

## Supplementary Material

**Supplementary Table 1. Clinical Summaries of ‘Converters’**

<b>Sex</b>	<b>Age at onset</b>	<b>Age at diagnosis</b>	<b>PRNP mutation</b>	<b>PRNP codon 129</b>	<b>Clinical features</b>
M	43	44	P102L	MM	Slowly progressive gait ataxia, dysarthria, LL paraesthesia, myoclonus, urinary frequency, UL ataxia, LL weakness, diplopia, extensor plantars, distal LL sensory deficits.
F	55	58	P102L	MV	Slowly progressive gait ataxia, LL dysaesthesia, dysarthria, myoclonus, UL ataxia, mild cognitive impairment, cerebellar eye signs, extensor plantars.
M	52	52	P102L	MV	Slowly progressive memory impairment, upper limb apraxia, right LL spasticity and extensor plantar.
F	50	51	P102L	MV	Slowly progressive gait ataxia and LL sensory deficits, micrographia, hearing impairment, urinary incontinence, mild cognitive impairment, dysarthria, extensor plantars.
F	56	56	P102L	MM	Slowly progressive gait ataxia and LL weakness, LL paraesthesia and sensory deficits, nocturnal myoclonus, mild forgetfulness, UL ataxia.
M	42	42	D178N	MV	Fatigue, daytime somnolence, fragmented sleep, hypophonia, vertigo, gait ataxia, dysarthria, dysautonomia, behavioural change, micrographia, cognitive decline, seizures.
F	41	45	5-OPRI	MM	Navigational difficulties, slowly progressive cognitive decline, behavioural change, sweet preference and weight gain, nocturnal myoclonus, limb apraxia.
F	25	25	6-OPRI	MM	Behavioural change, cognitive decline, apraxia.

**Note:** Symptoms are listed in order of onset. M=Male; F=Female; PRNP=Prion Protein Gene; MM=Methionine Homozygous; MV=Methionine-Valine Heterozygous; LL=Lower Limb; UL=Upper Limb

**Table 2. Descriptive characteristics and baseline neuropsychological tests for cross-sectional analysis.**

	Presymptomatic MRC = 20		Symptomatic MRC = 20		Symptomatic MRC < 20		Healthy control	
	<i>N</i>	Mean ( <i>SD</i> )	<i>N</i>	Mean ( <i>SD</i> )	<i>N</i>	Mean ( <i>SD</i> )	<i>N</i>	Mean ( <i>SD</i> )
Demographics								
Age	27	40.19 (11.86)	8	47.25 (16.25)	24	46.13 (8.81)	25	47.56 (13.55)
Education	27	2.52 (0.51)	8	2.38 (0.74)	24	2.25 (0.53)	25	2.36 (0.49)
Estimated pre-morbid functioning								
NART Errors	25	23.08 (9.42)	6	18.33 (9.97)	17	28.35 (14.53)	25	20.56 (8.42)
Intellectual functioning								
Verbal IQ	25	97.84 (12.74)	8	91.00 (24.74)	21	78.14 (15.83)*	25	97.44 (11.47)
Performance IQ	26	103.96 (16.42)	8	89.88 (23.86)*	21	76.81 (16.37)*	25	109.84 (18.40)
Visual perceptual function								
VOSP Object Decision	18	17.56 (1.38)	7	17.14 (2.19)	17	15.47 (3.64)*	25	18.44 (1.08)
VOSP Cube Analysis	23	9.48 (1.08)	7	8.71 (1.80)	17	6.71 (3.57)*	25	9.36 (1.35)
Visuoconstruction								
AMPIB Figure Copy	19	79.21 (1.51)	7	74.43 (10.92)	13	65.15 (25.59)*	25	79.08 (1.63)
Spelling								
Graded Difficulty Spelling Test	22	19.23 (5.72)	4	23.50 (4.04)	14	10.64 (9.72)*	24	19.46 (4.56)
Calculation								
Graded Difficulty Arithmetic Test	24	13.67 (5.10) *	5	11.60 (8.85)	17	5.88 (6.21)*	23	16.61 (3.54)

## Praxis

Gesture repetition, right hand	19	10.00 (0.00)	7	7.86 (2.97)*	17	5.94 (3.40)*	23	9.87 (0.63)
Gesture repetition, left hand	19	9.79 (0.71)	7	8.57 (2.57)	17	5.65 (4.12)*	24	9.88 (0.61)

## Memory

Recognition Memory Test, Words	24	48.00 (2.81)	5	46.00 (3.39)	13	38.85 (9.24)	25	46.68 (3.44)
Recognition Memory Test, Faces	25	40.48 (4.33)	5	37.60 (5.27)	15	33.27 (8.45)	25	38.68 (4.38)
AMIPB Figure delayed recall	19	58.63 (12.40)	8	38.25 (25.06)*	12	14.00 (15.96)*	25	61.44 (16.97)

## Language

Graded Naming Test	25	20.88 (3.33)	7	19.86 (4.60)	21	15.81 (5.81)*	25	22.16 (2.87)
Concrete synonyms	20	20.60 (2.52)	7	21.29 (2.69)	16	18.06 (5.43)	25	21.48 (2.26)
Semantic fluency	20	20.95 (4.75)	7	18.57 (7.21)	15	12.20 (6.62)*	24	21.88 (5.54)
TROG, total correct	17	38.24 (2.25)	7	36.00 (5.10)	17	26.88 (10.23)*	25	38.32 (1.28)

## Executive functioning

Trail Making Test, part B (time)	19	60.11 (22.59)	6	79.00 (38.47)	11	162.55 (100.41)*	25	59.84 (21.58)
Stroop test	22	104.77 (10.38)	7	76.43 (24.02)*	17	34.47 (33.31)*	25	103.16 (8.22)
Phonemic fluency	23	41.65 (12.53)	8	34.50 (12.93)	18	20.33 (12.35)*	24	43.04 (13.63)

## Information Processing Speed

Trail Making Test, part A (time)	19	26.42 (8.14)	8	53.75 (34.17)*	16	58.00 (45.85)*	25	29.00 (8.58)
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## Mood

HADS, Anxiety	18	7.61 (3.36)	7	9.14 (4.81)	6	6.33 (1.51)	16	8.38 (4.60)
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HADS, Depression	18	3.44 (3.43)	7	4.29 (2.56)	6	5.17 (3.19)	16	3.69 (3.46)
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**Note:** AMIPB = The Adult Memory and Information Processing Battery, HADS = Hospital Anxiety and Depression Scale, MRC = MRC Prion Disease Rating Scale, NART = National Adult Reading Test, SD = standard deviation, TROG = Test for Reception of Grammar, VOSP = Visual Object and Space Perception Battery. Level of education was categorised in the following way: 1 =  $\leq 9$  years, 2 = 10-12 years, 3 =  $>12$  years. \* = indicates significant difference from the control groups after adjusting for multiple comparisons (i.e.  $p < .017$ ).

**Table 3. Descriptive characteristics and baseline neuropsychological tests for longitudinal analysis.**

	Presymptomatic gene-positive controls		Converters		P value (2-tailed)
	N	Mean (SD)	N	Mean (SD)	
Demographics					
Age	16	36.63 (14.40)	8	39.13 (10.76)	.43
Education	16	2.63 (0.50)	8	2.13 (0.35)	.05
Estimated pre-morbid functioning					
NART Errors	15	24.13 (8.91)	8	24.50 (13.10)	.39
Intellectual functioning					
Verbal IQ	15	99.73 (13.87)	8	92.25 (13.02)	.16
Performance IQ	16	103.56 (17.95)	8	102.88 (18.08)	.86
Visual perceptual function					
VOSP Object Decision	15	17.93 (1.49)	8	18.38 (0.92)	.70
VOSP Cube Analysis	16	9.44 (1.26)	8	8.75 (1.83)	.38
Visuoconstruction					
AMIPB Figure copy	16	79.44 (0.89)	8	77.88 (2.85)	.29
Spelling					
Graded Difficulty Spelling Test	12	13.83 (5.89)	8	14.38 (5.15)	.67
Calculation					
Graded Difficulty Arithmetic Test	13	11.54 (5.71)	7	15.00 (5.03)	.76
Praxis					
Gesture repetition, right hand	15	10.00 (0.00)	8	9.88 (0.35)	.64
Gesture repetition, left hand	15	9.93 (0.26)	8	10.00 (0.00)	.83
Memory					
Recognition Memory Test, Words	16	48.31 (2.21)	8	46.75 (3.33)	.29
Recognition Memory Test, Faces	16	39.56 (6.15)	8	40.13 (4.82)	.59
AMIPB Figure delayed recall	16	59.31 (12.26)	8	52.50 (13.78)	.33
Language					
Graded Naming Test	15	19.80 (3.97)	8	21.13 (3.87)	.99
Concrete synonyms	15	20.07 (2.60)	8	19.75 (3.69)	.61
Semantic fluency	16	22.00 (4.79)	8	19.13 (4.02)	.23
TROG, total correct	15	38.40 (1.72)	8	36.88 (3.40)	.43
Executive functioning					
Trail-Making Test part B (time)	16	60.63 (22.94)	8	70.63 (22.59)	.23
Stroop test	16	102.69 (11.85)	8	104.13 (9.43)	.88
Phonemic fluency	16	38.50 (11.40)	8	36.88 (11.50)	.67
Information Processing Speed					
Trail-Making Test part A (time)	16	26.31 (9.98)	8	29.38 (5.73)	.48
Mood					
HADS, Anxiety	13	8.77 (3.06)	7	6.86 (3.02)	.20
HADS, Depression	13	4.31 (3.59)	7	3.29 (2.36)	.51

**Note:** AMIPB = The Adult Memory and Information Processing Battery, HADS = Hospital Anxiety and Depression Scale, MRC = MRC Prion Disease Rating Scale, NART = National Adult Reading Test, SD = standard deviation, TROG = Test for Reception of Grammar, VOSP = Visual

Object and Space Perception Battery. Level of education was categorised in the following way: 1 =  $\leq 9$  years, 2 = 10-12 years, 3 =  $>12$  years.

**Table 4. Frequency of mutation types in groups used in the cross-sectional analysis**

	Presymptomatic MRC = 20	Symptomatic MRC = 20	Symptomatic MRC < 20
5-OPRI	2	0	4
6-OPRI	1	2	4
A117V	1	0	2
D178N	3	1	3
E196K	0	1	0
E200K	7	1	0
P102L	13	2	7
Q212P	0	0	1
Y163X	0	1	3