Journal of the Neurological Sciences 289 (2010) 149–154

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Elucidating the genetics and pathology of Perry syndrome

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ARTICLE INFO

Available online 4 September 2009

Keywords:
Perry syndrome
Parkinsonism
Depression
Hypoventilation
Dynactin
DCTN1
p150^{glued}
TDP-43

ABSTRACT

Perry syndrome is characterized clinically by autosomal dominantly inherited, rapidly progressive parkinsonism, depression, weight loss and hypoventilation. In the seven families reported previously and the two new families presented herein (the Hawaii family and the Fukuoka-4 Japanese family), the mean disease onset age is 48 years (range: 35–61) and the mean disease duration five years (range: 2–10). Histology and immunohistochemistry show severe neuronal loss in the substantia nigra and locus coeruleus, with TDP-43-positive pathology in neurons (intranuclear and cytoplasmic inclusions, dystrophic neurites, axonal spheroids) and glial cells (glial cytoplasmic inclusions). Compared with other TDP-43-proteinopathies (amyotrophic lateral sclerosis and ubiquitin-positive frontotemporal lobar degeneration), the distribution is unique in Perry syndrome with pallidonigral distribution and sparing of the cortex, hippocampus and motor neurons. The genetic cause of Perry syndrome was recently identified with five mutations in the *dynactin* gene (*DCTN1*) segregating with disease in eight families. *DCTN1* encodes p150^{glued}, the major subunit of the dynactin protein complex, which plays a crucial role in retrograde axonal and cytoplasmic transport of various cargoes. Evidence suggests the Perry mutations alter the binding of p150^{glued} to microtubules. Further studies will examine reasons for the vulnerability of selected neuronal populations in Perry syndrome, and the link between the genetic defect and TDP-43 pathology.

1. Introduction

In 1975, Perry and collaborators reported a Canadian family with rapidly progressive autosomal dominant parkinsonism, depression, weight loss, sleep difficulties and central hypoventilation [1,2]. Over the next 30 years six additional families have been reported from Canada, the U.S., the U.K., France, Turkey and Japan (reviewed in [3]) [4–10]. Depression, apathy, weight loss and parkinsonism are early symptoms while central hypoventilation develops in later stages. The mean onset age is 48 years (range: 35–61, including two unpublished families, see below) and the mean disease duration five years (range: 2–10). Patients die of respiratory complications, sudden unexplained death or by suicide. Initial reports highlighted reduced taurine levels in CSF from patients with Perry syndrome, however this finding was not replicated in subsequent studies [1,2,4,8,9].

An international consortium was established in 2001 by ZKW and YT to expand the clinical, pathological and genetic characterization of Perry syndrome. In so doing, we have been able to reactivate seven of the eight previously published families and to identify two additional unreported kindreds from Hawaii and Japan (Fukuoka-4 family). Materials collected included detailed clinical information (eight families), brain tissue (eight patients from five families) and DNA samples (17 affected individuals from eight families and 74 unaffected family members).

Herein we present clinical data on two unpublished families (the Hawaiian and Fukuoka-4 families) with Perry syndrome, and review our recent discoveries in the pathological and genetic characterization of the disease.

2. Unpublished families

Patients were examined by movement disorders neurologists, and signed IRB-approved informed consent was obtained prior to enrollment.

The Hawaiian family originates from Japan. There are six affected individuals (two men) including two with clinical information and one with pathology (Fig. 1). The proband and her second cousin presented at age 47 with parkinsonism and later developed respiratory symptoms. The proband had partial benefit from levodopa. In contrast to previously reported families, symptoms did not include depression and weight loss.

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doi:10.1016/j.jns.2009.08.044

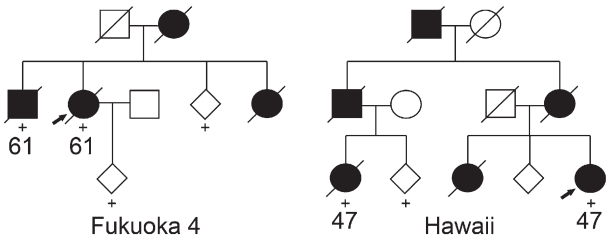

Fig. 1. Pedigrees of two new families with Perry syndrome. Circles, women. Squares, men. Diamonds, gender disguised. Diagonal lines, deceased. Black symbols, affected individuals. Numbers under symbols, ages of onset. "+", DNA sample available. Arrows, probands.

Neuropathologic examination of the proband's second cousin showed neuronal loss in the substantia nigra (SN) and the locus coeruleus, with no Lewy bodies.

The Fukuoka-4 family has four affected individuals (one man) over two generations (Fig. 1). Disease onset (61 years) and duration (three years) were similar in the proband and her brother. The initial symptom was resting tremor in the proband and weight loss in her brother; both later developed levodopa-responsive parkinsonism, weight loss and hypoventilation. Response to levodopa was transient and did not cause motor complications. The proband died of sudden death and her brother of respiratory failure. Of notice, these two patients did not develop depression or apathy, a feature found in all previously published families with Perry syndrome. Further, onset age in this family (61 years) was five years older than the upper range of onset age in other families. No autopsy was performed on these patients.

Genetic analysis showed that although these two families are of Japanese descent, they harbor distinct mutations from two different founders (see below).

3. Neuropathology

Previous reports have highlighted severe neuronal loss in the SN and locus coeruleus, with few to no Lewy bodies [3]. We examined autopsy material from eight patients with Perry syndrome (fixed and frozen tissue from two, paraffin-embedded fixed tissue from five, unstained tissue on glass slides from one). All patients had severe SN neuronal loss. Surviving SN neurons had intranuclear (NII) and cytoplasmic (NCI) inclusions that stained positive for transactive-response (TAR) DNA-binding protein of 43 kD (TDP-43) [11]. TDP-43 pathology also included dystrophic neurites, axonal spheroids and glial cytoplasmic inclusions (Fig. 2). Immunohistochemistry for tau and α-synuclein was negative. These findings show TDP-43-positive inclusions are characteristic of Perry syndrome and establish this condition as a TDP-43-proteinopathy.

TDP-43 was recently identified as the major ubiquitinated component of NCI and NII in ubiquitin-positive frontotemporal lobar degeneration (FTLD-U), frontotemporal dementia–motor neuron disease (FTD–MND) and amyotrophic lateral sclerosis (ALS) [12].

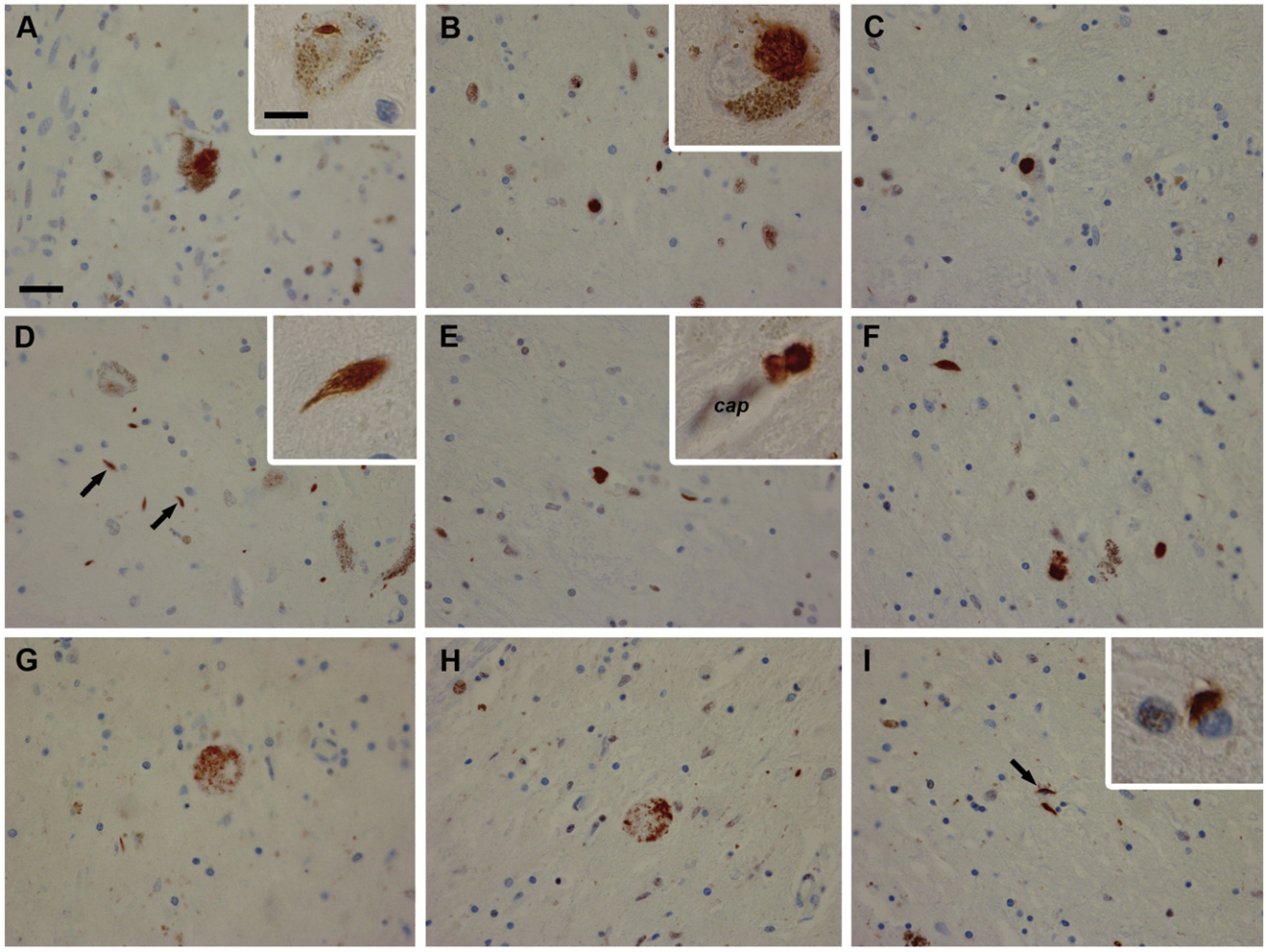

Fig. 2. TDP-43 immunohistochemistry of Perry patients shows NCI (A–C; higher magnification in inset of B), NII (inset in A), dystrophic neurites (D arrows, E and F; higher magnification in inset of D), axonal spheroids (G, H), glial cytoplasmic inclusions (I, arrow; higher magnification in inset of I), and a perivascular astrocytic inclusions (inset of E; cap = capillary). Scale bar: 25 μm (A–I), 10 μm (insets of A, B, D, E and I).
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