Journal of Alzheimer's Disease 34 (2013) 1–5
IOS Press

Supplementary Data

C9ORF72 Repeat Expansions in the Frontotemporal Dementias Spectrum of Diseases: A Flow-chart for Genetic Testing

Isabelle Le Ber[a,b,c,1], Agnès Camuzat[a,1], Lena Guillot-Noel[a,1], Didier Hannequin[d], Lucette Lacomblez[c,e,f], Véronique Golfier[g], Michèle Puel[h], Olivier Martinaud[d], Vincent Deramecourt[i], Sophie Rivaud-Pechoux[a], Stéphanie Millecamps[a], Martine Vercelletto[j], Philippe Couratier[k], François Sellal[l], Florence Pasquier[i], François Salachas[c], Catherine Thomas-Antérion[m], Mira Didic[n], Jérémie Pariente[h], Danielle Seilhean[a,e,o], Merle Ruberg[a], Isabelle Wargon[a,b,c], Frédéric Blanc[p], William Camu[q], Bernard-François Michel[r], Eric Berger[s], Mathilde Sauvée[t], Christel Thauvin-Robinet[u], Karl Mondon[v], Elisabeth Tournier-Lasserve[w], Cyril Goizet[x], Marie Fleury[p], Gabriel Viennet[s], Patrice Verpillat[a], Vincent Meininger[c], Charles Duyckaerts[a,e,o], Bruno Dubois[b,c,e], Alexis Brice[a,b,c,e,y,*] and the French research network on FTLD/FTLD-ALS[2]

[a]*CRicm-UMRS975, Paris, France*
[b]*AP-HP, Hôpital de la Pitié-Salpêtrière, Centre de Référence des Démences Rares, Paris, France*
[c]*AP-HP, Hôpital de la Pitié-Salpêtrière, Fédération des maladies du système nerveux, Paris, France*
[d]*INSERM: Institut National de la Santé et de la Recherche Médicale U614, CNR-MAJ & Département de Neurologie, Rouen University Hospital, France*
[e]*UPMC Univ Paris06, UMRS975, Paris, France*
[f]*AP-HP, Hôpital de la Salpêtrière, Service de pharmacologie, Paris, France*

[1]These authors contributed equally to this work.

[2]The French research network on FTLD/FTLD-ALS includes: Alexis Brice (Hôpital de la Salpêtrière, Paris), Frédéric Blanc (Hôpitaux Civils, Strasbourg) Françoise Clerget-Darpoux (Hôpital Paul Brousse, Villejuif), Philippe Couratier (CHU Limoges), Phillipe Corcia (CHU Tours), Mira Didic (CHU La Timone, Marseille), Bruno Dubois (Hôpital de la Salpêtrière, Paris), Charles Duyckaerts (Hôpital de la Salpêtrière, Paris), Véronique Golfier (CHU, Rennes), Didier Hannequin (Rouen University Hospital), Lucette Lacomblez (Hôpital de la Salpêtrière, Paris), Isabelle Le Ber (Hôpital de la Salpêtrière, Paris), Richard Levy (CHU Saint Antoine, Paris), Bernard-François Michel (CH Sainte-Marguerite, Marseille), Vincent Meininger (Hôpital de la Salpêtrière, Paris), Florence Pasquier (CHU, Lille), Catherine Thomas-Anterion (CHU Bellevue, Saint-Etienne), Michèle Puel (CHU Purpan, Toulouse), François Salachas (Hôpital de la Salpêtrière, Paris), François Sellal (CH Colmar), Martine Vercelletto (CHU Laennec, Nantes), Patrice Verpillat (Hôpital de la Salpêtrière, Paris), William Camu (CHU G. de Chauliac, Montpellier).

*Correspondence to: Pr. Alexis Brice, CR-ICM-UMRS_975, ICM, Hôpital de la Salpêtrière, 47, Boulevard de l'hôpital, 75 651 Paris Cedex 13, France. E-mail: alexis.brice@upmc.fr.

ISSN 1387-2877/13/$27.50 © 2013 – IOS Press and the authors. All rights reserved

[g]*Service de Neurologie, CHU, Rennes, France*
[h]*Inserm; Imagerie Cérébrale et Handicaps Neurologiques UMR 825; Université de Toulouse; UPS; Imagerie Cérébrale et Handicaps Neurologiques UMR 825; Service de Neurologie; Pôle Neurosciences; CHU Purpan, Toulouse, France*
[i]*Université Lille Nord de France, UDSL EA1046, CHU Lille-Bailleul Memory Center, Lille, France*
[j]*Service de Neurologie, CHU Guillaume et René Laënnec, Nantes, France*
[k]*Service de Neurologie, CHU Dupuytren, Limoges, France*
[l]*Service de Neurologie, CHG, Colmar & Unité INSERM: Institut National de la Santé et de la Recherche Médicale U-692, Université de Strasbourg, France*
[m]*Service de Neurologie, CHU Bellevue, Saint-Etienne, France*
[n]*APHM, CHU Timone, Service de Neurologie et Neuropsychologie, Aix-Marseille Univ, INSERM U 1106, Marseille, France*
[o]*Laboratoire de Neuropathologie R Escourolle, Hôpital de la Pitié-Salpêtrière, Paris, France*
[p]*Service de Neurologie, Hopitaux Civils, Strasbourg, France*
[q]*Clinique du motoneurone, CHU Gui de Chauliac, INSERM UMR 1051, Université Montpellier 1, Montpellier, France*
[r]*Service de Neurogériatrie, Hôpital Sainte Marguerite, Marseille, France*
[s]*Services de Neurologie & neuropathologie, CHU, Besançon, France*
[t]*Service de Neurologie, CHU, Nancy, France*
[u]*EA GAD, IFR Santé STIC, Université de Bourgogne; Centre de Génétique, CHU, Dijon, France*
[v]*Service de Neurologie, CHU, Tours, France*
[w]*Service de génétique moléculaire neuro-vasculaire, APHP-Hôpital Lariboisière, Paris, France*
[x]*Laboratoire Maladies Rares : Génétique et Métabolisme (MRGM), EA4576, Université Bordeaux et Service de Génétique Médicale, CHU Bordeaux, France*
[y]*AP-HP, Hôpital de la Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Paris, France*

Accepted 13 November 2012

DETAILED DESCRIPTION OF CASES

Patients with isolated parkinsonism at onset

Patient 1. The proband developed a parkinsonian syndrome at age 55. Initially, he had gait disorders with instability and falls, mainly caused by a severe leg tremor at rest and when walking. At age 57, he needed a cane, then a walker. He developed a restless legs syndrome and sleep disorders characterized by nocturnal agitation during REM sleep. On examination, axial rigidity and akinesia with camptocormia, and left-predominant limb rigidity and akinesia were present. Oculomotricity was normal. Limb reflexes were enhanced. His symptoms and gait partially improved with ropinirole. The UPDRS was 27. A DatScan showed bilateral presynaptic dopaminergic denervation of the striatum. At age 58, he developed progressive distal motor weakness in the lower limbs and left upper limb, associated with distal amyotrophy, fasciculations, bilateral plantar extensor, and a dropped head. There were no bulbar symptoms. Motor neuron disease was confirmed by electromyogram. He developed aggressiveness, irritability, impulsiveness, and indifference to others. His Mini-Mental State Exam (MMSE) score was 25/30. Brain magnetic resonance imaging (MRI) revealed moderate cortical atrophy. His mother had dementia at age 55 and died at age 72. His sister presented severe and recurrent depression at age 55, and was followed by a psychiatrist.

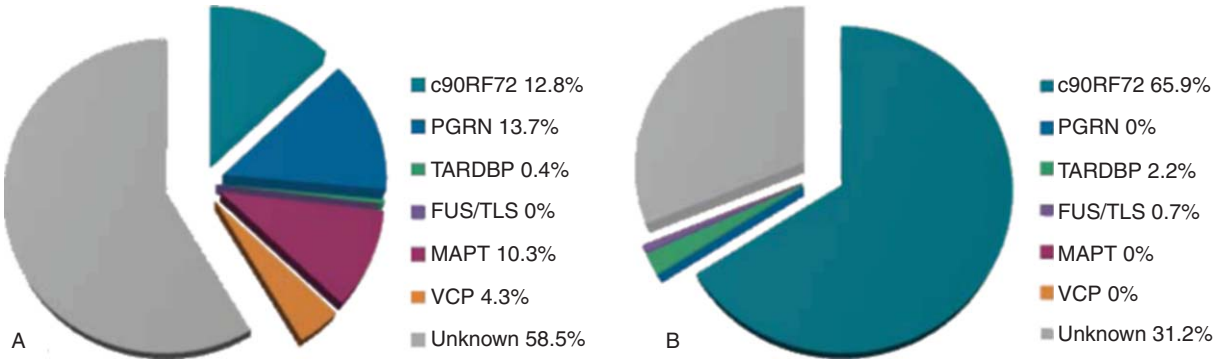
Patient 2. The patient presented with a parkinsonian syndrome at age 48, beginning with a bilateral lower limb tremor at rest and akinesia. She received levodopa (375 mg per day) and ropinirole with little effect. The symptoms progressively worsened. At age 54, she had bilateral upper limb rest tremor, bradykinesia, axial rigidity, and a severe gait disorder due to lower limb akinesia and freezing. She was dysarthric, hypophonic, with urinary incontinence. Ophthalmoplegia, hallucinations, pyramidal symptoms, apraxia, and dementia were absent. The MMSE score was 29/30. Her husband described sleep disorders and somnambulism.

A DatScan showed predominantly right presynaptic dopaminergic denervation of the striatum. She developed mild cognitive disorders at age 56; 9 years after disease onset. Her MMSE score was 25/30 (-2 in calculation, -1 repetition, -2 recall). At age 57, her Unified Parkinson's Disease Rating Scale (UPDRS) was scored 7 on, 20 off and her Hoehn and Yahr score was 4. She died at age 59.

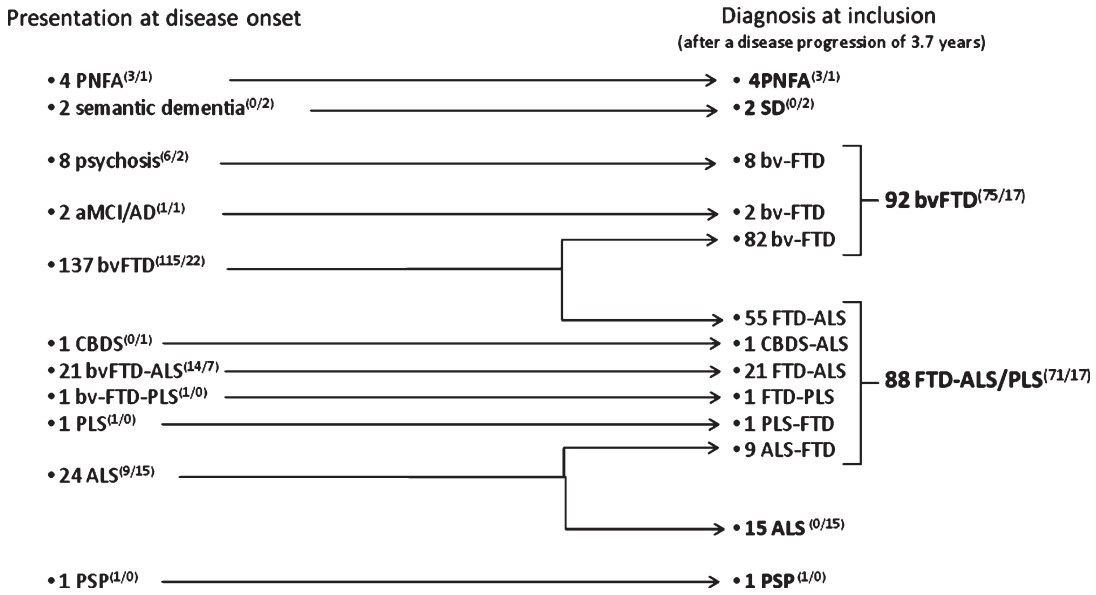
Patients with isolated primary lateral sclerosis at onset

Patient 1. The patient had isolated upper motor neuron disease revealed by a spastic paraparesis at age 30. She had a spastic gait with muscular weakness in the lower limbs and required a walker. On examination, reflexes were enhanced in the four limbs, and bilateral extensor plantar reflexes were observed. She had no bulbar symptoms. The upper motor symptoms progressed slowly and remained isolated for 22 years. Primary lateral sclerosis (PLS) was diagnosed. At age 52, she developed apathy, was socially withdrawn and performed rituals. Two years later, the MMSE score was 29/30 and the frontal assessment battery score was 14/18. On examination, reflexes of the four limbs were enhanced with lower limb spasticity and distal muscular weakness. Amyotrophy, fasciculations, and bulbar symptoms were absent. She is alive at age 56. Her sister had behavioral variant frontotemporal dementia (bvFTD) at age 48, but no motor neuron disorder. Her mother had FTD-ALS and died at age 62.

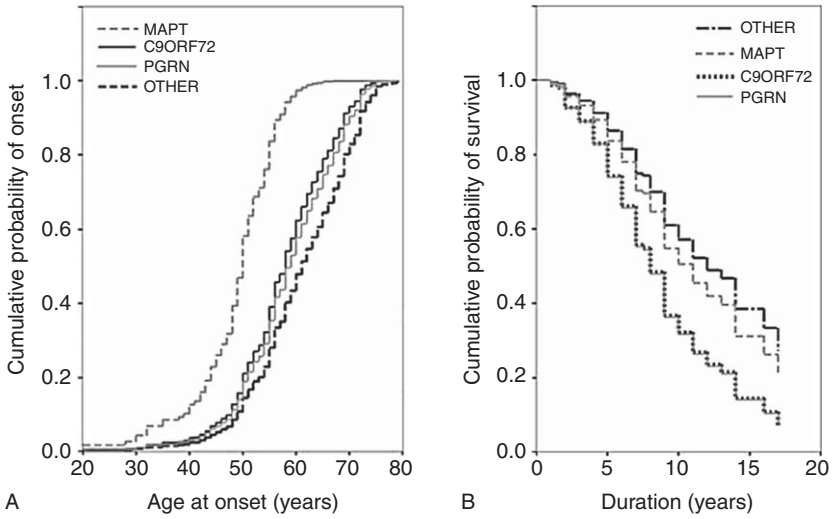
Patient 2. The proband showed personality changes and had behavioral disorders at age 45. He was aggressive, irritable, expressed anger, and spent money excessively. At age 48, he was disinhibited and presented hyperorality, impulsiveness, joviality, emotional lability, and imitation behavior. Reflexes were enhanced and bilateral plantar extensor reflexes were observed. He had spasticity but no muscular weakness or fasciculations. His speech was dysarthric and agrammatical, with stuttering. The neuropychological evaluation showed dysexecutive alterations. The MMSE score was 22/30. The isolated upper motor neuron signs that progressed slowly over a long period were consistent with primitive lateral sclerosis associated with bvFTD. The patient was institutionalized at age 54. He presented moderate akinesia and rigidity. At age 56 he was mute and severely apathetic. His tongue was amyotrophic, but no fasciculations were noted. He developed amyotrophy in the left hand and fasciculations in the upper limb. He died at age 56.



Supplementary Figure 1. Relative frequencies of mutations in *C9ORF72, PGRN, MAPT, VCP, TARDBP*, and *FUS/TLS* genes in patients with (A) familial FTD and (B) familial FTD-ALS.



Supplementary Figure 2. Clinical presentation at disease onset and diagnosis at inclusion after a disease progression of 3.7 years. AD; Alzheimer's disease; ALS, amyotrophic lateral sclerosis; aMCI, amnestic mild cognitive impairment; bvFTD, behavioral frontotemporal dementia; CBDS, corticobasal degeneration syndrome; PLS, primary lateral sclerosis; PSP, progressive supranuclear palsy; PNFA, progressive non–fluent aphasia; SD, semantic dementia. The number of probands and relatives with each phenotype is indicated in brackets (probands/relatives).



Supplementary Figure 3. Cox regression curves showing the cumulative probability of onset (A) and the cumulative probability of survival from disease onset (B) according to the mutation: *C9ORF72, PGRN, MAPT,* and FTD patients with no identified mutations (other). Onset in *C9ORF72* patients occurred later than in *MAPT* patients (46.8, 95%CI: 43.0–50.6) and earlier than in FTD patients without mutations (61.2, 95%CI: 59.8–62.7), but did not significantly differ from onset in *PGRN* patients (59.63 years; 95%CI: 57.6–61.7). The mean disease duration at death was significantly shorter in *C9ORF72* patients (9.5 years, 95%CI: 8.0–11.0) than in FTD patients with no mutations (other, 10.5, 95%CI: 9.5–11.6); it did not differ significantly from disease durations in *PGRN* (8.3, 95%CI 6.8–9.8, $p = 0.99$) and *MAPT* patients (10.5 years; 95%CI 8.2–12.8; $p = 0.17$).