Supplementary material patients clinical data

Patient #2 (FTD 85)

Gly174-Gly175 del GG (g. 4180-4185 delGAGGTG)

Patient #2 was seen at NIH approximately 4 years ago. At the time, she was 80 years old. Approximately 4 years before her evaluation, she noticed that she was having some difficulty speaking which gradually worsened. She had difficult "getting the words out" but denied problems understanding speech or word finding difficulty. She knew what she wanted to say, but had difficulty saying it, an experience that was very frustrating to her. She denied any other cognitive or memory symptoms, and an informant confirmed that she had not had any changes in personality, behavior, or eating habits since she became ill. Her medical history was notable for diabetes. Her family history is notable for a mother who died at the age of 86 from a stroke, but had three years of unspecified memory problems prior to her death (Figure 1-c). The patient does not know of anyone in her family who had aphasia. On her neurological examination, she had a moderate expressive aphasia with slow halting speech and dropped and mispronounced words. Her neurological examination was otherwise normal. She had an MRI which showed mild atrophy, with relatively greater atrophy in the temporal-parietal junction, left greater than right (Figure 3b). She had an FTD-PET which showed moderate reductions of glucose metabolism in the temporal and parietal lobes with relatively lesser reductions in the right hemisphere (Figure 3c). On neuopsychological testing, with some exceptions (digit span, and similarities subtests), she performed at or near normal levels on the Wechsler Adult Intelligence Scale III (WAIS III) (Wechsler, 1997). She had a total raw score on the Mattis Dementia Rating Scale of 127, in the mildly impaired range. She received a 26 out of 30 on a Folstein Mini-Mental State examination (Folstein et al., 1975), missing items when repeating words, and writing and repeating sentences. She was mildly impaired on the Boston Naming Test (Kaplan et al., 1983) and Token test (a test of receptive language) (De Renzi &Vignolo, 1962). Her memory, as measured by the Wechsler Memory Scale III (Wechsler, 1987), was within normal limits. She had normal letter fluency, but impaired letter fluency.

On the basis of her symptom presentation, she met criteria for PPA (Lund-Manchester, 1994). Her clinical presentation is typical for PPA with the exception of her relatively late age of onset (the median age of onset for PPA is 62 years old)(Le Rhun et al., 2005). At the time of evaluation, her expressive aphasia was isolated with relatively little other cognitive impairment and no behavioral symptoms or personality changes. Her imaging studies suggest, however, that she may develop other cognitive impairment, including memory symptoms, later in the courses of her illness. She was seen back at NIH approximately one year after her initial evaluation. Formal testing was not performed at that time, but she had had worsening of her aphasia without other cognitive complaints.

Patient #3 (CBS #135)

Gly175-Gly176 insGG (g. 4185-4186insGAGGTG)

Patient #3 was seen approximately 2.5 years ago. At the time, he was a 73 year-old right handed man. His symptoms started approximately 11 years before his evaluation. His first symptom was catching his left foot on the floor. This was followed by a sensation of heaviness and clumsiness in the left leg. His symptoms slowly worsened in his left leg and progressed to involve the left arm. By the time of evaluation, he was having these symptoms in his right arm and leg as well. He involuntarily dropped items held in his left hand. He also developed myoclonic jerks in his left hand and arm, and balance problems with falls. The patient had also developed cognitive symptoms – he described worsening memory and ability to perform mental tasks such as arithmetic. His symptoms were unresponsive to Sinemet. His past medical history was notable for viral meningitis when he was a child without sequelae. His father had a diagnosis of Parkinson's disease without cognitive involvement and died in his early 80's. His mother was with dementia at the age of 90 (Figure 1e).

On neurological examination, the patient held his left arm and leg in a dystonic posture. He had left sided neglect of his body and of his left visual field. He had normal muscle strength throughout with increased resistance to passive movement and some spasticity on his left side greater than his right side. He had no fasiculations. He had ideomotor apraxia, more on the left than on the right. He was impaired at localizing stimuli without visual input. He had a Parkinsonian gait and hyperreflexia on the left side. He had an MRI of the brain with spectroscopy which showed diffuse volume loss and a decreased NAA/cho ratio in the putamina, more on the right than the left (Figure 4b). He had an FTD-PET scan which showed mild to moderate reductions of glucose metabolism in the temporal and parietal lobes in the right hemisphere greater than the left hemisphere (Figure 4c). He had full neuropsychological testing which confirmed a neglect of the left side of his visual field. He showed severe impairment on general tests of cognition: He received a 61 out of 144 on the Mattis Dementia Rating Scale 2 (DRS-2) (Mattis, 1976), and a 14 out of 30 on a Folstein Mini-Mental State examination (Folstein et al., 1975). He was mildly impaired on the Boston Naming test (44 out of 60) (Kaplan, 1983) and severely impaired on a measure of receptive language, the Token Test (De Renzi & Vignolo, 1962). He showed marked apraxia, and severely impaired letter- and category-cued fluency. Since he was evaluated at NIH, the patient's symptoms have continued to worsen.

The patient was given a diagnosis of corticobasal syndrome (CBS) by published criteria (Boeve, 2005). Clinically, he demonstrates both cortical dysfunction with apraxia, dementia, and neglect, and basal ganglia dysfunction with Parkinsonism and increased resistance to passive movement.. He did not show signs or symptoms of ALS. He demonstrated relatively severe cognitive deficits, however, cognitive deficits are frequently observed in CBS (Boeve, 2005). The length of the patient's illness is unusual for CBS. The median survival time after onset of symptoms in one cohort was 7.9 years (Wenning et al, 1998) and our patient has now survived for 13 years since symptom onset. The patient's father had a diagnosis of Parkinson's disease, but may have had aspects of CBS. If the patient inherited his FUS/TSL mutation from his father, his father had

a different presentation of illness with less cognitive dysfunction than the patient, suggesting possible phenotypic variation within the family.