

Supporting Information (SI)

Hexameric Aggregation Nucleation Core Sequences and Diversity of Pathogenic Tau Strains

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Table S1. Oligo Primer Sequence Information for Truncation Mutagenesis. PCR annealing temperatures are calculated by IDT OligoAnalyzer Tool based on primer pair sequences and experimental reaction conditions.

Primers			Annealing Temp (°C)
N1	Forward	CATTCATATGGAATCTCCCCTGCAG	65.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAAACCCTGCTTGGCCAGG	
N2	Forward	CATTCATATGGTGACAGCACCCCTTA	64.7
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAAACCCTGCTTGGCCAGG	
N3	Forward	CATTCATATGGAAGAAGCAGGCATT	63.7
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAAACCCTGCTTGGCCAGG	
N4	Forward	AATTCATATGCAGACAGCCCCCGTGCCTAT	72.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAAACCCTGCTTGGCCAGG	
N5	Forward	TTAACATATGGTGACAGATAATTAATAAG	58.6
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAAACCCTGCTTGGCCAGG	
N6	Forward	TTAACATATGGTGCAAATAGTCTAC	59.1
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAAACCCTGCTTGGCCAGG	
N7	Forward	TTAACATATGGTGGAAGTAAAATC	57.1
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAAACCCTGCTTGGCCAGG	
N8	Forward	TTAACATATGAAAAAGATTGAAAC	54.5
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAAACCCTGCTTGGCCAGG	
C1	Forward	CATTCATATGGCTGAGCCCCGCCAG	71.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGATTTCCTCCGCCAGGGACGT	
C2	Forward	CATTCATATGGCTGAGCCCCGCCAG	71.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCTGGCCACCTCCTGGTTTAT	
C3	Forward	CATTCATATGGCTGAGCCCCGCCAG	71.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGACTGCCGCCTCCCGGGACGT	
C4	Forward	CATTCATATGGCTGAGCCCCGCCAG	71.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCTTCCCGCCTCCCGGCTGGT	
C5	Forward	CATTCATATGGCTGAGCCCCGCCAG	71.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCAGGCGGCTCTTGGCGGAAG	
C6	Forward	CATTCATATGGCTGAGCCCCGCCAG	71.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGCTTATTAATTATCTGCACCTTC	
C7	Forward	CATTCATATGGCTGAGCCCCGCCAG	71.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGTTTGTAGACTATTGACCTTC	
C8	Forward	CATTCATATGGCTGAGCCCCGCCAG	71.0
	Reverse	TTAACTCGAGTCAATGATGATGATGATGATGTATCTGCACCTTCCCGCCTC	

Table S2. Atomic interactions involving residues VYK of VQIVYK (PHF6) or INK of VQIINK (PHF6*) hexameric core sequences in diverse tau strains. Corresponding intra-molecular interactions are highlighted by arrows in Figure 6. Inter-atomic distances are measured using Pymol Molecular Display Software.

Protein	Residue 1	Residue 2	Distance (Å)	Type of bonding	Protein	Residue 1	Residue 2	Distance (Å)	Type of bonding	
Tau (Alzheimer's fold)					Tau (PSP fold)					
PDB access code:					PDB access code:					
5O3L	Y310/CB	L376/CD2	4.8	Hydrophobic	7P65	Y310/CB	P301/CG	4.7	Hydrophobic	
	Y310/CG	L376/CD2	4.5	Hydrophobic	Continued	Y310/CG	P301/CB	4.3	Hydrophobic	
	Y310/CD1	L376/CD2	4.0	Hydrophobic		Y310/CG	P301/CG	4.1	Hydrophobic	
	Y310/CD1	L376/CG	5.0	Hydrophobic		Y310/CD1	P301/CG	4.5	Hydrophobic	
	Y310/CD1	L376/CB	4.9	Hydrophobic		Y310/CD2	P301/CA	4.9	Hydrophobic	
	Y310/CE1	L376/CB	4.6	Hydrophobic		Y310/CD2	P301/CB	3.6	Hydrophobic	
	Y310/CZ	H374/CG	4.9	Hydrophobic		Y310/CD2	P301/CG	3.8	Hydrophobic	
	Y310/CZ	H374/CD2	4.7	Hydrophobic		Y310/CD2	P301/CD	4.6	Hydrophobic	
	Y310/CZ	H374/CB	4.7	Hydrophobic		Y310/CE1	H299/CB	4.3	Hydrophobic	
Y310/CE1				Y310/CE1		H299/CG	4.3	Hydrophobic		
Tau (CTE fold)										
PDB access code:										
6NWP	Y310/CB	L376/CD2	3.8	Hydrophobic	Y310/CE1	H299/CE1	4.6	Hydrophobic		
	Y310/CB	L376/CG	5.0	Hydrophobic	Y310/CE1	P301/CG	4.7	Hydrophobic		
	Y310/CG	L376/CB	4.7	Hydrophobic	Y310/CE1	P301/CD	5.0	Hydrophobic		
	Y310/CG	L376/CG	4.9	Hydrophobic	Y310/CE2	P301/CA	4.9	Hydrophobic		
	Y310/CG	L376/CD2	4.1	Hydrophobic	Y310/CE2	P301/CB	3.9	Hydrophobic		
	Y310/CD1	L376/CB	4.2	Hydrophobic	Y310/CE2	P301/CG	3.9	Hydrophobic		
	Y310/CD1	L376/CG	4.6	Hydrophobic	Y310/CE2	P301/CD	4.3	Hydrophobic		
	Y310/CD1	L376/CD1	4.8	Hydrophobic	Y310/CZ	H299/CA	4.7	Hydrophobic		
	Y310/CD1	L376/CD2	4.1	Hydrophobic	Y310/CZ	H299/CB	4.0	Hydrophobic		
	Y310/CD2	L376/CD2	4.9	Hydrophobic	Y310/CZ	H299/CG	4.2	Hydrophobic		
	Y310/CD2	H374/CE1	4.9	Hydrophobic	Y310/CZ	H299/CE1	4.6	Hydrophobic		
	Y310/CE1	L376/CA	4.9	Hydrophobic	Y310/CZ	P301/CB	4.7	Hydrophobic		
	Y310/CE1	L376/CB	4.3	Hydrophobic	Y310/CZ	P301/CG	4.4	Hydrophobic		
	Y310/CE1	L376/CG	5.0	Hydrophobic	Y310/CZ	P301/CD	4.5	Hydrophobic		
	Y310/CE2	H374/CB	4.2	Hydrophobic	Y310/OH	H299/ND1	2.5	Hydrogen bond		
	Y310/CE2	H374/CG	4.3	Hydrophobic	K311/CE	D348/CG	3.8	Hydrophobic		
	Y310/CE2	H374/CE1	4.6	Hydrophobic	K311/NZ	D348/OD2	2.9	Hydrogen bond		
	Y310/CZ	H374/CA	4.7	Hydrophobic	Tau (GGT fold)					
					PDB access code:					
		Y310/CZ	H374/CB	4.3	Hydrophobic	7P66	V309/CB	N296/CA	5.0	Hydrophobic
		Y310/CZ	H374/CG	4.5	Hydrophobic		V309/CB	N296/CB	4.3	Hydrophobic
		Y310/CZ	H374/CE1	4.8	Hydrophobic		V309/CB	N296/CG	4.5	Hydrophobic
		Y310/CZ	L376/CB	4.8	Hydrophobic		V309/CG1	N296/CA	4.9	Hydrophobic
	Y310/OH	H374/ND1	3.0	Hydrogen bond		V309/CG1	N296/CB	4.2	Hydrophobic	
Tau (Pick's fold)						V309/CG1	N296/CG	4.1	Hydrophobic	
PDB access code:										
6GX5	Y310/CD2	V337/CG2	4.4	Hydrophobic		V309/CG2	N296/CA	4.3	Hydrophobic	
	Y310/CE2	V337/CG2	4.8	Hydrophobic		V309/CG2	N296/CB	3.9	Hydrophobic	
Tau (CBD fold)						V309/CG2	N296/CG	4.6	Hydrophobic	
PDB access code:										
6TJO	V309/CB	I297/CG1	4.7	Hydrophobic		V309/CG2	I297/CG1	3.9	Hydrophobic	
	V309/CB	I297/CG2	4.9	Hydrophobic		V309/CG2	I297/CD1	4.2	Hydrophobic	
	V309/CG1	I297/CG1	4.4	Hydrophobic		Y310/CD1	I354/CG2	5.0	Hydrophobic	
	V309/CG1	I297/CD1	4.7	Hydrophobic		Y310/CD1	I354/CD1	5.0	Hydrophobic	
	V309/CG2	I297/CB	4.8	Hydrophobic		Y310/CE1	D348/CG	5.0	Hydrophobic	
	V309/CG2	I297/CG1	4.2	Hydrophobic		Y310/CE1	I354/CD1	4.7	Hydrophobic	
	V309/CG2	I297/CG2	3.9	Hydrophobic		Y310/CE2	D348/CB	4.6	Hydrophobic	
	Y310/CD1	V337/CG2	4.7	Hydrophobic		Y310/CE2	D348/CG	4.0	Hydrophobic	
	K311/CD	D295/CG	4.5	Hydrophobic		Y310/CZ	D348/CG	3.9	Hydrophobic	
	K311/CD	I297/CD1	5.0	Hydrophobic		Y310/OH	D348/OD1	2.8	Hydrogen bond	
	K311/CE	D295/CG	4.1	Hydrophobic		Y310/OH	D348/OD2	3.1	Hydrogen bond	
	K311/CE	I297/CD1	4.6	Hydrophobic		K311/CE	D348/CB	4.8	Hydrophobic	
	N279/CB	L376/CD1	4.4	Hydrophobic	Tau (GPT fold)					
	Tau (AGD fold)					PDB access code:				
7P6D					7P6A	V309/CB	V350/CG1	4.9	Hydrophobic	
V309/CB	V309/CB	I297/CG1	4.4	Hydrophobic		V309/CG1	V350/CB	4.7	Hydrophobic	
	V309/CG1	I297/CD1	4.3	Hydrophobic		V309/CG1	V350/CG1	4.3	Hydrophobic	
	V309/CG2	I297/CB	4.5	Hydrophobic		V309/CG1	V350/CG2	5.0	Hydrophobic	
	V309/CG2	I297/CG2	4.5	Hydrophobic		V309/CG2	V350/CG1	4.2	Hydrophobic	
	V309/CG2	I297/CD1	3.8	Hydrophobic		Y310/CG	I297/CD1	4.9	Hydrophobic	
	Y310/CD1	V337/CG2	4.3	Hydrophobic		Y310/CD2	I297/CG1	4.4	Hydrophobic	
	Y310/CE1	V337/CG2	4.4	Hydrophobic		Y310/CD2	I297/CD1	3.6	Hydrophobic	
	K311/CD	D295/CG	4.5	Hydrophobic		Y310/CE2	D295/CB	5.0	Hydrophobic	
	K311/CE	D295/CG	4.2	Hydrophobic		Y310/CE2	I297/CB	4.9	Hydrophobic	
	K311/NZ	D295/OD2	2.9	Hydrogen bond		Y310/CE2	I297/CG1	4.0	Hydrophobic	
	K311/NZ	D295/OD1	3.0	Hydrogen bond		Y310/CE2	I297/CD1	3.7	Hydrophobic	
						Y310/CZ	D295/CB	4.4	Hydrophobic	
Tau (PSP fold)										
PDB access code:										
7P65	V309/CB	D348/CG	5.0	Hydrophobic	Y310/CZ	I297/CD1	5.0	Hydrophobic		
	V309/CB	V350/CG2	4.8	Hydrophobic	K311/CD	D348/CB	5.0	Hydrophobic		

V309/CG1	D348/CB	4.9	Hydrophobic	K311/CD	V350/CG2	4.5	Hydrophobic
V309/CG1	D348/CG	4.0	Hydrophobic	K311/CE	D348/CB	3.9	Hydrophobic
V309/CG2	V350/CB	4.9	Hydrophobic	K311/CE	D348/CG	4.0	Hydrophobic
V309/CG2	V350/CG1	4.8	Hydrophobic	K311/CE	V350/CG2	4.7	Hydrophobic
V309/CG2	V350/CG2	3.8	Hydrophobic	K311/NZ	D348/OD2	2.4	Hydrogen bond
Y310/CB	P301/CB	4.8	Hydrophobic				
