz C, et al. Ann Neurol 2007;61:435–445; 3. Chang XL, et al. Mol Neurobiol 2016;53:3349–3359

Potential mechanisms for the role of TDP-43 in Alzheimer’s disease

Aβ-dependent pathway

Aβ accelerates TDP-43 phosphorylation and aggregation in cytosol. TDP-43 oligomers and Aβ are capable of cross seeding with each other to form amyloid oligomers

Aβ-independent pathway

The role of TDP-43 in AD may include perturbation of the physical neuronal function, mitochondria, and Ca2+ homeostasis; dysregulation of the stress response; and inflammation

- Neuronal dysfunction
- Mitochondrial dysfunction
- Inflammatory cytokines and neuroinflammation
- Dysregulated stress response
- Cognitive impairment
- Neurotoxicity

Aβ, amyloid beta; AD, Alzheimer's disease; AICD, APP intracellular domain; APP, amyloid beta precursor protein; TDP-43, transactive response DNA binding protein

Chang XL, et al. Mol Neurobiol 2016;53:3349–3359

Cerebrovascular disease and Alzheimer's disease

CVD is known to induce Aβ deposition and affect the age of onset of sporadic AD.[1] CVD exacerbates cognitive impairment and increases the likelihood of clinical dementia symptoms[2]

Aβ deposition has been shown to cause cerebrovascular degeneration,[1,2] while vascular lesions are directly involved in AD pathogenesis[2]

CVD also impairs Aβ clearance, mainly driven by vascular mediated systems, including active transport across the BBB, and perivascular lymphatic / paravascular glymphatic drainage systems.[2] CVD may also disturb homeostasis between Aβ production and clearance, thereby contributing to Aβ burden[2]

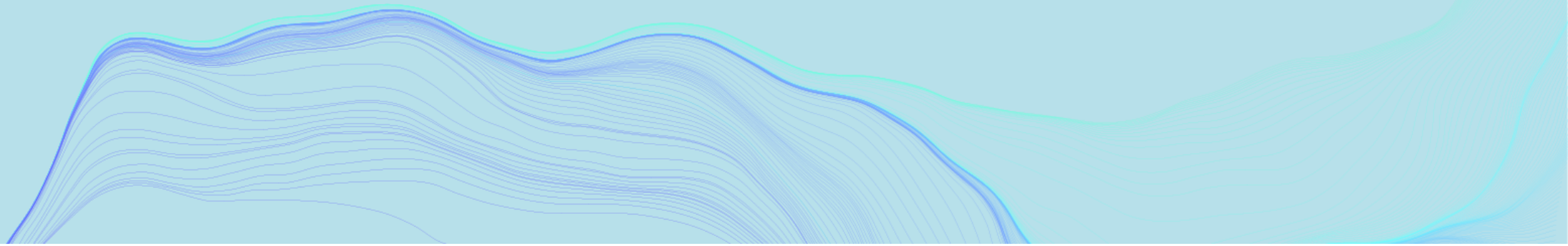
One of the mechanisms linking CVD to AD is **decreased cerebral blood flow**.[2] Cerebral hypoperfusion is known to cause BBB dysfunction leading to other deleterious modifiers of AD, such as oxidative stress, mitochondrial dysfunction, neuroinflammation, and reduced cerebral perfusion, which leads to accelerated neurodegeneration[3]

There is limited evidence to describe the relationship between tau pathology and CVD.[2] **Some studies have shown that CVD may influence tau pathology as well as Aβ**[4,5]

Aβ, amyloid beta; AD, Alzheimer's disease; BBB, blood-brain barrier; CVD, cerebrovascular disease

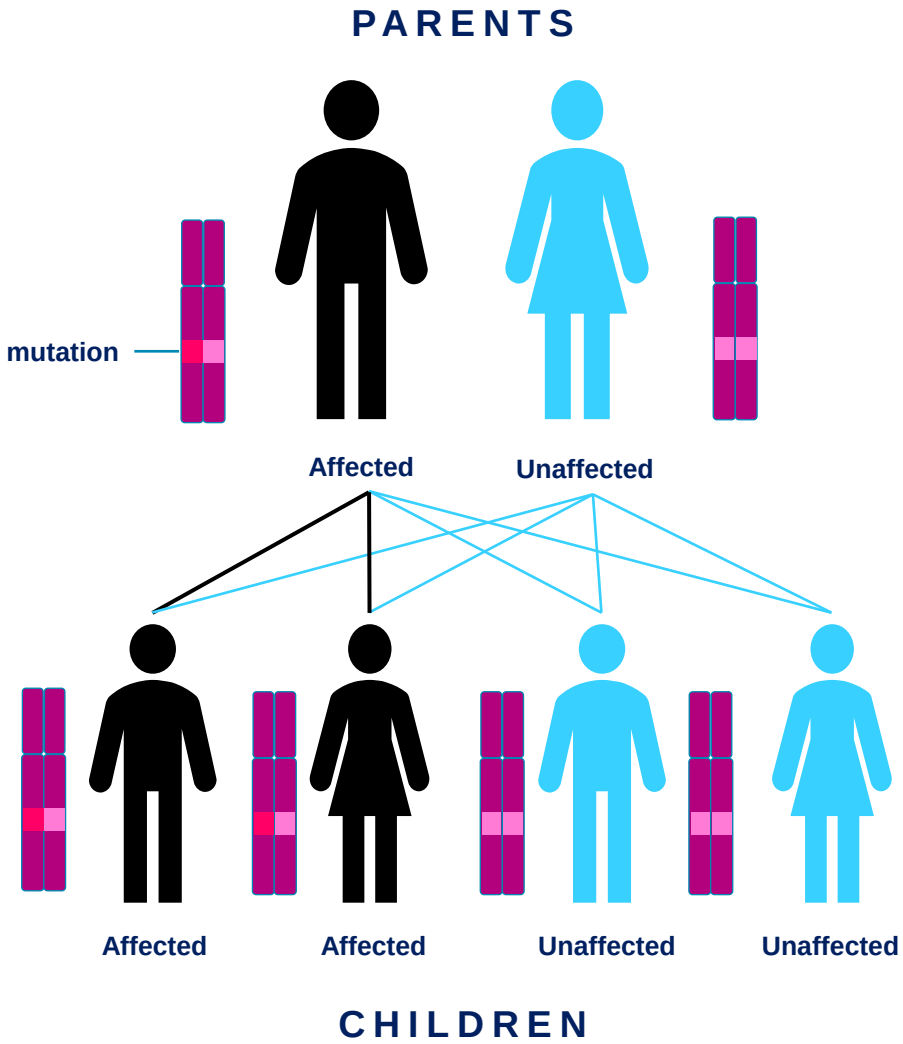
1. Lee CW, et al. Curr Alzheimer Res 2014;11:4–10; 2. Saito S, Ihara M. Curr Opin Psychiatry 2016;29:168–173; 3. Di Marco LY, et al. Neurobiol Dis 2015;82:593–606; 4. Iliff JJ, et al. J Neurosci 2014;34:16180–16193; 5. Nation DA, et al. JAMA Neurol 2015;72:546–553

Types of Alzheimer’s disease



Familial Alzheimer’s disease

- Familial AD, also known as dominantly inherited AD, is diagnosed in families in which multiple persons are affected in more than one generation[1]
- Approximately 60% of early-onset AD cases have multiple cases of AD within their families, and of these familial AD cases, 13% are inherited in an autosomal dominant manner with multiple generations affected[2]
- Cases of familial AD are predominantly diagnosed in individuals **aged <65 years**[1]
- Familial AD is usually due to rare and highly penetrant mutations in **genes involved in Aβ production and clearance:**[1,3]
  - ***APP***, ***PSEN1***, and ***PSEN2***[1]



Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein; PSEN, presenilin

1. Piaceri I, et al. Front Biosci (Elite Ed) 2013;5:167–177; 2. Bekris LM, et al. J Geriatr Psychiatry Neurol 2010;23:213–227; 3. Kazim SF, Iqbal K. Mol Neurodegener 2016;11:50

Mutations associated with familial Alzheimer's disease

APP

- ***APP* mutations are autosomal dominant** and cause an increase or alteration in Aβ production[1]
- *APP* mutations are responsible for only a small percentage of familial AD cases[1]

PSEN1

- Critical component of the γ-secretase enzyme[2]
- ***PSEN1* mutations are autosomal dominant**
- Most common genetic cause of familial AD[1]
- Cause the most severe forms of dominantly inherited AD, with an earlier age of onset and rapid progression[1]
- Associated with seizures, myoclonus, and language deficits[1]

PSEN2

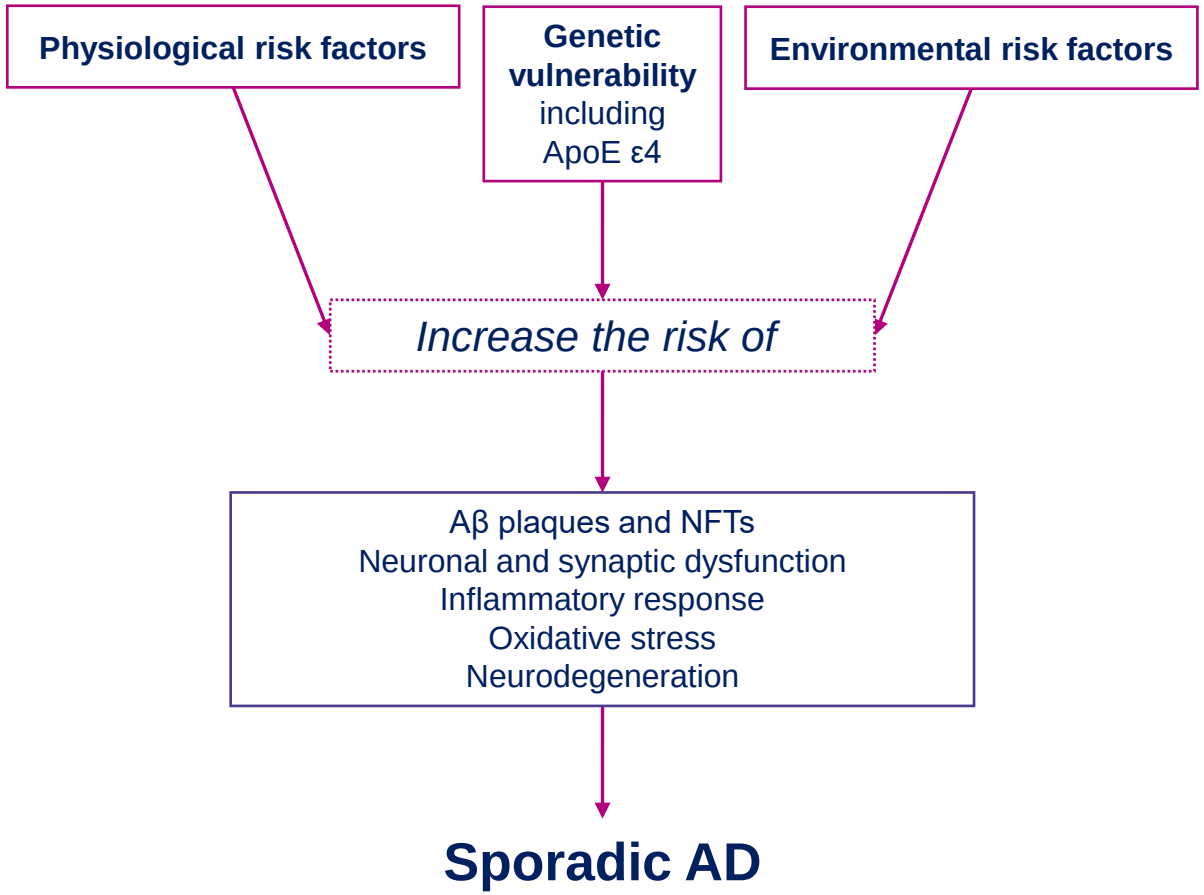
- Critical component of the γ-secretase enzyme[1,2]
- ***PSEN2* mutations are autosomal dominant**
- Very rare cause of familial AD[1]
- Wide range in age of onset, which can vary among affected family members[1,3]

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein; PSEN, presenilin

1. Piaceri I, et al. Front Biosci (Elite Ed) 2013;5:167–177; 2. Karch CM, Goate AM. Biol Psychiatry 2015;77:43–51; 3. Larner AJ, Doran M. J Neurol 2006;253:139–158; 4. Jayadev S, et al. Brain 2010;133:1143–1154

Sporadic Alzheimer's disease

- Sporadic AD, accounts for >95% of AD cases[1,2]
- The etiopathogenic mechanisms thought to cause sporadic AD are complex and most likely result from a **combination of genetic and environmental influences**[3]
- The presence of one or two ApoE ε4 alleles is also known to increase the risk of sporadic AD[4]
- Environmental factors associated with sporadic AD include:
  - Head trauma, hypertension, vitamin deficiencies, hypercholesterolemia, diabetes (MCI), and obesity[2,5]



Aβ, amyloid beta; AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4; MCI, mild cognitive impairment; NFT, neurofibrillary tangle

1. Zhong W, et al. Alzheimers Dement 2022 Feb;18(2):222-239; 2. Kazim SF, Iqbal K. Mol Neurodegener 2016;11:50; 3. Piaceri I, et al. Front Biosci (Elite Ed) 2013;5:167–177; 4. Corder EH, et al. Science 1993;261:921–923;
5. 2021 Alzheimer's disease facts and figures. Alzheimer's Dement 2021;17:327–406

Comparison between familial and sporadic Alzheimer's disease

AD does not only occur in patients over the age of 65[1]

	Familial	Sporadic
Age of onset[1-3]	Early onset Usually but not always <60 years	Predominantly late onset* Usually but not always >60 years *sporadic atypical cases can be early onset
Proportion of AD cases	~1%[2,3]	>95%[2,4]
Causes / Risk factors[2,3,5]	Generally dominantly inherited causes: • Mutations in *APP, PSEN1*, and *PSEN2* genes	Genetic vulnerability, including *APOE ε4* Environmental risk factors
Clinical symptoms[2,3]	• No significant differences have been observed between the clinical symptoms of familial and sporadic AD[1,2]	

AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; APP, amyloid beta precursor protein; PSEN, presenilin

1. Smirnov DS, et al. Neurology 2021;96:e2272–e2283; 2. Kazim SF, Iqbal K. Mol Neurodegener 2016;11:50; 3. Bekris LM, et al. J Geriatr Psychiatry Neurol 2010;23:213–227; 4. Zhong W, et al. Alzheimers Dement 2022 Feb;18(2):222-239;
5. 2021 Alzheimer's disease facts and figures. Alzheimers Dement 2021;17:327–406

Etiologic variation in Alzheimer's disease

Typical AD[1]

- An early significant and progressive episodic memory deficit that remains dominant in the later stages of the disease
- Followed by, or associated with, other cognitive impairments (**executive dysfunction**, **language**, **praxis**, and **complex visual processing** impairments) and neuropsychiatric changes

Mixed AD[1]

- Fulfill the diagnostic criteria for typical AD
- Additionally present with clinical and brain imaging / biological evidence of other comorbid disorders such as cerebrovascular disease or Lewy body dementia

Atypical AD[1]

- Less common and well-characterized clinical phenotypes of the disease that occur with Alzheimer's pathology
- These clinical syndromes include **primary progressive non-fluent aphasia, logopenic aphasia, frontal variant of AD, and posterior cortical atrophy**

AD, Alzheimer's disease

1. Dubois B, et al. Lancet Neurol 2010;9:1118–1127

Alzheimer’s disease: atypical presentations

Atypical presentations of AD most often include syndromes in which the episodic memory impairment appears later in the disease course and non-amnestic focal cortical syndromes appear early[1]

Posterior cortical atrophy

- Associated with a variety of underlying pathologies, but AD is the most common underlying cause of PCA[2]
- Progressive decline in visuospatial, visuoperceptual, literacy, and praxic skills[2]
- Pathology affects parietal, occipital, and occipito-temporal cortex[2]
- Age of clinical onset is typically 50 to 65 years[2]

Logopenic progressive aphasia

- Recognized as an atypical focal language variant of AD[3]
- Characterized as a primary phonological loop deficit leading to:[3]
  - Impaired sentence repetition and comprehension with slow spontaneous speech
  - Long, frequent word-finding pauses

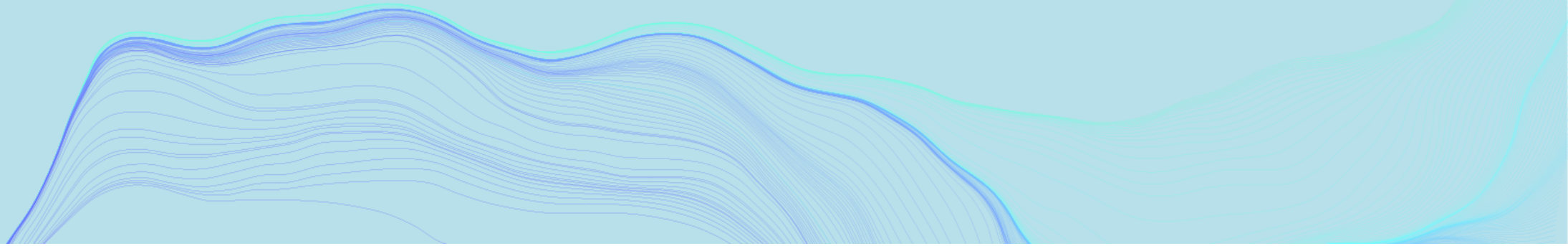
Frontal variant

- Presents with disproportionate executive dysfunction and behavioral changes relevant to memory deficits[4]
- Often difficult to distinguish clinically from those with behavioral variant frontotemporal dementia[4]

AD, Alzheimer’s disease; PCA, posterior cortical atrophy

1. Dickerson B, et al. CNS Spectr 2017;22:439–449; 2. Schott JM, Crutch SJ. Continuum (Minneap Minn) 2019;25:52–75; 3. Beber BS, et al. Dement Neuropsychol 2014;8:302–307; 4. Wong S, et al. Neurocase 2019;25:48–58

The amyloid cascade hypothesis



The amyloid cascade hypothesis

In 1907, Alois Alzheimer first described plaques and tangles in the brain of a 51-year-old woman[1]

The **amyloid cascade hypothesis** was first described by Hardy and Higgins in 1992, in which they suggested "**Aβ… is the causative agent in AD pathology**. **NFTs, cell loss, vascular damage, and dementia follow as a direct result of Aβ deposition**"[2]

The amyloid cascade hypothesis has since become the **dominant model of AD pathogenesis** and is guiding the development of several potential treatments,[3] including amyloid-modifying immunotherapies, with potential disease-modifying effects

The amyloid cascade hypothesis proposes that **changes in APP and/or Aβ homeostasis lead to the aggregation of Aβ and deposition in plaques**, and that these events are sufficient to initiate the cascade of pathological abnormalities associated with AD[4]

APP proteolysis, by secretase enzymes, results in cleavage within the Aβ domain, generating nonamyloidogenic fragments that are reported to possess neurotrophic and neuroprotective properties[5]

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein; NFT, neurofibrillary tangle

1. Alzheimer A, et al. Clin Anat 1995;8:429–431; 2. Hardy JA, Higgins GA. Science 1992;256:184–185; 3. Selkoe DJ, Hardy J. EMBO Mol Med 2016;8:595–608; 4. Hardy J, Selkoe DJ. Science 2002;297:353–356; 5. Ring S, et al. J Neurosci 2007;27:7817–7826

This is the current working hypothesis used for drug discovery, but the mechanisms are not fully understood

The amyloid cascade hypothesis

Dominantly inherited
(missense mutations in the *APP*, *PSEN1,* or *PSEN2* genes)

Trisomy 21

- ↑ relative Aβ42 production throughout life

Accumulation and oligomerization of Aβ42 in limbic and association cortices

Subtle effects of Aβ oligomers on synaptic efficacy

Gradual deposition of Aβ42 oligomers as diffuse plaques

Microglial and astrocytic activation and attendant inflammatory responses

Altered neuronal ionic homeostasis, oxidative injury

Altered kinase / phosphatase activities lead to tangles

Widespread neuronal / synaptic dysfunction and selective neuronal loss with attendant neurotransmitter deficits

Non-dominant forms of AD – including sporadic AD (failure of Aβ clearance)

- Gradually rising Aβ42 levels in the brain

Cognitive symptoms and eventually dementia

This is the current working hypothesis used for drug discovery, but the mechanisms are not fully understood

Image from: Selkoe DJ, Hardy J. EMBO Mol Med 2016;8:595–608 (CC-BY 4.0 https://creativecommons.org/licenses/by/4.0/)

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein; PSEN, presenilin

Evidence to support the amyloid cascade hypothesis

Aβ was recognized as the primary component of neuritic plaques in the brain tissue of patients with AD[1]

All patients with AD undergo progressive Aβ deposition followed by surrounding neuritic and glial cytopathology in brain regions serving memory and cognition[2]

Mutations within and immediately flanking the Aβ region of APP cause aggressive forms of familial AD[2]

Inheritance of a missense mutation in APP that decreases the production and aggregation of Aβ provides lifelong protection against AD and age-related cognitive decline[2]

People with Down's syndrome carry three copies of APP, which is on chromosome 21. Consequently, almost all individuals with Down's syndrome develop AD neuropathological characteristics[3]

- Aβ deposition occurs before tau pathology in Down's syndrome[4]

NB this is the current working hypothesis used for drug discovery, but the mechanisms are not fully understood

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein

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Other co-factors in the pathophysiology of Alzheimer's disease pathogenesis

Many alternative co-factor models have been integrated into the amyloid-tau hypothesis as the links between them have become stronger

Co-factors	Rationale
Calcium[1]	Aβ oligomers can increase cytoplasmic Ca^{2+} levels, inducing Ca^{2+}-mediated apoptosis. The APP intracellular domain may also contribute to remodeling of the Ca^{2+} signaling pathway, further inducing apoptosis
Glutamate[2]	Aβ has been shown to increase neuronal susceptibility to glutamate-induced excitotoxicity through glutamate dysregulation
Inflammation[3]	In AD, soluble Aβ oligomers and Aβ fibrils bind to multiple receptors on microglia causing release of inflammatory cytokines and chemokines, disruption of Aβ phagocytosis by microglia, reduced microglia-derived neurotrophic factors, eg brain-derived neurotrophic factor
Cholinergic pathway[4]	Cholinergic depletions can impair attention and reduce the plasticity of the hippocampus.[4] Additionally, loss of cortical cholinergic innervation is associated with neurofibrillary tangles in the nucleus basalis, and correlations have been found between Aβ pathology and the activity of acetyltransferase, an acetylcholine-synthesizing enzyme[5]

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