Tau in Richardson’s syndrome (RS) and progressive supranuclear palsy-parkinsonism (PSP-P)

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In 1963 Dr J Clifford Richardson presented the clinical report of 8 cases of ‘heterogeneous system degeneration’ to The American Neurological Association. The patients presented with:

- supranuclear gaze palsy
- pseudobulbar palsy
- nuchal dystonia
- dementia

Neuropathology of six of the cases were presented to the Annual Meeting of the American Association of Neuropathologists by Dr Jerzy Olszewski in 1963

- extensive subcortical neurofibrillary degeneration in the globus pallidus, subthalamic nucleus, substantia nigra and dentate nucleus

Progressive supranuclear palsy (PSP)

- Sporadic neurodegenerative disorder of late adult life
  - Median age of onset ~ 64 years (range: 50 – 77 years)
  - Median duration from onset to death ~ 5.8 years
- The most common form of atypical parkinsonism
  - 2 to 6% of all patients with parkinsonism seen in specialist clinics in the USA and Europe
  - Prevalence: 6.0 to 6.4/100,000 in the UK (14/100,000 in Guadeloupe)
- One of the ‘primary tauopathies’ with both neuronal and glial accumulation of abnormal, mostly four-repeat-type (4R) tau
- Robust genetic association between PSP and MAPT H1 (H1c) haplotype
Detergent insoluble tau is not composed exclusively of 4R tau, but a mixture of 4R and 3R. In AD there is less 4R than 3R, whereas the ratio is reversed in PSP.
Association of *tau* H1 haplotype with PSP

- Association of A0/A0 genotype
  - Conrad *et al.* 1997

- Association of H1/H1 haplotype
  - Baker *et al.* 1999

**Diagram:**
- Promoter
- Exons: Ex -1, Ex 1, Ex 2, Ex 3, Ex 4, Ex 5, Ex 7, Ex 9, Ex 10, Ex 11, Ex 12, Ex 13
- (TG)$_n$
- Association of A0/A0 genotype
- Conrad *et al.* 1997

- A0
- ATG
- ~80kb

- Association of H1/H1 haplotype
- Baker *et al.* 1999
**Tau gene haplotype and genotype association with PSP**

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<tr>
<th>Haplotype</th>
<th>Controls</th>
<th>PSP Cases</th>
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<tr>
<td>H1</td>
<td>110 (0.786)</td>
<td>83 (0.988)</td>
</tr>
<tr>
<td>H2</td>
<td>30 (0.214)</td>
<td>1 (0.012)</td>
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\[ \chi^2 = 18.033 \]

\[ p = 2.17 \times 10^{-5} \]

<table>
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<tr>
<th>Genotype</th>
<th>Controls (n=70)</th>
<th>PSP Cases (n=42)</th>
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<tr>
<td>H1/H1</td>
<td>43 (0.614)</td>
<td>41 (0.976)</td>
</tr>
<tr>
<td>H1/H2</td>
<td>24 (0.343)</td>
<td>1 (0.024)</td>
</tr>
<tr>
<td>H2/H2</td>
<td>3 (0.043)</td>
<td>0 (0)</td>
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\[ \chi^2 = 18.35479 \]

\[ p = 0.00010 \]
The H2 clade is essentially a single non-recombining haplotype covering several genes and ~1.6 Mb on chromosome 17q21.

A complete absence of recombination between H1 and H2.

The H1 clade shows considerable diversity and has a normal pattern of linkage dysequilibrium except with H2.

A variant of H1, MAPT, is largely responsible for the association between the H1 haplotype and PSP (and CBD).


The structure of the tau haplotype in controls and in progressive supranuclear palsy

Alan M. Pittman¹,²,†, Amanda J. Myers³,†, Jaime Duckworth³, Leslie Bryden³, Melissa Hanson³, Patrick Abou-Sleiman², Nicholas W. Wood², John Hardy¹,³, Andrew Lees¹,² and Rohan de Silva¹,²,*e

¹Reta Lila Weston Institute of Neurological Studies, University College London, Windeyer Building, 46 Cleveland Street, London W1T 4JF, UK, ²Department of Molecular Neuroscience, Institute of Neurology, Queen Square, London WC1N 3BG, UK and ³Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Building 10, Bethesda, MD 20892, USA
Cytoskeletal pathology is neuronal and glial in PSP

Neurofibrillary tangles
Astrocytes: Tufted astrocytes

Oligodendroglia: Coiled body

Cytoskeletal pathology is neuronal and glial in PSP

Caudate nucleus

AT8

4R

Internal capsule

AT8
Cortical pathology in progressive supranuclear palsy

Tau

Tufted astrocyte

Neurofibrillary tangle

Premotor cortex

Motor cortex

Neurofibrillary tangle

Tufted astrocyte

Betz cell
The clinical and pathological spectrum of Steele–Richardson–Olszewski syndrome (progressive supranuclear palsy): a reappraisal

S. E. Daniel,¹,² V. M. S. de Bruin⁴ and A. J. Lees¹,³

The nucleus raphe interpositus in the Steele–Richardson–Olszewski syndrome (progressive supranuclear palsy)

T. Revesz,¹ H. Sangha² and S. E. Daniel¹,²

Pathological, clinical and genetic heterogeneity in progressive supranuclear palsy

H. R. Morris,¹,³ G. Gibb,⁴ R. Katzenschlager,¹ N. W. Wood,¹ D. P. Hanger,⁴ C. Strand,¹ T. Lashley,¹ S. E. Daniel,² A. J. Lees,¹,²,³ B. H. Anderton⁴ and T. Revesz¹,²
Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson’s syndrome and PSP-parkinsonism

David R. Williams, Rohan de Silva, Dominic C. Paviour, Alan Pittman, Hilary C. Watt, Linda Kilford, Janice L. Holton, Tamas Revesz and Andrew J. Lees
Insoluble tau in RS and PSP-P

Williams et al. *Brain* 2005; 128: 1247-1258
Hypothesis: The increased contribution by 3-repeat tau isoforms to the total insoluble-tau fraction in PSP-P suggests that biological differences may exist between the two PSP phenotypes

To investigate whether regional differences exist in tau load between the two major clinical phenotypes (RS and PSP-P)
42 cases with neuropathological diagnosis of PSP
- 24 Richardson’s syndrome; 12 PSP-P; 6 pure akinesia with gait freezing
- 26M; 16F
- Mean age of onset was 66.5 years (range 44.4-87.5)
- Mean age at death was 75.6 years (60.9-95.8)
- Mean disease duration was 9.1 years (1.2-17.3)

Williams et al.: Brain 130:1566-1576, 2007
Materials and methods

- Immunohistochemistry: AT8 antibody (tau, Ser202/Thr205)
- 17 brain regions with variability of tau pathology or predicted to contribute to the clinical features of disease
- Unbiased morphometry was used for absolute counts of
  - Neurofibrillary tangles
  - Tufted astrocytes
  - Coiled bodies
  - Neuropil threads
- Absolute counts were used to generate a five point grading scale
  - Grade 4 = highest value (100%)
  - Grade 3 = set at 75%
  - Grade 2 = set at 50%
  - Grade 1 = set at 25%
  - Grade 0 = no lesion

Williams et al.: Brain 130:1566-1576, 2007
Differences in tau load between RS and PSP-P

- The diagnosis of PSP was confirmed in all 42 cases
- The overall tau severity was greater in the RS group (median 155) than in the PSP-P group (median 116) (Mann Whitney U, p=0.002)
- CB+threads were the major contributor to the overall tau load
- The intra-rater SD = 0.012, implied that the variability of counting was less than 2%

Williams et al.: Brain 130:1566-1576, 2007
• The mean regional tau-severity was higher in RS than PSP-P or PAGF in all brain regions
• The difference with PSP-P was significant in all regions except the putamen and subthalamic nucleus

Williams et al.: Brain 130:1566-1576, 2007
The PSP tau score (the sum of graded CB+Th pathologies in the substantia nigra, caudate and dentate nucleus) shows a high correlation with the overall tau load (Σ all lesion grades in all 17 regions).
Differences in tau load between RS and PSP-P

Overall tau severity (sum of all graded tau pathologies in all 17 regions) according to clinical group

PSP tau score (sum of graded CB+Th pathologies in the substantia nigra, caudate and dentate nucleus) according to clinical group

Williams et al.: Brain 130:1566-1576, 2007
PSP tau scores 4-5

Williams et al.: Brain 130:1566-1576, 2007
PSP tau scores 6-7

Williams et al.: Brain 130:1566-1576, 2007
PSP tau scores > 7

Williams et al.: Brain 130:1566-1576, 2007
Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson’s syndrome

David R. Williams, Janice L. Holton, Catherine Strand, Alan Pittman, Rohan de Silva, Andrew J. Lees, and Tamas Revesz
Are Richardson’s syndrome and PSP-P: two nosological entities?

- The classical clinical description of PSP does not adequately describe ~ 1/3 of cases in the pathologically proven series of PSP.
- Data indicate that PSP-P represents a second discrete clinical phenotype.
- There are biochemical and pathological differences between RS and PSP-P.
- Further studies are required to establish the biological significance of these observed differences.
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Queen Square Brain Bank for Neurological Disorders
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Different tau pathology pattern in two clinical phenotypes of progressive supranuclear palsy
Jellinger, K.

- N = 30 autopsy confirmed PSP cases, 18 RS and 12 PSP-P
- This study reports the confirmation of the existence of two distinct clinical phenotypes in patients with pathologically proven PSP and
- demonstrated significant differences in the severity and distribution of tau pathology (RS > PSP-P).