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Tau Alternative Splicing and Frontotemporal Dementia

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Abstract

A number of neurodegenerative diseases are characterized by the presence of abundant deposits containing Tau protein. Expression of the human tau gene is under complex regulation. Mutations in the tau gene have been identified in patients with frontotemporal lobe dementia. These mutations affect either biochemical/biophysical properties or the delicate balance of different splicing isoforms. In this review, we summarize recent advances in our understanding of genetics and molecular pathogenesis of tauopathies with the focus on frontotemporal lobe dementia. We review published studies on tau pre-mRNA splicing regulation. Understanding molecular mechanisms of tauopathies may help in developing effective therapies for neurodegenerative tauopathies and related disorders, including Alzheimer disease.

Keywords

frontotemporal dementia; tau alternative splicing

Frontotemporal dementia (FTD) is characterized by memory deficits and impaired cognition associated with degenerative changes in the frontal and temporal lobes of the brain. FTD belongs to a group of genetically and phenotypically heterogeneous disorders named tauopathies. A major neuropathological hallmark of tauopathies is the filamentous deposits containing hyperphosphorylated tau protein in neurons and glia of affected individuals. The term tauopathy was first used to describe familial dementia cases with abundant tau deposits in the frontotemporal regions of affected brains.[1] Tauopathies include Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), FTDs, Down Syndrome (DS), several variants of Prion Diseases and Alzheimer disease (AD).

The tau gene encodes microtubule-associated proteins that stabilize the microtubule cytoskeleton and promote microtubule assembly. The fact that Tau dysfunction leads to neurodegenerative diseases indicates that Tau protein is critical for neuronal function. A large number of studies show that Tau plays an important role in neuronal integrity and axonal transport by regulating microtubule stability and dynamics.[2-4] The human tau gene is located on chromosome 17q21, occupies over 100 kb, and contains 16 exons.[5,6] Human tau gene undergoes alternative splicing to produce six isoforms (Fig. 1). Alternative splicing of exons

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2, 3, and 10 generates tau proteins containing 3 or 4 microtubule binding repeats, Tau3R or Tau4R.[6,7] In the adult human brain, the ratio of 3R and 4R tau transcripts is approximately one. This delicate balance of Tau3R versus Tau4R appears to be critical for neuronal function. Mutations that disrupt this balance lead to the development of tauopathy (Fig. 2, Table 1). Alternative splicing of the tau gene is also regulated during development. Tau3R is the predominant isoform in the fetal brain, whereas Tau4R isoform increases to the same level as Tau3R during the post-natal period.[8] The functional difference between Tau3R and Tau4R remains unclear, although in-vitro studies suggest that Tau4R is more efficient at promoting microtubule assembly and has greater MT binding affinity than Tau3R.[9-12]

FTDP-17: CLINICAL AND NEUROPATHOLOGICAL FINDINGS

Frontotemporal dementia occurs in both familial and sporadic forms. One of the best-characterized form of FTDs is frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). Clinical manifestations of FTDs include behavioral/personality changes and motor disturbances that are associated with severe cognitive impairment. Clinical phenotypes of FTDs can vary significantly, ranging from emotional blunting, loss of insight, disinhibition, mental rigidity, mood instability, and impaired judgment/executive functions to language deficit. Neuropathological features of FTDP-17 are frontotemporal atrophy with abundant Tau-containing deposits in the frontotemporal cortex accompanied by neuronal loss, gliosis, and cortical spongiform changes.[13-15] The Tau-containing deposits are often in the form of filamentous inclusions named neurofibrillary tangles (NFTs) containing hyperphosphorylated Tau protein. A series of genetic studies of FTDP-17 patients have identified at least 25 different mutations in the tau gene on chromosome 17. These and subsequent studies have provided a molecular basis for our understanding of FTDP-17 pathogenesis.

The clinical presentation of FTDP-17 can differ not only between mutations, but also within a single mutation and sometimes within the same family. For example, clinical variability has been reported in nine UK families carrying the +16 tau mutations.[16]

Similarly, for patients carrying the P301L missense mutation, clinical diagnoses have ranged from PSP to CBD and PiD.[17-20] The N279K missense mutation typically leads to clinical manifestations similar to PSP, with dementia.[16,21-23] On the other hand, similar clinical phenotypes can result from different mutations. For instance, Parkinsonism is frequently present in individuals with tau mutations affecting tau exon 10 splicing, whereas PiD without motor dysfunction has often been diagnosed in individuals with different missense mutations in exon 9 (G272V and K257T) and exon 13 (G389R)[18] (Fig. 2, Table 1). Taken together, these studies indicate that there is extensive clinical overlap between the various tauopathies. Emerging data suggest that the genetic background may affect the phenotypic manifestations of a particular FTDP-17 mutation. For example, a comparison of two kindreds with the N279K mutation revealed different haplotypes.[23] It is likely that the clinical variations between different tauopathies associated with tau gene mutations may result from compounding effects by other genetic and/or epigenetic modifiers.

Neuropathological changes in FTDP-17 brains have been characterized by the presence of abundant filamentous inclusions containing hyperphosphorylated Tau protein. However, the morphology, Tau protein isoform composition, and distribution of tau filaments/deposits appear to vary with the types of tau mutations. Missense mutations located outside exon 10, lead to the Tau pathology that is largely neuronal, without a prominent glial component. Some of these mutations, such as missense mutation V337M in exon 12, lead to the formation of both paired helical filaments (PHF) and straight filaments (SF) that contain all six tau isoforms and resemble those seen in AD.[18] By contrast, a mutation in exon 13, G389R, leads to the

neuropathology more closely resembling PiD, with a large number of Tau-immunoreactive Pick-body–like and axonal inclusions[1] (Table 1). The P301L and P301S missense mutations within exon 10 lead to a pathology that is both neuronal and glial[17-18,24] (Fig. 2, Table 1). Analysis of insoluble Tau protein from brains of patients carrying the P301L mutation has revealed the presence of narrow, twisted-ribbon structures composed of Tau4R, with a small amount of Tau3R isoform.

Intronic *tau* mutations that increase the inclusion of exon 10 have been associated with a widespread neuronal and glial pathology, with the glial component being more prominent than that produced by the P301L and P301S mutations. Ultrastructurally, wide twisted ribbon-like filaments composed largely of Tau4R isoforms, have been observed in individuals with the τ3, τ11, τ12, τ13, +14, and τ16 intronic mutations1[25-27] (Fig. 2, Table 2). These filaments look much like those found in the brains of CBD patients. Neuronal and glial pathology has also been reported for several coding-region mutations that increase exon10 inclusion (Table 1). It remains unclear what factors determine the extent of neuronal versus glial involvement and to what degree glial Tau pathology contributes to clinical manifestations and progression of FTD patients.

It is obvious from these data that there is great variability in the morphology of the Tau filaments in the patients carrying different mutations. Although Tau filament morphology may reflect the Tau isoform composition, other factors might be involved. Two types of Tau filaments that are consistently observed are the PHFs seen in AD brains that contain all six tau isoforms, and the wide twisted-ribbon shaped filaments composed mainly of Tau4R found in brains with tau splicing mutations.

GENETICS OF FRONTOTEMPORAL DEMENTIAS

Frontotemporal dementias are genetically heterogeneous. FTDs share common clinical and neuropathological features with other neurodegenerative diseases involving extensive neuronal loss and neurofibrillary tangle formation in the brain, for example, Alzheimer disease (AD). It is not clear yet, whether genetic players in neurodegenerative diseases such as AD may also act as genetic modifiers for FTDs. The genetics of FTDP-17 is best understood among different types of familial FTDs. A number of mutations have been identified in either exonic or intronic regions of the tau gene. These mutations can be classified as missense mutations that alter Tau peptides or splicing mutations that affect the balance of different tau splicing isoforms. Missense mutations may alter Tau protein sequence in the conserved residues within or near the microtubule binding domains. Splicing mutations can occur in the coding region or intronic regions. Some mutations can affect both peptide sequence and alternative splicing of the tau gene (eg, N279K). A few single nucleotide changes that do not affect Tau peptide sequence (silent mutations [eg, L284L, N296N, and S305S]) affect alternative splicing of the tau gene (Table 1). Missense mutations have been found in exon 9, 10, 12, and 13 (eg, K257T, G272V, K280, P301L, P301S, V337M, G389R, and R406W) (Table 1). Most splicing mutations are within or near intron 10 (eg, at +3, +11, +12, +13, +14, +16 nucleotides, Fig. 2, Table 2). In addition, sequence polymorphisms have been reported to define two specific haplotypes (H1 and H2). It appears that carriers of the H1H1 tau haplotype have a greater risk for PSP, CBD, PD, and FTD.[28-32] The H1 haplotype is very common in the general population, and the mechanism for this association is not clear.

There is a significant variation in clinical manifestations of FTDP-17 patients. Patients with the same P301L mutation may have distinct phenotypes.[19] Conversely, patients with different haplotypes may share common clinical phenotypes.[20] The correlation between genotypes and phenotypes in FTDP-17 patients is not simple. It is likely that other genetic modifier genes will emerge in the future.

Molecular Pathogenesis of FTDP-17

A large number of studies have been carried out since genetic mutations were first reported in FTDP-17 patients. Biochemical studies on the various missense mutations associated with FTDP-17 have provided insights into the function of Tau protein. Two models have been proposed to explain the molecular mechanisms underlying neurodegeneration caused by mutations in the tau gene: loss-of-function versus gain-of-function toxicity.[10,12,33,34] These two models are not necessarily exclusive of each other. It is possible that both cytotoxicity of mutant Tau proteins and loss of a balanced regulation of the microtubule cytoskeleton contribute to the pathogenesis of FTDs. Missense mutations including K257T, G272V, K280, P301L, P301S, V337M, G389R, and R406W affect the binding of Tau protein to the microtubules and microtubule assembly[12,33-35] (Table 1). Mutant Tau protein has an increased tendency to self-assemble into paired helical filaments (PHFs) in vitro.[36,37] It has been suggested that the sequence 306-VIVYK-311 act as a nucleation sequence to initiate PHF formation.[38,39] Missense mutations associated with FTDP-17 such as R406W and V337M lead to increased Tau phosphorylation that is associated with reduced microtubule binding and increased Tau aggregation.[40] Most splicing mutations disrupt the delicate balance between Tau3R and Tau4R isoforms. A general picture that has emerged from biochemical studies is that both missense and splicing mutations in the tau gene lead to the dissociation of Tau protein from mictotubules and an increase in the pool of unbound Tau that is believed to cause NFT formation.

Missense mutations that decrease the affinity of Tau for microtubules are likely to increase the level of free Tau protein. Splicing mutations, on the other hand, increase the amount of Tau4R while decreasing the level of Tau3R. Analyses of NFTs from affected brains show that NFTs contain predominantly Tau4R.[35,41] Biochemical studies suggest that Tau4R has stronger activity in promoting microtubule assembly and stabilization than Tau3R.[12] It has been proposed that Tau4R and Tau3R may bind to distinct sites on microtubules.[11,42,43] In-vitro cell culture experiments suggest that expression of mutant Tau reduces the axonal transport of vesicles and cell organelles, leading to the starvation of the synapse and increased oxidative stress and neurodegeneration.[3,44,45] There is no single unified theory to explain the molecular pathogenesis of all tau mutations. In addition, protein kinases and phosphatases have been implicated in post-translational modification of Tau proteins. These studies have been covered by several recent reviews.[46,47] In addition, Tau function is modulated by chaperones such as Hsp70 and CHIP (carboxyl terminus of the Hsc70-interacting protein), and this may influence the level of normal Tau protein and clearance of the mutant Tau proteins.[48,49]

A number of studies have been carried out to understand the mechanisms regulating the ratio of Tau4R/Tau3R since the report of splicing mutations in FTDP-17 patients. Two models have been proposed for the regulatory elements in tau pre-mRNA, a stem-loop model and a linear cis-element model (Fig. 3). The nucleotide sequence around the 5′ splice site, biochemical experiments, thermodynamic analysis, and NMR structural analyses support the presence of a stem loop structure.[14,50-55] In this model, the nucleotide sequence flanking the 5′ splice site of exon 10 forms a stem-loop structure that prevents the maximal binding of U1-snRNP to this 5′ splice site. Consistently, alterations in the mutant background by inserting compensatory base-pairing nucleotides that restore the predicted stem-loop pairing or binding to an antisense oligomer result in the wild-type tau exon 10 splicing pattern.[50-56] This model provides a good explanation for the enhancement of exon 10 inclusion by various intronic or exonic point mutations in this region. In the linear cis-element model, multiple weak interactions between factors binding to sequences inside intron 9, exon 10, and intron 10 act in a linear fashion to modulate the splicing of exon 10. This model was proposed based primarily on mutagenesis experiments carried out using a tau minigene containing exon 10 with 33 and 51 nucleotides flanking intron sequence inserted into a heterologous HIV tat gene splicing cassette.[57-59] It

is interesting to note that the protein-RNA interactions involved in exon 10 alternative splicing regulation are highly dynamic and that the two models do not exclude each other. The PCR results obtained from the tau minigene by Schellenberg and colleagues do not rule out the possibility of the stem-loop structure. It is possible that multiple RNA-protein interactions modulate the stability of the stem-loop structure in cells. Such RNA-protein interactions may undergo changes during development, offering one explanation for the developmental regulation of tau exon 10 splicing.

Both models described above for tau exon 10 splicing regulation suggests that trans-acting factors interact with splicing regulatory sequences inside and flanking exon 10, and that mutations associated with FTDP-17 may affect such RNA-protein interactions. A systematic search for proteins that modulate tau exon 10 alternative splicing has been initiated using an expression cloning strategy (Wu, unpublished results). Several protein factors have been identified using biochemical assays or transfection-PCR approaches that interact with tau pre-mRNA and influence tau exon 10 splicing, including SR-domain containing proteins and an hnRNP protein.[52,60-62] The physiological roles of these protein factors in regulating tau exon 10 splicing remains to be elucidated using strategies such as knock-out.

Animal Models of FTDP-17

A number of attempts have been made to create animal models for tauopathies, in particular, FTDP-17. This topic has been covered in several recent reviews.[63-67] Transgenic mice have been made expressing the human Tau protein in neurons and glia. Abundant Tau4R filaments were found in mouse models with either P301L or P301S mutations.[68,69] The filamentous Tau was hyperphosphorylated, similar to that found in affected human brains. In such mice, hyperphosphorylation of Tau preceded filament formation, axonal transport was affected, and mice showed severe memory deficits.[70-72] Various mouse models of tauopathies indicate a connection between the development of Tau filaments and neurodegeneration. Interestingly, rodent tau gene sequence in intron 10 resembles that in human FTDP-17 patients carrying intronic mutations. Consistently, post-natal mice and rats express predominantly Tau4R, similar to that in FTDP-17 patients[55] (Jiang and Wu, unpublished observation). The modeling of tau mutations with splicing variants expressing higher Tau4R has been more complicated, and the pathology was seen more in the ventral root and spinal cord, in contrast to human brain lesions.[73,74] In *C.elegans* and *D. melanogaster*, overexpression of the tau gene resulted in nerve cell degeneration, but with apparent absence of Tau filaments,[75,76] although hyperphosphorylation of tau is seen in flies.[77] Inhibition of GSK3-beta reverses the axon transport and locomotor phenotypes in flies overexpressing human Tau protein.[78] Also a recent study in C.elegans expressing P301L and V337M 4R-tau isoforms have shown increased neuronal dysfunction and accumulation of insoluble tau.[79] Studies are still underway to further our understanding of genetic interactions involved in the pathogenesis of tauopathies.

FUTURE DIRECTIONS AND CONCLUSION

Since cloning of the human tau gene and, in particular, the discovery of tau mutations in FTD patients, genetic, molecular, biochemical, and animal studies have significantly advanced our understanding of tau gene function and its changes in tauopathies. Multiple tau gene alterations have been reported, including pathogenic mutations for FTDP-17 and polymorphisms contributing to risk factors for other forms of tauopathies. Underlying mechanisms include changes in the biochemical/biophysical properties of Tau proteins and disruption of the delicate balance of distinct tau splicing isoforms, leading to abnormal behaviors of these tau gene products in neurons affected. The variation in the clinical manifestations and the lack of simple genotype-phenotype correlations suggest the existence of genetic or epigenetic modifier factors. Such modifiers, in theory, can be enzymes that affect the post-translational

modifications/clearance of Tau proteins or factors that influence the balance of different tau splicing isoforms at the post-transcriptional level. Although a common theme is emerging that the hyperphosphorylated Tau protein that accumulates in filamentous forms disrupts neuronal function, it remains to be elucidated which protein kinases/phosphatases and protein degradation enzymes play crucial roles for developmental regulation and pathologic alterations of tau gene function. Animal models are being established to study human tauopathies. We are just at the very beginning stage of understanding the role of alternative splicing in tau gene function and in the pathogenesis of neurodegenerative disorders such as frontotemporal lobe dementia.

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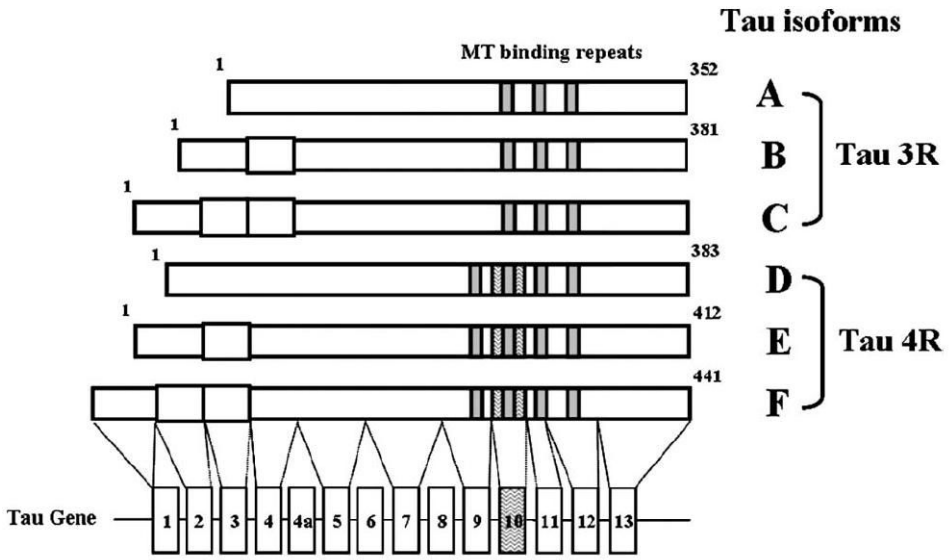

FIGURE 1.

Diagrammatic representation of the six splicing isoforms of human tau transcipts generated by alternate splicing of the tau pre-mRNA. The human tau gene contains 16 exons. Alternative splicing of exon 2, 3, and 10 produces the isoforms. The shaded boxes depict the MT binding repeats.

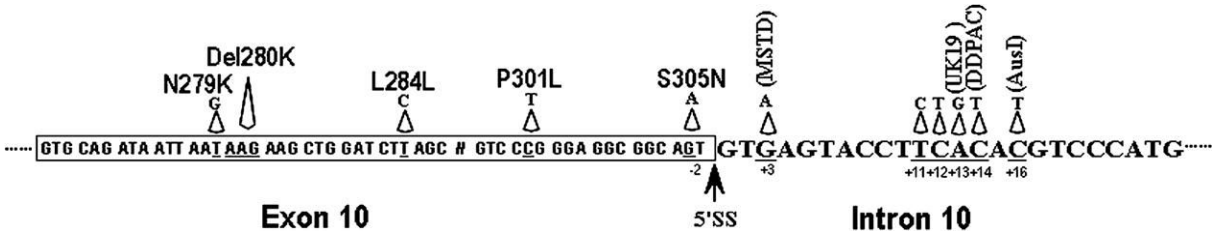

FIGURE 2.

A schematic representation of tau mutations identified at exon 10 and its following intron. The 5′ splice site is marked as 5′ SS. The arrows indicate various missense and splicing mutation found in this region.

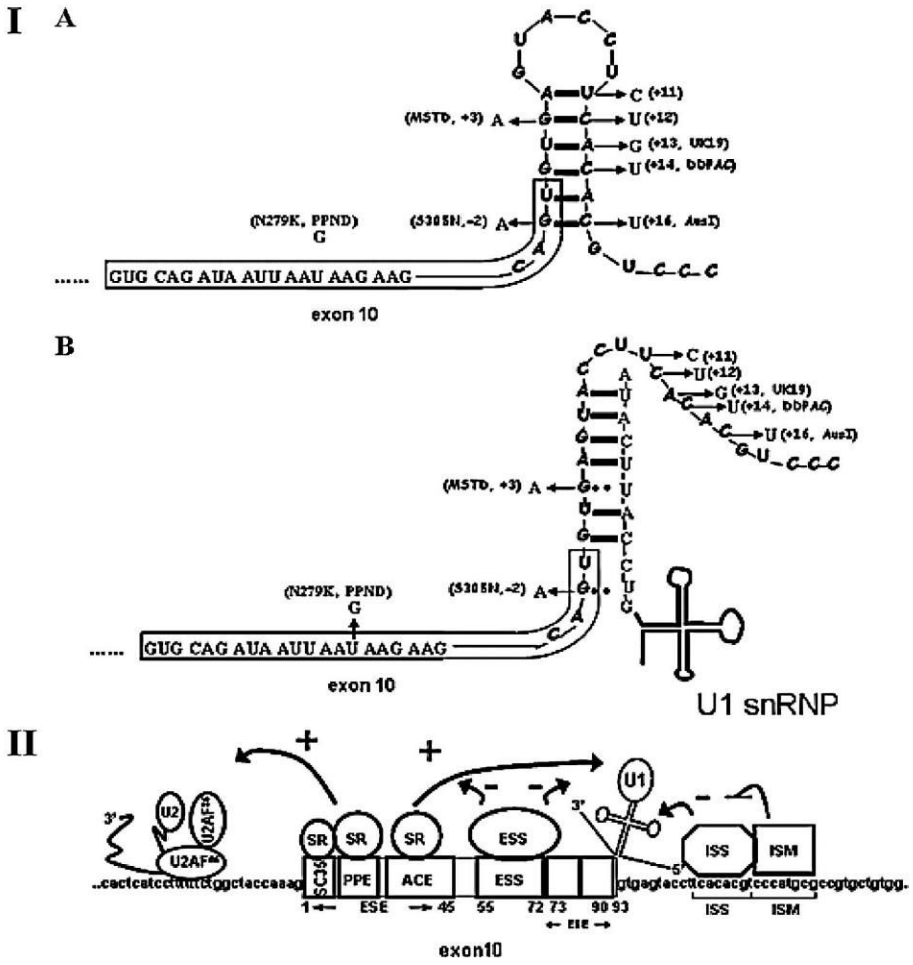

FIGURE 3.

Two proposed models for tau exon 10 splicing. Part I. A stem-loop model. In wild-type tau pre-mRNA, a putative stem-loop structure forms around the 5′ splice site of exon 10, as depicted in panel A of Part I. The base-pairing interaction between U1 snRNA and the 5′ splice site is shown in panel B of Part I. The stem-loop structure prevents efficient interaction of U1 snRNA with the 5′ splice site and leads to partial skipping of exon 10. Splicing mutations destabilize this stem loop leading to increased access of U1snRNP and thus increased exon 10 splicing. Part II. A linear pre-mRNA model. The putative splicing factor interactions with exonic and intronic splicing regulatory sequences modulate the use of the weak exon 10 5′ and 3′ splice sites. Based on the RT-PCR data obtained with a chimeric tau splicing minigene, it was proposed that exon10 splicing elements include three exonic splicing enhancer (ESE) elements at the 5′ end of exon10 and two ESE elements at the 3′ end of exon10, and an exon splicing repressor (ESS) sequence between these two ESEs. It was also postulated that intron10 regulatory sequences contain a bipartite regulatory intronic splicing silencer and modulator (ISS and ISM) element. SR factors are speculated to interact with these ESE elements to recruit and stabilize U1 and U2 snRNP interactions with the 5′ and 3′ splice sites, respectively. These exon-bridging interactions ultimately help in defining the exon. For *tau* E10 definition, the positive roles of the ESEs (arrows with +) and ISM are critical because of weak 3′ and 5′ splice sites as well as the inhibitory ESS and ISS elements (arrows with −). The positive role of the ISM on E10 splicing is indirect and ISS-dependent. Adapted with permission from D'Souza and Schellenberg, 2003.

TABLE 1

Missense Mutations Associated With FTDP-17

Missense Mutation	Exon Splicing	MT Binding	Phenotype	Cells	EM	Inclusion Body	Reference
Exon 9							
K257T	No change	Reduced	PiD-like	N		Picks bodies	90
I260V	Not studied	NA	NA	N			83
L266V	Decreased 4R (Decreased Ex 10 utilization)	Reduced	PiD-like	N			91
G272V	No change	Reduced	FTDP-17	N			41
Exon 10							
N279K	Increased 4R (Increased Ex 10 utilization)	Variable	PSP-like	N,G	TF	NFT	20
ΔK280	Decreased 4R	Reduced	FTDP-17			NFT	84
L284L	Increased 4R	Normal	AD-like	N,G	TF	NFT, β-A	57
ΔN296	No change	Reduced	PSP-like	N			86
P301L	No change	Reduced	FTDP-17	N,G	TF	NFT, β-A	41
P301S	No change	Reduced	FTDP-17, CBD-like	N,G	TF	NFT	24
S305N	Increased 4R	No change	CBD-like	N,G	TF	NFT	51
Exon 11							
L315R	No change	Reduced	PiD-like	N,G		Pick-like bodies	87
S320F	No change	Reduced	PiD-like	N		Pick-like bodies	88
Exon 12							
Q336R	No change	Increased	PiD-like	N	TF,SF	Pick-like bodies	89
V337M	No change	Reduced	FTDP-17	N	PF,SF	NFT	13
Exon 13							
G389R	No change	Reduced	PiD-like	N	TF,SF	Pick-like bodies	82
R406W	No change	Reduced	PSP-like	N	PHF,SF	NFT, Pick-like bodies	41

4R, Four microtubule binding repeat tau; PiD, Pick's Disease; CBD, corticobasal degeneration; FTDP-17, frontotemporal dementia like parkinsonism-17; PSP, progressive supranuclear palsy; AD, Alzheimer disease; PHF, paired helical filaments; TF, twisted filaments; NFT, neurofibrillary tangles; SF, straight filaments; N, neuron; G, glial cells; NA, data not available.

TABLE 2

Splicing Mutations Associated With FTDP-17

Splicing Mutations	Exon Splicing	MT Binding	Phenotype	Cells	EM	Inclusion Body	Reference
Exon 10							
ΔK280	Decreased 4R	Reduced	FTDP-17	N		NFT	84
N296H	Increased 4R	NA	CBD-like	N,G	PHF		85
S305N	Increased 4R	No change	CBD-like	N,G	TF	NFT	51
S305S	Increased 4R	NA	PSP-like	N,G	TF	NFT	22
E10+3	Increased 4R	No change	FTDP-17	N,G	TF	NFT	15
E10+11	Increased 4R	No change	FTDP-17	N		NFT	26
E10+12	Increased 4R	No change	FTDP-17	N,G	TF	NFT	80
E10+13	Increased 4R	No change	FTDP-17	N,G	TF	NFT	41
E10+14	Increased 4R	No change	FTDP-17, PSP-like	N,G	TF	NFT	41
E10+16	Increased 4R	No change	AD-, PiD, PSP, CBD-like, FTDP-17	N,G	TF	NFT	41

4R, Four microtubule binding repeat tau; PiD, Pick's disease; CBD, corticobasal degeneration; FTDP-17, frontotemporal dementia like parkinsonism-17; PSP, progressive supranuclear palsy; AD, Alzheimer disease; PHF, paired helical filaments; TF, twisted filaments; NFT, neurofibrillary tangles; SF, straight filaments; N, neuron; G, glial cells; NA, data not available.

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