

Tau is central in the genetic Alzheimer–frontotemporal dementia spectrum

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In contrast to the common and genetically complex senile form of Alzheimer’s disease (AD), the molecular genetic dissection of inherited presenile dementias has given important mechanistic insights into the pathogenesis of degenerative brain disease. Here, we focus on recent genotype–phenotype correlative studies in presenile AD and the frontotemporal dementia (FTD) complex of disorders. Together, these studies suggest that AD and FTD are linked in a genetic spectrum of presenile degenerative brain disorders in which tau appears to be the central player.

Introduction

Through the genetic dissection of Alzheimer’s disease (AD), we hope to increase our mechanistic understanding of this prevalent and untreatable disorder in which intra- and extraneuronal protein aggregates (known as tau tangles and amyloid plaques, respectively) accumulate in the degenerating brain. In particular, genetic studies of the rare and genetically simple early onset or presenile (onset before 65 years of age) forms of AD have led to the identification of several single gene lesions in the amyloid precursor protein (APP) [1] and the presenilins (PS) [2,3]. In addition, mutations in the gene encoding the microtubule associated protein tau (MAPT) cause autosomal dominant forms of frontotemporal dementia (FTD) [4,5], a degenerative brain disease that has overlapping features with AD (Box 1). Collectively, the discovery of these mutations has been highly instructive in delineating our current mechanistic understanding of AD and FTD. For detailed and up-to-date information on *APP*, *PS* and *MAPT* mutations, please see our interactive AD and FTD mutation database (<http://www.molgen.ua.ac.be/ADMutations>).

By contrast, similar to most frequent diseases, the genetic architecture of the common late-onset or senile form of AD (age of onset above 65 years; ~90% of all AD patients) is complex. So far the $\epsilon 4$ allele of the gene encoding apolipoprotein E (APOE) is the only well-established genetic risk-factor for late-onset AD, but the underlying mechanism remains poorly defined [6–8]. In addition, several studies have investigated numerous

candidate loci and genes, but none of these has reached the established position of *APOE*. The current status of potential candidate risk genes and loci has been extensively reviewed recently [9]; for an update, see the Alzheimer’s Research Forum genetic database, ‘Alzgene’ (<http://www.alzgene.org>).

In this review, we emphasize that careful genotype–phenotype correlative studies, including molecular genetic, biochemical, neuropathological and clinical investigations of inherited presenile forms of AD and FTD, are instrumental in defining the complete phenotypic spectrum associated with mutations in *APP*, *PS* and *MAPT* and will significantly advance our biological understanding of these diseases. More specifically, we review recent exciting evidence that AD-causing *PS* mutations have intrinsic loss-of-function properties and that *PS* loss-of-function has a role in FTD and amyloid-independent

Glossary

Cerebral amyloid angiopathy (CAA): CAA is a histopathological term referring to the deposition of $A\beta$ in the blood vessel walls of the brain (angiopathy), thereby predisposing individuals to brain bleeding (haemorrhagic strokes). Severe CAA and haemorrhagic stroke are characteristic features of mutations affecting the α -secretase-cleavage site of APP. CAA is a frequent observation in AD brains but usually does not result in strokes.

Progressive supranuclear palsy (PSP): PSP is a sporadic neurodegenerative Parkinson-like movement disorder. PSP is characterized by vertical eye movement disturbances, rigidity (resistance to imposed movement), severe gait and balance problems and FTD-like dementia later in the disease course. Abundant tau pathology in the form of tau tangles characterizes PSP neuropathologically. PSP is part of the FTD spectrum of disorders.

Corticobasal degeneration (CBD): CBD is a sporadic neurodegenerative Parkinson-like movement disorder and has many clinical overlapping features with PSP. The major difference with PSP is a marked asymmetry of the symptoms at onset. CBD is further characterized by impaired balance and abnormal muscle postures of the limb (dystonia). FTD-like dementia is also often observed later in the disease course. Abundant tau pathology in the form of fine filaments characterizes CBD neuropathologically. CBD is part of the FTD spectrum of disorders.

Spastic paraparesis: Spastic paraparesis is characterized by insidiously progressive bilateral lower extremity weakness and spasticity. The primary pathology in spastic paraparesis is degeneration of the distal ends of the long spinal axons of the cortical motor neurons. Some *PS* mutations are associated with AD and spastic paraparesis.

Pick bodies: Pick bodies are tau-positive cytoplasmic neuronal inclusion and are the pathological hallmark lesions of Pick’s disease, a neuropathological subtype of tau-positive FTD. Pick bodies are not related to the Lewy bodies observed in Parkinson’s disease, which are tau-negative and α -synuclein-positive.

Niemann-Pick disease type C (NPC): NPC is a recessive lysosomal disorder of childhood probably caused by lysosomal storage of cholesterol. In NPC the neuronal degeneration is characterized by prominent tau pathology in the form of AD-like tau tangles. Mild adult-onset forms of this disease exist and then present as psychiatric disease and presenile dementia.

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Box 1. Overlap between presenile AD and FTD

FTD and AD are primary degenerative dementias, meaning that a gradual loss of neurons is responsible for the progressive brain dysfunction. Within the group of presenile dementias (onset <65 years of age), FTD is the second most common form of neurodegenerative dementia after AD. Clinically, AD is primarily a disease of memory and cognition caused by a more generalized brain atrophy, starting in the medial temporal lobe. The hallmarks of FTD are behavior and/or language dysfunction caused by a more focal degeneration mainly affecting the frontal and temporal brain regions. Nevertheless and despite the existence of useful clinical diagnostic criteria for both disorders, the distinction between

presenile AD and FTD can be difficult, especially in presenile cases, which often have an atypical presentation. In particular, the inherited forms of FTD have an extremely broad phenotype ranging from typical FTD to cases where parkinsonism, amyotrophy or AD-like memory impairment are the major disabling features. In addition, focal variants of AD, where memory loss is not a prominent early feature, are relatively common in a presenile setting and can mimic FTD. Because deposition of tau protein aggregates in affected brain regions is a common feature in AD and tau-positive FTD, it is likely that both disorders share a common pathogenetic mechanism.

neurodegeneration. In addition, we review recent studies that further confirm the primary genetic role of *MAPT* in the FTD complex of disorders and give an update on a novel genetic form of FTD linked to the *MAPT* region with the striking absence of demonstrable *MAPT* mutations and tau pathology.

Defining the extremes: APP versus MAPT phenotypes

APP disorders: the 'amyloidocentric' view

Initial genetic linkage studies mainly targeted chromosome 21, because the brains of almost all middle-aged Down syndrome patients, who have a trisomy of chromosome 21, contain the neuropathological hallmarks of AD. The underlying hypothesis was that in Down syndrome patients, AD is caused by over-representation of a gene on chromosome 21 as a result of the trisomy 21, whereas in AD, a mutation in that gene might result in the production of an abnormal protein or the overproduction of a normal protein [10,11]. Since the identification of the first AD-causing mutation in *APP* at 21q21 [1], 18 different causative *APP* mutations have now been reported (Figure 1; AD and FTD Mutation Database: <http://www.molgen.ua.ac.be/ADMutations>). Strikingly, all of these mutations cluster at, or are near to, sites within *APP* that are normally cleaved by proteases called the α -, β - and γ -secretases. These enzymatic activities regulate the metabolism of *APP* including the generation of the A β peptide, which is the major constituent of the amyloid plaques. Interestingly, the phenotypic outcome of these mutations is strongly dependent on which cleavage site is mutated. For example, mutations affecting the α -cleavage site promote the self-aggregation of mutated A β peptides, leading to severe amyloid deposition within the cerebral vessel walls or cerebral amyloid angiopathy (CAA) and hence strongly predispose affected individuals to haemorrhagic strokes (Figure 2). However, with the exception of the Dutch APP E693Q mutation, which causes a pure CAA-related haemorrhagic stroke phenotype [12,13], these mutations at the α -cleavage site also lead to the deposition of amyloid plaques and tau tangles in the brain parenchyma in addition to CAA, which together result in a combined neurodegenerative and haemorrhagic stroke disorder as illustrated by the Flemish APP A692G mutation [14,15]. However, mutations affecting the β - [16] and γ -secretase sites [1] favor the release of amyloidogenic A β 42 from its precursor and mostly result in typical AD phenotypes characterized by amyloid plaques and tau tangles with CAA being less prominent.

Interestingly, the Austrian APP T714I mutation, which is located at the γ -secretase-cleavage site of *APP*, results in an extremely aggressive AD phenotype with an onset age of ~35 years and is characterized by tau tangles and extensive deposition of nonfibrillar 'cotton wool' amyloid plaques [17].

Together, genotype–phenotype correlation studies of *APP* mutations strongly implicate various forms of A β

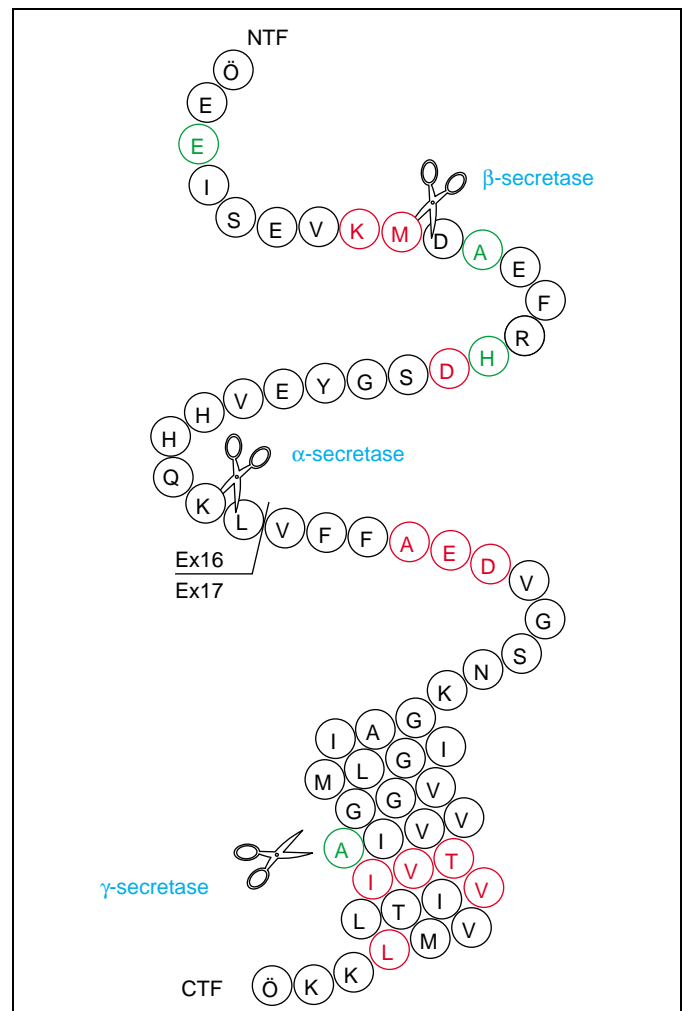
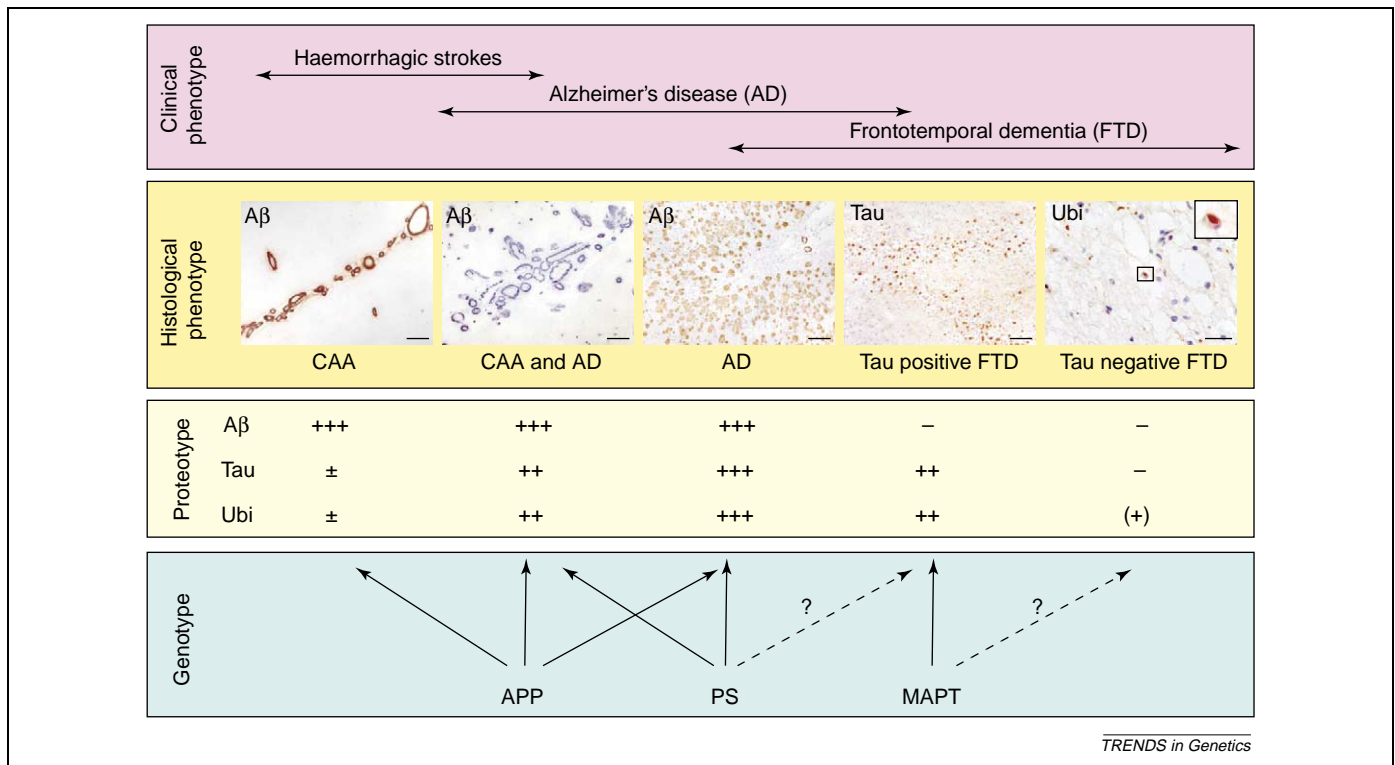


Figure 1. APP mutations. Schematic representation of the protein sequence encoded by exons 16 and 17 of *APP*. Each circle represents an amino acid; those with pathogenic missense mutations are shown in red and those with non-pathogenic missense mutations are in green. Pathogenic mutations are always at or close to sites that are cleaved by the α -, β - or γ -secretases. The figure was adapted with permission from the Alzheimer Research Forum (<http://www.alzforum.org/>) and can also be found at our AD and FTD mutation database available at <http://www.molgen.ua.ac.be/ADMutations>.



TRENDS in Genetics

Figure 2. The genetic AD–FTD spectrum of degenerative brain disease. This figure integrates the genotype–proteotype–phenotype correlations and suggests the existence of a genetically interconnected spectrum of AD and FTD disorders. The FTD complex of disorders includes PSP and CBD, sporadic disorders with prominent parkinsonism neuropathologically characterized by tau deposits. Throughout the spectrum the involvement of tau either histopathologically or genetically appears to be a constant characteristic. Images in the histological phenotype panel represent prototypical examples of neuropathological dementia subtypes. CAA: Aβ-positive blood vessels in the temporal region of a patient with the Dutch APP E693Q mutation; CAA and AD: Aβ-positive blood vessels and dense cored plaques in the temporal region of a patient with the Flemish APP A692G mutation; AD: Aβ-positive dense cored plaques in the temporal region of a patient with the PS1 I143T mutation; Tau positive FTD: tau-positive Pick bodies in the hippocampus of a patient with the PS1 G183V mutation; Tau negative FTD: cytoplasmic and intranuclear ubiquitin (Ubi) positive inclusions in the temporal region of a patient of a family linked to the MAPT locus but without MAPT mutations. Scale bars represent 200 μm except in Tau negative FTD, where the scale bar corresponds to 50 μm. In the proteotype panel: +++ indicates highly abundant; ++ indicates abundant; (+) indicates present but inconsistently; ± indicates sometimes present and – means absent. In the genotype panel: arrows correspond to clearly established genotype–phenotype links, and dashed arrows correspond to probable links that need confirmation.

deposition, ranging from vascular CAA and fibrillar core-containing plaques to non-fibrillar ‘cotton wool’ plaques, as an essential characteristic of AD (Figure 2). Interestingly, our own morphological studies of APP mutations in human and mouse have strongly implicated the vascular system in the formation of core-containing amyloid plaques suggesting that vascular damage might be an important contributing factor to AD pathogenesis [15,18]. Importantly and with the possible exception of the Dutch APP mutation, tau deposits in the form of tangles are a consistent but downstream consequence throughout the APP spectrum of disorders.

MAPT disorders: the ‘tauocentric’ view

In 1998, the first mutations in MAPT causing autosomal dominant FTD were identified [4,5] and 40 different causative MAPT mutations have now been reported (Figure 3 and FTD Mutation Database: <http://www.molgen.ua.ac.be/FTDMutations>) [19]. Interestingly, nearly all mutations are located in the C-terminus of the protein and include missense, silent and intronic variations in addition to two single codon deletions clustered in or near the microtubule-binding domains. Importantly and in sharp contrast to APP phenotypes, MAPT disorders are neuropathologically characterized by absence of Aβ deposits but share with AD the invariable presence of

different forms of tau aggregates and are therefore called pure tauopathies [20] (Figure 2). Clinically, MAPT mutations most typically present with FTD. However, the spectrum of MAPT disease is surprisingly wide and ranges from phenotypes in which FTD is accompanied by severe parkinsonism and motor neuron disease to degenerative disorders that are, as in the case of the MAPT R406W mutation, clinically hardly distinguishable from AD [21,22].

More recently, several autosomal dominant FTD families have been described that lack visible tau positive lesions but are still conclusively linked to a chromosomal region that contains MAPT [23–25]. In these families, the neuropathological phenotype has been described as either ‘dementia lacking distinctive histopathology’ [23] or ‘FTD with tau-negative and ubiquitin-positive inclusions’ [24,25], although it is currently unclear if these represent distinct disease entities or are pathological manifestations of the same primary defect. Strikingly however and consistent with the absence of tau-positive lesions, no causative MAPT mutations have been found in these families, despite extensive sequencing of the whole genomic MAPT locus [26]. Although this might be explained by a defect in another gene in close proximity to MAPT [24], others have suggested that this FTD subtype is a ‘no tau tauopathy’ caused by a primary tau

mechanism explaining this well-replicated association remains unresolved, *in vitro* studies have suggested that the *MAPT* H1 haplotype might be more efficient at driving *MAPT* gene expression than the H2 haplotype [40]. To further understand the genetic mechanism explaining the association, we recently generated a high-density single nucleotide polymorphism (SNP) map by sequencing 138 kb of the genomic region of *MAPT* (R. Rademakers *et al.*, personal communication) and identified a 22-kb PSP-risk-containing regulatory region in the large intron preceding the first coding exon of *MAPT*, which was fully explained by one SNP, htSNP167, creating a transcription factor CP2 (TFCP2) binding site. Recently, Pittman *et al.* [41] published SNP haplotype association data from a PSP patient–control sample that overlapped with the extended American sample we used in our study and identified a 56.3-kb risk-increasing interval that also contained htSNP167.

Together these data strongly indicate that *MAPT*, through a toxic gain-of-function mechanism, is capable of inducing neuronal death leading to a wide range of degenerative phenotypes that can be grouped under the FTD or Pick complex of degenerative brain disorders [36] (Figure 2). A toxic gain-of-function is also supported by

several animal model studies in which overexpression of mutant and wild-type tau causes neurodegeneration [42,43,32].

In between the extremes: PS disorders?

Although the phenotypes induced by APP and *MAPT* lesions are strongly supportive for an ‘amyloidocentric’ and ‘tauocentric’ view of neurodegeneration, respectively, recent genetic evidence suggests that these pathways might converge at the level of PS (Figure 2).

First, strong evidence exists for a direct etiological link between PS and APP processing. Since the identification of mutations in PS [2,3], the most common cause of inherited presenile AD, 154 different PS mutations (144 in *PS1* and ten in *PS2*), mostly of the missense type, have been identified (Figure 4 and AD Mutation Database: <http://www.molgen.ua.ac.be/ADMutations>). Similar to mutations at the β - or γ -secretase-cleavage site, PS mutations generally result in typical AD phenotypes with amyloid plaques and tau tangles. In addition, AD-causing PS mutations increase the *in vitro* ratio of A β 42 to A β 40? [44], and it is now well established that PS is a core component if not the catalytic subunit of the multimeric γ -secretase [45,46]. In general, patients with *PS1*

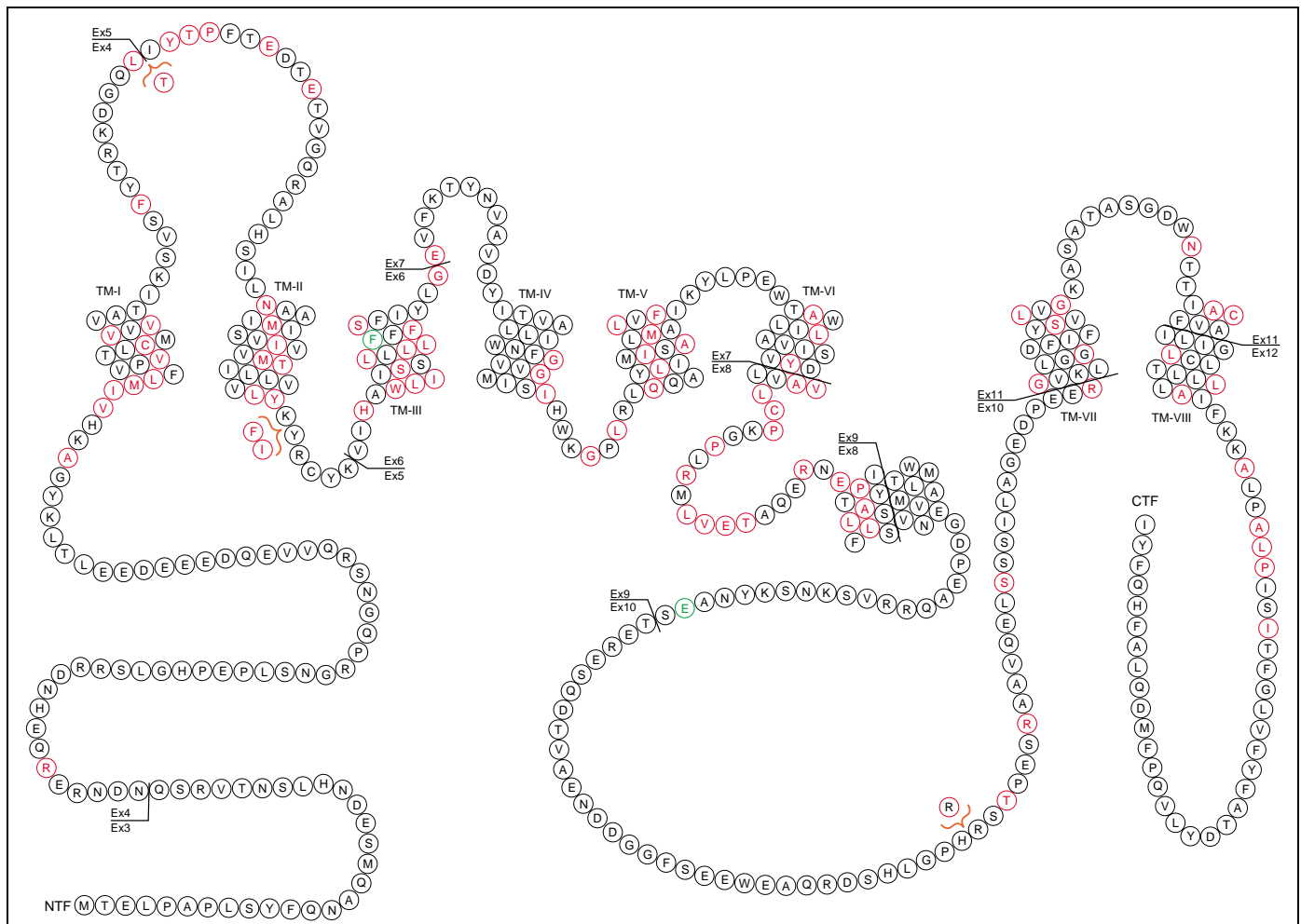


Figure 4. PS mutations. Schematic representation of PS1, the most frequently mutated gene in presenile AD. Each circle represents an amino acid; those with pathogenic missense mutations are shown in red and those with non-pathogenic missense mutations are in green. The predicted transmembrane regions of the protein (TM) are also shown. This figure was adapted with permission from the Alzheimer Research Forum (<http://www.alzforum.org/>). *PS2* mutations are not shown but can also be found at our online AD and FTD mutation database available at <http://www.molgen.ua.ac.be/ADMutations>.

mutations have a more aggressive disease course and earlier age of onset compared with those carrying *PS2* mutations [47].

Interestingly, *PS* mutations appear capable of inducing a relatively wide spectrum of clinical and neuropathological phenotypes. However, some *PS* mutations, particularly in cases in which the mutation lies beyond codon 200, are associated with a prominent CAA [48], sometimes, even reminiscent of the Flemish APP A692G α -secretase mutation [14] (e.g. the PS1 L282V mutation [49]). In contrast to mutations at the APP α -secretase-cleavage site and with one reported exception [50], *PS*-related CAA is generally not sufficiently severe to cause haemorrhagic strokes. Another type of *PS* mutations leads to 'variant' AD, presenting with spastic paraparesis and diffuse 'cotton wool' plaques [51,52], similar to those observed in carriers of the Austrian APP mutation [17]. It was suggested that cases with 'variant' AD represent an aggressive subtype of AD because *PS* mutations causing this condition lead to exceptionally high *in vitro* amyloid concentrations [53]. Nevertheless, although these *PS* mutations have interesting and unusual features, they are consistent with aberrant APP processing being the primary underlying mechanism in these disorders. Again, it is important to emphasize that all these *PS* mutations also lead to prominent tau pathology, albeit to a different extent. Unfortunately, no studies are available that, similar to CAA [48], have systematically addressed whether the severity of tau pathology is also determined by *PS* mutation position.

More recently, the phenotypic spectrum of *PS* mutations has been extended to FTD [54]. For example, PS1 L113P, G183V and insArg352 were identified in families with clinical FTD [55–57]. Interestingly, neuropathological examination in a patient with PS1 G183V revealed tauopathy in the form of Pick bodies and complete absence of amyloid plaque pathology [57]. Consistent with the idea that *PS* mutations can produce Pick bodies [57], co-existent AD and Pick body pathology was observed in patients with PS1 M146L and A260V mutations [58,59].

Together, the phenotypic spectrum associated with *PS* mutations appears to be broad, ranging from phenotypes strongly resembling the *APP* mutations at the α -secretase-cleavage site to FTD without A β pathology (Figure 2).

Do *APP* and *PS* mutations have gain- or loss-of-function properties?

An important but still unresolved issue, with respect to clinical *APP* and *PS* mutations, is whether they represent gain- or loss-of-function alleles. The answer to this question is important not only from a mechanistic point of view, but also with respect to the development of therapeutics targeting the γ -secretase complex. Indeed, if *APP* and *PS* mutations reduce γ -secretase cleavage of APP, the proposed use of γ -secretase inhibitors as therapeutic agents in AD might lead to an unwanted enhancement of the neuronal degeneration.

Because of their dominant mode of inheritance and ability to increase the ratio of A β 42 to A β 40 *in vitro* [44], *APP* and *PS* mutations are generally considered toxic

gain-of-function alleles in the context of AD pathogenesis. However, when taking, for example, Notch signaling as a functional readout of *PS* or γ -secretase function, several studies suggest that AD-causing *PS* mutations are intrinsically at least partial loss-of-function mutations. Indeed, loss of Notch cleavage or signaling has been demonstrated in mammalian cell lines [60,61] and in *Caenorhabditis elegans* [62,63]. Further support for this idea comes from a strong loss-of-function mutation in the *C. elegans PS* homologue *sel-12* (C60S), isolated in a forward genetic screen [64], which corresponds to the human PS1 C92S mutation and is known to cause AD [65] by increasing the ratio of A β 42 to A β 40 [66,67]. Nevertheless, the situation is not completely clear because, although all *PS* mutations and the partial reduction of normal PS1 activity [68] increase the ratio of A β 42 to A β 40, the total loss of *PS* results in loss of both A β 40 and A β 42 [45]. In addition, it is not well established if the increased A β 42:A β 40 ratio induced by the *PS* mutation is caused by a decrease in A β 40, an increase in A β 42 or a combination of both.

Interestingly, recent studies show that with respect to the generation of A β peptides from APP, AD-causing *PS* mutations have reliable loss-of-function properties. In a recently developed, highly reproducible cellular assay, we observed that all nine tested *PS* mutations consistently decreased A β 40 and accumulated direct γ -secretase substrates in the form of APP C-terminal fragments, a sign of decreased *PS* activity (S. Kumar-Singh *et al.*, unpublished). Although the A β 42:A β 40 ratio was significantly increased for all, in only four *PS* mutations a significant increase in A β 42 was noted. A recent report on *PS2* mutations has also shown A β 40 loss [69] and similar results were obtained using *PS*-deficient cells (B. De Strooper *et al.*, unpublished). The interesting conclusion from these studies is that AD-related *PS* mutations are less efficient in cleaving several γ -secretase substrates including APP and therefore behave as intrinsic biological partial loss-of-function alleles regarding γ -secretase function. Consistent with decreased γ -secretase activity for clinical AD mutations, a recent study has shown that both *PS* and *APP* mutations located in the vicinity of the γ -secretase-cleavage site reduce γ -secretase-mediated liberation of the APP C-terminal fragment [70].

Together these results suggest that the consistently increased A β 42:A β 40 ratios induced by AD-causing *APP* and *PS* mutations are the consequence of reduced γ -secretase activity. However, the exact mechanism is not understood.

Is there a role for loss of *PS* in amyloid-independent neurodegeneration?

With respect to this gain- versus loss-of-function discussion, interesting results have come from several recent studies. Conditional knockout mice lacking both *PS* in the post-natal forebrain showed progressive synaptic impairments and, importantly, severe age-dependent neurodegeneration characterized by cytoplasmic accumulations of hyperphosphorylated tau [71,72] but no A β deposits [73]. Because these results show that complete loss of *PS* can lead to an amyloid-independent form of tau-positive

neurodegeneration, recent findings of PS mutations in FTD become highly intriguing. It was suggested that the PS1 G183V mutation, which is associated with FTD and with tauopathy in the form of Pick's disease but not with A β plaques, might also have loss-of-function properties because it affects the splice signal at the junction of the sixth exon and intron [57]. Interestingly, follow-up studies indeed revealed that this mutation, in addition to producing full-length PS1 G183V protein, also generates alternative transcripts that either lack exon six or exons six and seven leading to truncated proteins. In addition, cellular γ -secretase assays show that the truncated proteins behave as complete null alleles also suggesting a loss-of-function mechanism (Dermaut *et al.*, unpublished). Strikingly, a loss-of-function mechanism has also been proposed for the PS1 insArg352 mutation that strongly inhibits γ -secretase cleavage of both Notch and APP [74] and is associated with FTD [56] without amyloid pathology (B. Boeve, personal communication).

Although additional confirmation is needed to establish a role of PS in amyloid-independent FTD, these studies suggest that throughout the PS spectrum of disorders, ranging from AD with a strong amyloid component to possibly tau-positive AD [57], partial PS loss-of-function might be the common theme, an idea that is also supported by studies suggesting that AD-risk-increasing alleles in the regulatory region of *PS1* significantly decrease PS expression levels [75,76]. In addition, several recent cell biological studies have suggested that PS mutations through reduced PI3K-Akt signaling promote glycogen synthase kinase 3 β (GSK3 β) activity and hence tau hyperphosphorylation [77–79], further suggesting a direct mechanistic link between PS loss-of-function and tau pathology.

Another line of recent evidence has linked dysfunction of the endosomal-lysosomal degradative system to loss of PS function [80,81]. This is interesting, because neurodegeneration is a frequent observation in lysosomal disorders [82] and abnormalities in the endosomal-lysosomal system have long been thought to be an early and prominent feature in AD [83]. In addition, tauopathy in the form of tau tangles is a highly consistent feature in the lysosomal disorder Niemann-Pick Type C [84] that, in its adult onset form, can present with FTD-like dementia. Strikingly, the recent finding that mutations in the charged multivesicular body protein 2B (CHMBP2B) on chromosome 3 cause FTD [85] further implicates dysfunctional late-endosomal or lysosomal activity in neuronal degeneration.

Is tau the central molecule in the AD–FTD spectrum?

When placed in the context of previous genotype–phenotype correlation studies, recent findings show that FTD and AD not only share important clinical and neuropathological features but are also etiologically linked at the molecular genetic level, implying that these disorders are part of a genetically interconnected spectrum of presenile degenerative brain disorders. In addition, recent studies showing that: (i) genetic alterations at the level of *MAPT* are strongly associated with different types of tau-mediated neurodegeneration; (ii)

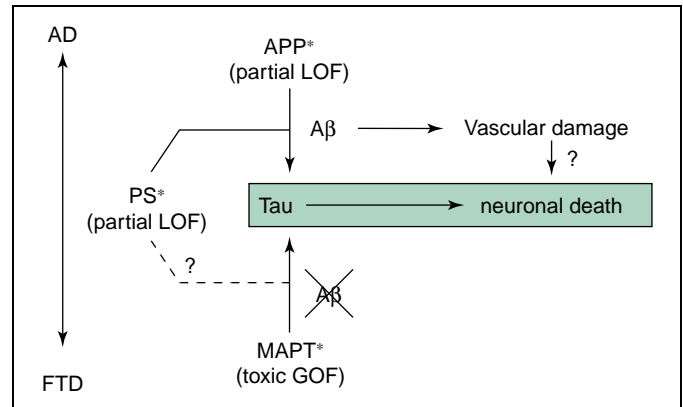


Figure 5. Tau is central in the AD–FTD spectrum. A speculative model for tau-mediated neurodegeneration in the genetic AD–FTD spectrum of brain disorders. The asterisks (*) refer to disease-associated genetic alterations in APP, PS and MAPT that, through gain- (GOF) or loss-of-function (LOF) mechanisms, result in tau-positive neurodegeneration (shown in the center). The relative presence (shown in the upper panel) or absence (lower panel) of A β pathology is indicated (A β). The diagram shows that, in addition to tau pathology, APP and typical PS mutations lead to A β -positive pathology causing vascular damage and hence neuronal death. By contrast, genetic alterations in *MAPT* lead to A β -independent tau-mediated neuronal death. Recent evidence suggests that loss of PS function might result in A β -negative tau-mediated neurodegeneration (dashed line) further emphasizing that tau is the central molecule in the AD–FTD spectrum.

AD-causing PS mutations are intrinsically loss-of-function alleles; and (iii) PS loss-of-function can lead to tau pathology, lead us to propose that tau is the major player throughout this AD–FTD spectrum (Figure 5). Within this framework, the further etiologic and mechanistic establishment of PS loss-of-function in amyloid-independent and tau-mediated neurodegeneration as well as the identification of the molecular defect leading to tau-negative FTD (caused by *MAPT* or another gene nearby) are the most exciting and important future research topics.

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