

Bernardino Ghetti - selected publications

- 1 Ghetti, B., Spina, S., Murrell, J. R., Huey, E. D., Pietrini, P., Sweeney, B. et al. (2008). In vivo and postmortem clinicoanatomical correlations in frontotemporal dementia and parkinsonism linked to chromosome 17. *Neurodegener.Dis.*, 5, 215-217.  
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BACKGROUND: Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) is associated with mutations in the Microtubule-Associated Protein Tau(MAPT) gene or the Progranulin(PGRN) gene. MAPT mutations lead to widespread deposition of hyperphosphorylated tau protein (FTDP-17T). PGRN mutations are associated with ubiquitin- and TDP-43-positive inclusions in the frontotemporal cortex, striatum and hippocampus (FTDP-17U). Despite the differences, FTDP-17T and FTDP-17U share a largely overlapping clinical phenotype. OBJECTIVE: To determine whether neuroimaging studies may allow an in vivo early differentiation between FTDP-17T and FTDP-17U. METHODS: We studied 25 individuals affected with FTDP-17T associated with either the exon 10+3 (24 subjects) or the G335S (1 subject) MAPT mutation, as well as 3 FTDP-17U individuals, who were carriers of the A9D, IVS6-2A>G or R493X PGRN mutation. Neuroimaging studies, obtained along the course of the disease, were compared to the neuropathologic findings. RESULTS: FTDP-17T cases were associated with symmetric frontotemporal atrophy. Behavioral changes constituted the predominant clinical presentation. Conversely, an asymmetric degenerative process was seen in all 3 PGRN cases, who presented with either corticobasal syndrome (A9D) or frontotemporal dementia and language deterioration (IVS6-2A>G and R493X). CONCLUSION: Neuroimaging data, in the early disease stage of FTDP-17, may offer the possibility of an early differentiation of FTDP-17T and FTDP-17U phenotypes, independent of the genetic analysis
- 2 Ghetti, B., Hutton, M. L., & Wszolek, Z. K. (2003). Frontotemporal dementia and parkinsonism linked to chromosome 17 associated with the Tau gene mutations (FTDP-17T). In D.Dickson (Ed.), *Neurodegeneration: The molecular pathology of dementia and movement disorders* (pp. 86-102). Basel: ISN Neuropathology Press.
- 3 Ghetti, B., Murrell, J. R., Zolo, P., Spillantini, M. G., & Goedert, M. (2000). Progress in hereditary tauopathies: a mutation in the Tau gene (G389R) causes a Pick disease-like syndrome. *Annals of the New York Academy of Sciences*, 92052-62, -62.  
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We describe the clinical and pathologic phenotypes of the G389R mutation in exon 13 of the Tau gene. Progressive aphasia and memory disturbance are the initial signs and begin in the fourth or fifth decade of life, followed by apathy, indifference, hyperphagia, rigidity, pyramidal signs and dementia. Death occurs after two to five years. Magnetic resonance imaging and neuropathologic studies show frontal and temporal atrophy. Pick body-like and axonal filamentous inclusions found in the neocortex and subcortical white matter, respectively, are tau immunoreactive. Immunoblot analysis of sarkosyl-insoluble tau shows two major bands of 60 and 64 kDa that, upon dephosphorylation, resolve into four bands of three- and four-repeat isoforms. Isolated tau filaments are often straight and occasionally twisted. Recombinant mutant tau protein shows a reduced ability to promote microtubule assembly, suggesting that this may be the primary effect of the mutation. The present findings indicate that the G389R mutation in Tau can cause a dementia similar to that in Pick's disease
- 4 Murrell, J. R., Hake, A. M., Quaid, K. A., Farlow, M. R., & Ghetti, B. (2000). Early-onset Alzheimer disease caused by a new mutation (V717L) in the amyloid precursor protein gene. *Archives of Neurology*, 57, 885-887.  
Notes: CONTEXT: Alzheimer disease is the most common form of dementia. Mutations in the genes amyloid precursor protein (APP), presenilin 1(PS1) and presenilin 2(PS2) have been found in early-onset familial forms of Alzheimer disease OBJECTIVE: To determine the cause

of dementia in a family with early-onset illness. DESIGN, SETTING, AND PARTICIPANTS: A family with a history of dementia was referred to the Indiana Alzheimer Disease Center, Indianapolis. All the research in this study was done in a university or university hospital. The proband and her 4 siblings took part in the study. The proband, who is still alive, showed symptoms of Alzheimer disease at 38 years of age. Genomic DNA was obtained from blood samples of 5 family members. The APP and PS1 genes of the proband were screened for mutations by amplification followed by direct sequencing. RESULTS: Sequence of exon 17 of the APP gene revealed a single nucleotide (guanine to cytosine) substitution in 1 allele, resulting in an amino acid change at codon 717 (valine to leucine). Each of the proband's siblings were tested for this mutation by direct sequencing. Two of the 4 were found to have the mutation; one of whom was recently clinically diagnosed at the age of 36 years. CONCLUSIONS: A novel mutation in the APP gene (V717L) has been found in a family with a history of dementia, beginning in the mid to late 30s. The age of onset in this family is earlier than most of the other families with Alzheimer disease who also have APP mutations

- 5 Ghetti, B., Murrell, J., & Spillantini, M. G. (1999). Mutations in the Tau gene cause frontotemporal dementia. *Brain Research Bulletin*, 50, 471-472.

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- 6 Spillantini, M. G., Murrell, J. R., Goedert, M., Farlow, M. R., Klug, A., & Ghetti, B. (1998). Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proceedings of the National Academy of Sciences of the United States of America*, 95, 7737-7741.

Notes: Medical Research Council Centre for Brain Repair and Department of Neurology, University of Cambridge, Robinson Way, Cambridge CB2 2PY, UK. mgs11@cam.ac.uk ; ABSTRACT: Familial multiple system tauopathy with presenile dementia (MSTD) is a neurodegenerative disease with an abundant filamentous tau protein pathology. It belongs to the group of familial frontotemporal dementias with Parkinsonism linked to chromosome 17 (FTDP-17), a major class of inherited dementing disorders whose genetic basis is unknown. We now report a G to A transition in the intron following exon 10 of the gene for microtubule-associated protein tau in familial MSTD. The mutation is located at the 3' neighboring nucleotide of the GT splice-donor site and disrupts a predicted stem-loop structure. We also report an abnormal preponderance of soluble tau protein isoforms with four microtubule-binding repeats over isoforms with three repeats in familial MSTD. This most likely accounts for our previous finding that sarkosyl-insoluble tau protein extracted from the filamentous deposits in familial MSTD consists only of tau isoforms with four repeats. These findings reveal that a departure from the normal ratio of four-repeat to three-repeat tau isoforms leads to the formation of abnormal tau filaments. The results show that dysregulation of tau protein production can cause neurodegeneration and imply that the FTDP-17 gene is the tau gene. This work has major implications for Alzheimer's disease and other tauopathies

- 7 Spillantini, M. G., Bird, T. D., & Ghetti, B. (1998). Frontotemporal dementia and Parkinsonism linked to chromosome 17: a new group of tauopathies. *Brain Pathology*, 8, 387-402.

Notes: MRC Brain Repair Centre and Department of Neurology, University of Cambridge, UK. mgs11@cam.ac.uk ; ABSTRACT: Frontotemporal dementia is a neurological disorder characterised by personality changes, deterioration of memory and executive functions as well as stereotypical behaviour. Sometimes a Parkinsonian syndrome is prominent. Several cases of frontotemporal dementia are hereditary and recently families have been identified where the disease is linked to chromosome 17q21-22. Although, there is clinical and neuropathological variability among and within families, they all consistently present a symptomatology that has led investigators to name the disease "Frontotemporal Dementia and Parkinsonism linked to chromosome 17." Neuropathologically, these patients present with atrophy of frontal and temporal cortex as well as of basal ganglia and substantia nigra. In the majority of cases these features are accompanied by neuronal loss, gliosis and microtubule-associated protein tau deposits which can be present in both neurones and glial cells. The distribution, structural and

biochemical characteristics of the tau deposits differentiate them from those present in Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy and Pick's disease. No beta- amyloid deposits are present. The clinical and neuropathological features of the disease in these families suggest that Frontotemporal Dementia and Parkinsonism linked to chromosome 17 is a distinct disorder. The presence of abundant tau deposits in the majority of these families define this disorder as a new tauopathy

- 8 Spillantini, M. G., Goedert, M., Crowther, R. A., Murrell, J. R., Farlow, M. R., & Ghetti, B. (1997). Familial multiple system tauopathy with presenile dementia: a disease with abundant neuronal and glial tau filaments. *Proceedings of the National Academy of Sciences of the United States of America*, *94*, 4113-4118.  
Notes: Medical Research Council Cambridge Centre for Brain Repair, University of Cambridge, United Kingdom. mgs11@cam.ac.uk  
Neurofibrillary lesions made of hyperphosphorylated microtubule-associated protein tau constitute not only one of the defining neuropathological features of Alzheimer disease but also are present in a number of other neurodegenerative diseases with dementia. Here we describe a novel autosomal dominant disease named familial "multiple system tauopathy with presenile dementia," which is characterized by abundant fibrillary deposits of tau protein in both neurons and glial cells. There are no detectable deposits of beta-amyloid. The tau deposits are in the form of twisted filaments that differ in diameter and periodicity from the paired helical filaments of Alzheimer disease. They are stained by both phosphorylation-independent and -dependent anti-tau antibodies. Moreover, tau immunoreactivity coexists with heparan sulfate in affected nerve and glial cells. Tau protein extracted from filaments of familial multiple system tauopathy with presenile dementia shows a minor 72-kDa band and two major bands of 64 and 68 kDa that contain mainly hyperphosphorylated four-repeat tau isoforms of 383 and 412 amino acids