Pathophysiology of tau accumulation in PSP

Huw Morris
UCL Institute of Neurology
Overview

1) What is the evidence that tau is the central player in PSP?
2) What diseases and related disease models are relevant?
3) What mechanisms might be important...and where are the therapeutic targets
4) What are the next steps?
Association of an extended haplotype in the \textit{tau} gene with progressive supranuclear palsy

Matt Baker, Irene Litvan$^1$, Henry Houlden, Jennifer Adamson, Dennis Dickson, Jordi Perez-Tur, John Hardy, Timothy Lynch$^2$, Eileen Bigio$^3$ and Mike Hutton$^*$
The microtubule associated protein tau

**MAPT**: Alternative splicing of exons 2, 3 and 10

**Tau protein**: Six isoforms in CNS

Courtesy of John Hardy
PD is negatively associated with the \textit{MAPT} H2 haplotype

A common inversion under selection in Europeans

Hreinn Stefansson\textsuperscript{1,3}, Agnar Helgason\textsuperscript{1,3}, Gudmar Thorleifsson\textsuperscript{1}, Vilgerdur Steinthorsdottir\textsuperscript{1}, Gíslí Masson\textsuperscript{1}, John Barnard\textsuperscript{2}, Adam Baker\textsuperscript{1}, Aslaug Jonasdottir\textsuperscript{1}, Andres Ingaon\textsuperscript{1}, Vala G Gudnadottir\textsuperscript{1}, Natasa Desnica\textsuperscript{1,2}, Andrew Hicks\textsuperscript{1}, Arnaldur Gyffason\textsuperscript{1}, Daniel F Gudbjartsson\textsuperscript{1}, Guðrún M Jónsdóttir\textsuperscript{1}, Jesús Sainz\textsuperscript{3}, Kari Agnarsson\textsuperscript{1}, Birgitta Birgisdottir\textsuperscript{1}, Shyamali Ghosh\textsuperscript{1}, Adalheidur Olafsdottir\textsuperscript{2}, Jean-Baptiste Cazier\textsuperscript{4}, Kristleifur Kristjansson\textsuperscript{1}, Michael L Frigge\textsuperscript{1}, Thorgerir E Thorgeirsson\textsuperscript{1}, Jeffrey R Guschen\textsuperscript{1}, Augustine Kong\textsuperscript{1,3} & Kari Stefansson\textsuperscript{1,3}

Evolutionary toggling of the \textit{MAPT} 17q21.31 inversion region

Michael C Zody\textsuperscript{1,2,5}, Zhuoshi Jiang\textsuperscript{3,6}, Hon-Chung Fung\textsuperscript{1,4}, Francesca Antonacci\textsuperscript{7}, LaDeana W Hillier\textsuperscript{6}, Maria Francesca Cardone\textsuperscript{2}, Tina A Graves\textsuperscript{6}, Jeffrey M Kidd\textsuperscript{8}, Ze Cheng\textsuperscript{9}, Amr Abouelheil\textsuperscript{1}, Lü Chen\textsuperscript{3}, John Wallis\textsuperscript{5}, Jarret Glasscock\textsuperscript{5}, Richard K Wilson\textsuperscript{6}, Amy Denise Reily\textsuperscript{9}, Jaime Duckworth\textsuperscript{6}, Mario Ventura\textsuperscript{7}, John Hardy\textsuperscript{4}, Wesley C Warren\textsuperscript{6} & Evan E Eichler\textsuperscript{2}

![Diagram showing evolutionary toggling of the MAPT 17q21.31 inversion region](image-url)

Courtesy of John Hardy
There are two association signals at the MAPT locus

H1/H2
H1c –rs242557

ORIGINAL ARTICLE

Linkage disequilibrium fine mapping and haplotype association analysis of the tau gene in progressive supranuclear palsy and corticobasal degeneration


Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy

Günter U Höglinger¹,³⁰, Nadine M Melhem²,³⁰, Dennis W Dickson³,³⁰, Patrick M A Sleiman⁴,³⁰, Li-San Wang⁵, Lambertus Klei², Rosa Rademakers³, Rohan de Silva⁶, Irene Litvan⁷, David E Riley⁸, John C van Swieten⁹, Peter Heutink¹⁰, Zbigniew K Wszolek¹¹, Ryan J Uitti¹¹, Jana Vandrovčová⁶, Howard I Hurtig¹², Rachel G Gross¹², Walter Maetzler¹³,¹⁴, Stefano Goldwurm¹⁵, Eduardo Tolosa¹⁶, Barbara Borroni¹⁷, Pau Pastor¹⁸–²⁰, PSP Genetics Study Group²⁹, Laura B Cantwell⁵, Mi Ryung Han⁵, Alissa Dillman²¹, Marcel P van der Brug²², J Raphael Gibbs⁶,²¹, Mark R Cookson²¹, Dena G Hernandez⁶,²¹, Andrew B Singleton²¹, Matthew J Farrer²³, Chang-En Yu²⁴,²⁵, Lawrence I Golbe²⁶, Tamas Revesz²⁷, John Hardy⁶, Andrew J Lees⁶,²⁷, Bernie Devlin², Hakon Hakonarson⁴, Ulrich Müller²⁸,³⁰, Gerard D Schellenberg⁵,³⁰
### Table 2  Results from stage 1, stage 2 ai

<table>
<thead>
<tr>
<th>Chr. band</th>
<th>SNP</th>
<th>SNP location</th>
<th>Gene or nearby gene</th>
<th>Joint P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q25.3</td>
<td>rs1411478</td>
<td>179,229,155</td>
<td>STX6</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>2p11.2</td>
<td>rs7571971</td>
<td>88,676,716</td>
<td>EIF2AK3</td>
<td>0.79 (0.74–0.85)</td>
</tr>
<tr>
<td>3p22.1</td>
<td>rs1768208</td>
<td>39,498,257</td>
<td>MOBP</td>
<td>0.75 (0.69–0.81)</td>
</tr>
<tr>
<td>17q21.31</td>
<td>rs8070723</td>
<td>41,436,651</td>
<td>MAPT</td>
<td>0.72 (0.67–0.78)</td>
</tr>
<tr>
<td>rs242557</td>
<td></td>
<td>41,375,823</td>
<td>MAPT</td>
<td>5.46 (4.72–6.31)</td>
</tr>
<tr>
<td>rs242557c</td>
<td></td>
<td>–</td>
<td>MAPT</td>
<td>0.51 (0.47–0.55)</td>
</tr>
<tr>
<td>rs242557c</td>
<td>rs8070723</td>
<td></td>
<td></td>
<td>0.70 (0.65–0.76)</td>
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</tbody>
</table>
MAPT – Alternative splicing of tau
eIF2AK3/PERK – ER unfolded protein response
STX6 – trans-Golgi – Endoplasmic trafficking
MOBP – Myelin Associated Oligodendrocyte Basic Protein highly expressed in brainstem
What is the evidence that tau is the central player in PSP?
Clinicopathologic assessment and imaging of tauopathies in neurodegenerative dementias

Melissa E Murray¹, Naomi Kouri¹, Wen-Lang Lin¹, Clifford R Jack Jr², Dennis W Dickson¹ and Prashanthi Vernuri²

1. Alzheimer’s disease
2. Non-Guamanian motor neuron disease with neurofibrillary tangles
3. Amyotrophic lateral sclerosis of Guam
4. Parkinsonism–dementia complex of Guam
5. Argyrophilic grain disease
6. Pick’s disease
7. Chronic traumatic encephalopathy
8. Postencephalitic parkinsonism
9. Corticobasal degeneration
10. Progressive supranuclear palsy
11. Diffuse neurofibrillary tangles with calcification
12. SLC9A6-related mental retardation
13. Down’s syndrome
14. Subacute sclerosing panencephalitis
15. Familial British dementia
16. Tangle predominant dementia
17. Familial Danish dementia
18. White matter tauopathy with globular glial inclusions
19. Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations)
20. Subacute sclerosing panencephalitis
21. Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations)
22. Tangle predominant dementia
23. Gerstmann–Sträussler–Scheinker disease
24. White matter tauopathy with globular glial inclusions
25. Guadeloupean parkinsonism
26. Niemann–Pick disease, type C
27. Myotonic dystrophy
28. Neurodegeneration with brain iron accumulation
Clinicopathologic assessment and imaging of tauopathies in neurodegenerative dementias

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Non-Guamanian motor neuron disease with neurofibrillary tangles

Amyotrophic lateral sclerosis of Guam

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Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations)

Gerstmann–Sträussler–Scheinker disease

Guadeloupean parkinsonism

Myotonic dystrophy

Neurodegeneration with brain iron accumulation

Niemann–Pick disease, type C
Association of missense and 5’-splice-site mutations in tau with the inherited dementia FTDP-17
Is the Mendelian disease FTDP-17 a good model for the sporadic disease PSP and will this help us develop new therapies?
Table 1. MAPT mutations causing a PSP-like syndrome

<table>
<thead>
<tr>
<th>Mutation</th>
<th>References</th>
<th>Number</th>
<th>Initial features</th>
<th>AAO years</th>
<th>Duration years</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>R5L</td>
<td>Poorkaj et al. [8]</td>
<td>1</td>
<td>falls, dysarthria, micrographia</td>
<td>62</td>
<td>5</td>
<td>tau 4R&gt;3R</td>
</tr>
<tr>
<td>N279K</td>
<td>Delisle et al. [6]</td>
<td>2</td>
<td>parkinsonism, apathy, bradyphrenia</td>
<td>40</td>
<td>7</td>
<td>tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>attentional problems, apathy</td>
<td>41</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Tsuboi et al. [9]</td>
<td>N/A</td>
<td>report of 5 families with parkinsonism/supranuclear palsy</td>
<td>41–45(^1)</td>
<td>6–8.5(^1)</td>
<td>N/A</td>
</tr>
<tr>
<td>δN296</td>
<td>Pastor et al. [19]</td>
<td>2</td>
<td>gaze palsy, memory/language problems, emotional lability</td>
<td>38</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>personality change, parkinsonism</td>
<td>39</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Rossi et al. [11]</td>
<td>1</td>
<td>antecollis, dysarthria, falls, slowing of ocular movements</td>
<td>36</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>P301L</td>
<td>Kaat et al. [14]</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>G303V</td>
<td>Ros et al. [12]</td>
<td>3</td>
<td>akinetic-rigid syndrome, falls, gaze palsy, dysarthria</td>
<td>37</td>
<td>8</td>
<td>tau 4R&gt;3R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td>41</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>late 30s</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>S305S</td>
<td>Stanford et al. [7]</td>
<td>3</td>
<td>apathy, memory/language problems</td>
<td>53</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>clumsiness, dysarthria, rigidity</td>
<td>47</td>
<td>4</td>
<td>tau 4R&gt;3R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dementia, apathy, language problems</td>
<td>49</td>
<td>7</td>
<td>N/A</td>
</tr>
<tr>
<td>10+3</td>
<td>Spina et al. [13]</td>
<td>2</td>
<td>postural imbalance, dizziness, stiff neck</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10+16</td>
<td>Morris et al. [10]</td>
<td>1</td>
<td>fatigue, apathy, micrographia, falls</td>
<td>40</td>
<td>5</td>
<td>tau</td>
</tr>
</tbody>
</table>

**Novel L284R MAPT Mutation in a Family with an Autosomal Dominant Progressive Supranuclear Palsy Syndrome**

Jonathan D. Rohrer\(^a\)  Dominic Paviour\(^{a,b}\)  Jana Vandrovcova\(^b\)  John Hodges\(^c\)
Rohan de Silva\(^b\)  Martin N. Rossor\(^a\)
Missense mutations outside exon 10

Missense mutations in exon 10

Intronic and exonic mutations which affect exon 10 splicing
Destabilization of microtubules

Enhanced filament/aggregate formation

Alteration in the 4R/3R ratio

Alteration in Ser/Thr phosphorylation sites
<table>
<thead>
<tr>
<th></th>
<th>PSP</th>
<th>FTDP17T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exon 10 splicing</td>
<td>Exon 10 coding</td>
</tr>
<tr>
<td>Genetics</td>
<td>H1/H1c</td>
<td>+3, +16, N279K, R5L</td>
</tr>
<tr>
<td>Clinical</td>
<td>Parkinsonism, Gait, SNGP</td>
<td>Parkinsonism, Gait SNGP</td>
</tr>
<tr>
<td>EM</td>
<td>Straight filaments</td>
<td>Slender twisted filaments</td>
</tr>
<tr>
<td>Protein</td>
<td>4R&gt;3R</td>
<td>4R&gt;3R</td>
</tr>
<tr>
<td>RNA</td>
<td>4R&gt;3R</td>
<td>4R&gt;3R</td>
</tr>
<tr>
<td>Glial Pathology</td>
<td>Tufted astrocytes</td>
<td>TA ++, Oligodendroglial coiled bodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo


Noble W et al. PNAS 2005;102:6990-6995
Brain homogenates from human tauopathies induce tau inclusions in mouse brain

Florence Clavaguera, Hiroya Su Akatsu, Graham Fraser, R. Anthony Crowther, Stephan Frank, Jürgen Hench, Alphonse Probst, David T. Winkler, Julia Reichwald, Matthias Staufenbiel, Bernardino Ghetti, Michel Goedert, and Markus Tolkay

Anti-Tau Antibodies that Block Tau Aggregate Seeding In Vitro Markedly Decrease Pathology and Improve Cognition In Vivo

Kiran Yanamandra, Nila Khoury, Hong Jiang, Thomas E. Mohan, Shengmei Ma, Susan E. Maloney, David F. Wozniak, Marc L. Diamond, and David M. Holtzman

Figure 3. AFM Analysis of Isolated Tau Aggregates from P301S Mouse Brain

Tau aggregates were isolated by IP from TBB lysates of 13-month-old P301S mouse brains by using anti-tau antibodies HJ8.5, HJ9.3, and HJ9.4 and control antibody HJ3.4. Each column represents the IP material from each antibody. Black arrows indicate the areas magnified. Bottom panel shows a magnified area of the top panel. Scale bar represents 1 μm in all top panel images and represents 200 μm in bottom panel images. Morphology of the aggregated species found by each anti-tau antibody appears unique. Anti-Aβ antibody HJ3.4 did not IP any aggregates.
Can we link the Mendelian and non-Mendelian diseases?
Do the genetic risk factors for PSP recapitulate Mendelian disorders?

Tau expression varies in different brain regions and disease states

Elisa Majounie a,b, William Cross a, Victoria Newsway a, Allissa Dillman b, Jana Vandrovcova c, Christopher M. Morris d, Michael A. Nalls b, Luigi Ferrucci e, Michael J. Owen a, Michael O’ Donovan a, Mark R. Cookson b, Andrew B. Singleton b, Rohan de Silva c, Huw R. Morris a,*
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The effect of age and the H1c MAPT haplotype on MAPT expression in human brain

Jesse B.G. Hayesmoore, Nicholas J. Bray, William C. Cross, Michael J. Owen, Michael C. O'Donovan, Huw R. Morris
The *MAPT* H1c risk haplotype is associated with increased expression of tau and especially of 4 repeat containing transcripts

Amanda J. Myers,\textsuperscript{a} Alan M. Pittman,\textsuperscript{b,c} Alice S. Zhao,\textsuperscript{a} Kristen Rohrer,\textsuperscript{a} Mona Kaleem,\textsuperscript{a} Lauren Marlowe,\textsuperscript{a} Andrew Lees,\textsuperscript{b,c,d} Doris Leung,\textsuperscript{a} Ian G. McKeith,\textsuperscript{c} Robert H. Perry,\textsuperscript{c} Chris M. Morris,\textsuperscript{c} John Q. Trojanowski,\textsuperscript{c} Christopher Clark,\textsuperscript{f} Jason Karlawish,\textsuperscript{f} Steve Arnold,\textsuperscript{f} Mark S. Forman,\textsuperscript{f} Vivianna Van Deerlin,\textsuperscript{f} Rohan de Silva,\textsuperscript{a,b} and John Hardy\textsuperscript{a,b,c}

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**H1c vs other H1**

- 10% increase in total tau
- 25% increase in 4R tau
PSP

- MAPT expression and splicing
- PERK
- MOBP
- STX6
- Activation of UPS
- Mitochondrial failure
- MAPT aggregation
- MAPT clearance

FTDP-17

- MAPT splicing, Coding mutation
- Age
- Neuronal and glial tau accumulation
- Microtubule destabilization
- Spread
What are the therapeutic targets?

- Reduction in tau levels
- Anti-tau aggregation therapy
- Kinase inhibitors; Phosphatase enhancers
- Autophagy stimulation
- Microtubule stabilizing agents
- Anti-tau propagation therapies
- Alteration in 4R:3R tau ratio
What are the therapeutic targets?

Reduction in tau levels

Alteration in 4R:3R tau ratio

Anti-tau aggregation therapy: Grape seed extract, Methylene blue

Kinase inhibitors; Phosphatase enhancer: SVP, Lithium, Tideglusib –ve

Autophagy stimulation: Trehalose

Microtubule stabilizing agents: Davuentide –ve; EpothiloneD

Anti-tau propagation therapies: Immunization
Overview

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Pathophysiology of tau accumulation in PSP

Huw Morris
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