

## Neuronal subpopulations and genetic background in tauopathies: a catch 22 story?

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Historically, frontotemporal dementia (FTD) were often classified as a form of Pick's disease, even when Pick cells or Pick bodies were not found. However, this denomination may involve different subgroups of pathologies, and the Lund and Manchester groups published in 1994 a consensus on Clinical and Neuropathological Criteria for Frontotemporal Dementia [3]. This publication clarified the position of Pick's disease within FTD, and several of the reported cases of familial Pick's disease were probably cases of familial FTD. Indeed it is difficult to ascertain families which have the classic pathological features of Pick's disease from the literature, because they often have unusual clinical features. Also, in 1996, Brun and Passant characterized "Frontal lobe degeneration" as a subgroup of frontotemporal dementia distinct from the others because of the lack of tau pathology and histological hallmarks, apart from neuronal loss, spongiosis and astrogliosis [4].

In 1994, Wilhelmsen and colleagues have described an autosomal dominantly-inherited disease related to familial FTD, characterized by adult-onset behavioral disturbances, frontal lobe dementia, parkinsonism and amyotrophy [25]. They demonstrated a genetic linkage between this pathology, denominated disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), and chromosome 17q21–22. Since then, several families sharing a linkage with chromosome 17q22–22 have been described. Although clinical and neuropathological heterogeneity, they have been included in a group of pathologies referred to as frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) [12]. Recently, FTDP-17 has been related to mutations on the tau gene. Tau mutations always segregate with the pathology and are not found in the control subjects, suggesting their pathogenic role (for review, [14]).

In this article, Reed and colleagues review correlations between genotypes and phenotypes in FTDP-17. In fact, both clinical and neuropathological differences could be described among and within the families with FTDP-17, usual symptoms include behavioral changes, loss of frontal executive functions, language deficit and hyperorality. Parkinsonism and amyotrophy are described in some families, but are not consistent features. Neuropathologically, brains of FTD patients exhibit an atrophy of frontal and temporal lobes, a severe neuronal cell loss, a grey and white matter gliosis, and a superficial laminar spongiosis. One of the main important characteristic is the filamentous pathology affecting the neuronal cells, or the both neuronal and glial cells in some cases. Amyloid aggregates are rare.

To date, 19 mutations have been described in the tau gene among the different families with cases diagnosed as FTDP-17 (Table 1 of Reed article). Ten missense mutations in coding regions K257T and I260V, G272V, N279K, P301L, P301S, S305N, V337M, G389R, R406W, two silent mutations L284L and S305S, one single amino acid deletion ( $\Delta$ K280), and five intronic mutations in the splicing region following exon 10 at position +3, +12, +13, +14 and +16 have been reported. A sixth intronic mutation with a likely pathogenic effect was recently described at position +33.

Of course, mutations of the tau gene and their involvement in FTDP-17 may emphasize the fact that abnormal tau proteins play a central role in the etiopathogenesis of neurodegenerative disorders, without any implication of the amyloid cascade. The functional effects of the mutations suggest that a reduced ability of tau to interact with microtubules may be upstream of hyperphosphorylation and aggregation. These mutations may also lead to an increase in free cytoplasmic tau (especially 4R-tau isoforms), and therefore facilitating their aggregation into filaments. Reed and colleagues suggest that polymorphisms in the tau gene may explain other tauopathies including progressive supranuclear palsy (PSP) and corticobasal degeneration. They

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distinguish tauopathies where tau dysfunction is a primary event in the degenerating process and those including Alzheimer's disease (AD) and post-encephalitic parkinsonism (PEP) where it is a secondary event. Indeed, in Alzheimer's disease, mutations on amyloid precursor protein (APP) and presenilins genes clearly indicate that the etiopathogenesis is different from that of FTDP-17. No tau mutations and/or polymorphisms are linked to the disease [7,18,22]. In this respect, it should be noted that many neuropathological aspects of tauopathies may be rather related to tau metabolism than genetic defects [8].

First, tauopathies exhibit different laminar and regional distributions of tau aggregates. For instance, in Alzheimer's disease, neurofibrillary tangles (NFT) correspond to tau aggregation into paired helical filaments (PHF), within certain vulnerable neuronal populations. At the microscopic level, NFT are preferentially observed in the large pyramidal cells of the hippocampus and the entorhinal cortex, and the supragranular (II–III) and infragranular (V–VI) layers of the association cortical areas, while primary sensory and motor cortex are relatively spared. Many cortical and subcortical areas, such as nucleus basalis of Meynert, amygdala, locus coeruleus and dorsal raphe, are also affected by NFT formation [1]. Conversely, the immunohistochemical analysis of the brain of PEP cases demonstrated that NFT are found in variable densities in the hippocampus and entorhinal cortex, in neocortical areas 4, 9 and 20 and in subcortical regions. Higher NFT densities are observed in the hippocampus (CA1 and subiculum) and area 20, compared to areas 4 and 9, and the putamen, indicating that some regions are preferentially affected by the degenerative process. In addition, and contrasting with AD cases, NFT are more numerous in supragranular than in the infragranular layers [6]. Finally, in PSP, NFT were first described in basal ganglia, brainstem, and cerebellum, and the subcortical localization of the neuropathological lesions initially led to the definition of PSP as a model of "subcortical dementias." Later on, degenerative profiles have been described in the perirhinal, inferior temporal and prefrontal cortex, with variable densities of NFT among cases. These studies also demonstrated that the primary motor cortex is more severely affected than neocortical association areas compared to AD [15,16]. Furthermore, glial fibrillary tangles have also been described [17]. These data suggest that particular cell subpopulations are vulnerable in a given tauopathy.

Second, these vulnerable neurons degenerate following precise pathways. Regarding encephalopathy such as PEP, it is clear that a virus follows neural networks for its propagation. It is now well established that there is also a sequential degeneration of vulnerable networks of neurons in AD and PSP. In AD, both biochemical and neuropathological studies show that NFT formation starts in the hippocampal formation (from transentorhinal to entorhinal and then hippocampus), progresses sequentially as follows anterior, inferior and medium temporal cortex, and then spreads into polymodal association areas, unimodal areas

and primary and/or sensory areas [2,9,11]. Vulnerable neurons are present in the hippocampal formation and it may explain why NFT are consistently found in this region in aging. However, in AD, APP dysfunction is likely to intensify this process and allows for a propagation of the degenerating process [9]. In PSP, NFT formation starts in subcortical structures and then progresses or not into frontal cortex. In fact, a factorial analysis of NFT density in cortex and subcortex isolated two factors, cortical and subcortical, both linked to the pedunclopontine nucleus. This suggests a prominent role of this nucleus in the spread of the lesions. The presence of cortical NFT could be related to the selective involvement of cortical pathways perhaps connected with the pedunclopontine nucleus [24]. The most likely hypothesis is a retrograde degeneration of neuronal connections that link Brodmann areas 4 and 6 to pedunclopontine nucleus [20,24]. Altogether, these data suggest that degeneration of vulnerable neurons expands along neuronal networks in a precise, hierarchical and sequential process and never at random or globally.

Third, the different vulnerable neurons among tauopathies exhibit specific phenotypes. In fact, in absence of pathogenic mutations, tau isoforms are differentially distributed in neuronal subpopulations. For instance, 4R-tau isoforms are not detected by *in situ* hybridization in granular cells of the dentate gyrus [13] and Delacourte and colleagues clearly demonstrated that only three microtubule-binding domains (3R) tau isoforms are found in Pick bodies bearing cells such as granule cells [10]. In fact, biochemical analysis indicates that tauopathies may be classified using electrophoretic tau profiles [5]. In Pick's disease, these 3R-tau isoforms migrate as a major tau doublet at 60 and 64 kDa with a minor band at 68 kDa. Thus, all vulnerable neurons are connected and exhibit the same pool of tau isoforms. This observation is also true for AD and PSP. In AD, PHF are mainly made of a tau triplet at 60, 64 and 68 kDa, with a minor band at 72–74 kDa corresponding to the phosphorylation of all six tau isoforms and suggesting that vulnerable neurons contain all tau isoforms. In PSP, a tau doublet of 64 and 68 kDa with a minor band at 72–74 kDa is found indicating that mostly 4R tau isoforms aggregate into filaments. Moreover, the Pick doublet tau 60 and 64 and Pick bodies are not labeled using the 12E8 antibody directed against phosphorylated Ser262 [10,19,21]. Since it was shown that 3R-tau isoforms can be phosphorylated on Ser262 using transfection experiments, this lack of immunoreactivity may reflect a particular phenotype of vulnerable neurons to the Pick-type degeneration [19]. This is of particular interest since this phosphorylation at this site may be protective in the tau aggregation process [23]. These data suggest that subpopulations of neurons characterized by particular sets of both tau isoforms and kinase/phosphatases may be vulnerable in one given disorder. This is a striking difference with FTDP-17 where Reed and colleagues review that both glial cells and neurons are affected in both

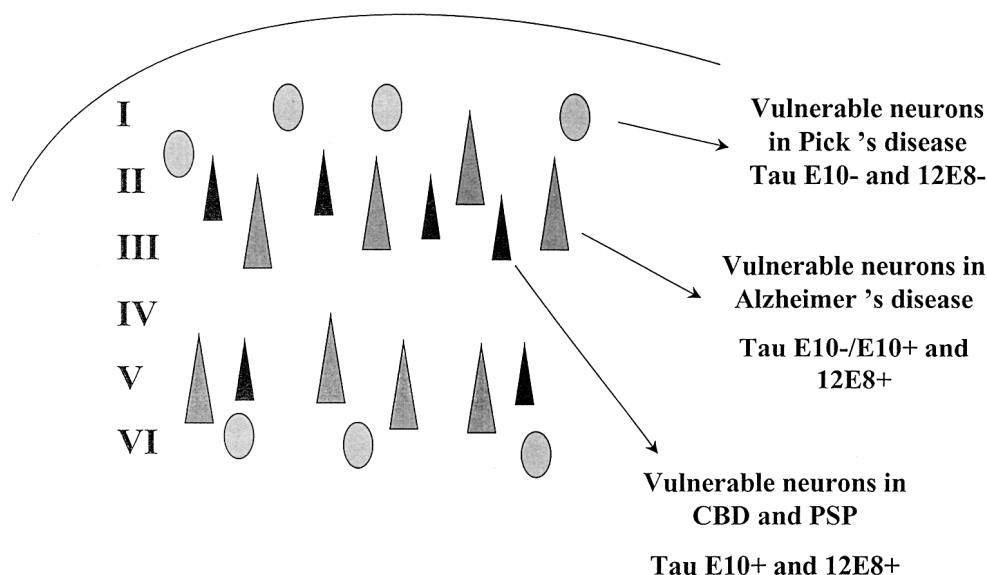


Fig. 1. Schematic representation of the laminar distribution (layers I-VI) of neurons in human isocortex. Since both electrophoretic tau profiles and laminar and regional distributions of NFT are different among tauopathies, different tau isoforms (with or w/o exon10; E10+ and E10- respectively) are likely to be expressed in subsets of neurons that exhibit different vulnerability in addition to different sets of enzymes (kinases able to phosphorylate Ser262 and 356 and generate 12E8 epitope). Following abnormal phosphorylation, tau isoforms aggregate into filaments and display a particular electrophoretic profile when analyzed by immunoblotting.

cortical and subcortical areas. Tau mutations affect all brain cell types without any specificity in FTDP-17.

From these studies, it is clear that FTDP-17 may be considered as a tauopathy where tau dysfunction is a primary event in the etiopathogenesis. However, the number of families with tau mutations is really small compared to other tauopathies without tau mutations. For these latter ones, tau is likely to be instrumental but the pathophysiological process is essentially linked to environmental and genetic risk factors that lie on specific neuronal networks involving subsets of neurons with defined phenotypes sustained by different pools of tau isoforms and/or kinases (Fig. 1). In this respect, NFT formation affects subpopulations of neurons with a particular regional and laminar distribution [15,16,24]. However, H1 tau haplotype is overrepresented in PSP cases suggesting that tau polymorphisms may affect splicing and lead to overexpression and aggregation of 4R tau isoforms (for reviews, Reed et al. this volume, 8). Altogether, these data indicate that tau polymorphisms are likely to be more efficient only in a subset of cells.

## References

- [1] Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cereb Cortex* 1991;1:103–16.
- [2] Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging* 1995;16:271–8 [discussion 278–84].
- [3] Brun A, Englund B, Gustafson L, Passant U, Mann DMA, Neary D, Snowden JS. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry* 1994;57:416–8.
- [4] Brun A, Passant U. Frontal lobe degeneration of non-Alzheimer type. Structural characteristics, diagnostic criteria and relation to other frontotemporal dementias. *Acta Neurol Scand Suppl* 1996;168:28–30.
- [5] Buée L, Delacourte A. Comparative biochemistry of tau in progressive supranuclear palsy, corticobasal degeneration, FTDP-17 and Pick's disease. *Brain Pathol* 1999;9:681–93.
- [6] Buée-Scherrer V, Buée L, Leveugle B, Perl DP, Vermersch P, Hof PR, Delacourte A. Pathological tau proteins in postencephalitic parkinsonism: comparison with Alzheimer's disease and other neurodegenerative disorders. *Ann Neurol* 1997;42:356–9.
- [7] Crawford F, Freeman M, Town T, Fallin D, Gold M, Duara R, Mullan M. No genetic association between polymorphisms in the Tau gene and Alzheimer's disease in clinic or population based samples. *Neurosci Lett* 1999;266:193–6.
- [8] Delacourte A, Buée L. Tau pathology: a marker of neurodegenerative disorders. *Curr Opin Neurol* 2000;13:371–6.
- [9] Delacourte A, David J, Sergeant N, Buée L, Watzte A, Vermersch P, Ghazali F, Fallet-Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology* 1999;52:1158–65.
- [10] Delacourte A, Sergeant N, Watzte A, Gauvreau D, Robitaille Y. Vulnerable neuronal subsets in Alzheimer's and Pick's disease are distinguished by their tau isoform distribution and phosphorylation. *Ann Neurol* 1998;43:193–204.
- [11] Duyckaerts C, Colle MA, Dessi F, Grignon Y, Piette F, Hauw JJ. The progression of the lesions in Alzheimer disease: insights from a prospective clinicopathological study. *J Neural Transm Suppl* 1998; 53:119–26.
- [12] Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. *Ann Neurol* 1997;41:706–15.
- [13] Goedert M, Spillantini MG, Potier MC, Ulrich J, Crowther RA. Cloning and sequencing of the cDNA encoding an isoform of microtubule-associated protein tau containing four tandem repeats: differ-

- ential expression of tau protein mRNAs in human brain. *EMBO J* 1989;8:393–9.
- [14] Goedert M, Spillantini MG. Tau mutations in frontotemporal dementia FTDP-17 and their relevance for Alzheimer's disease. *Biochim Biophys Acta* 2000;1502:110–21.
- [15] Hauw JJ, Verny M, Delaere P, Cervera P, He Y, Duyckaerts C. Constant neurofibrillary changes in the neocortex in progressive supranuclear palsy. Basic differences with Alzheimer's disease and aging. *Neurosci Lett* 1990;119:182–6.
- [16] Hof PR, Delacourte A, Bouras C. Distribution of cortical neurofibrillary tangles in progressive supranuclear palsy: a quantitative analysis of six cases. *Acta Neuropathol* 1992;84:45–51.
- [17] Komori T. Tau-positive glial inclusions in progressive supranuclear palsy, corticobasal degeneration and Pick's disease. *Brain Pathol* 1999;9:663–79.
- [18] Kwon JM, Nowotny P, Shah PK, Chakraverty S, Norton J, Morris JC, Goate AM. Tau polymorphisms are not associated with Alzheimer's disease. *Neurosci Lett* 2000;284:77–80.
- [19] Mailliot C, Sergeant N, Bussière T, Caillet-Boudin ML, Delacourte A, Buée L. Phosphorylation of specific sets of tau isoforms reflects different neurofibrillary degeneration processes. *FEBS Lett* 1998;433:201–4.
- [20] Nieuwenhuys R, Veening JG, van Domburg P. Core and paracores; some new chemoarchitectural entities in the mammalian neuraxis. *Acta Morphol Neerl Scand* 1988;26:131–63.
- [21] Probst A, Tolnay M, Langui D, Goedert M, Spillantini MG. Pick's disease: hyperphosphorylated tau protein segregates to the somato-axonal compartment. *Acta Neuropathol (Berl)* 1996;92:588–96.
- [22] Roks G, Dermaut B, Heutink P, Julliams A, Backhovens H, Van de Broeck M, Serneels S, Hofman A, Van Broeckhoven C, van Duijn CM, Cruts M. Mutation screening of the tau gene in patients with early-onset Alzheimer's disease. *Neurosci Lett* 1999;277:137–9.
- [23] Schneider A, Biernat J, von Bergen M, Mandelkow E, Mandelkow EM. Phosphorylation that detaches tau protein from microtubules (Ser262, Ser214) also protects it against aggregation into Alzheimer paired helical filaments. *Biochemistry* 1999;38:3549–58.
- [24] Verny M, Duyckaerts C, Agid Y, Hauw JJ. The significance of cortical pathology in progressive supranuclear palsy. Clinico-pathological data in 10 cases. *Brain* 1996;119:1123–36.
- [25] Wilhelmsen KC, Lynch T, Pavlou E, Higgins M, Nygaard TG. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21–22. *Am J Hum Genet* 1994;55:1159–65.