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Natural History of Vanishing White Matter

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Supplementary Table 1. Health Utilities Index Classification System

1A. HUI Scoring

HUI Mark 2 - SELF-CARE	
1	Eats, bathes, dresses, and uses the toilet normally for age
2	Eats, bathes, dresses, or uses the toilet independently with difficulty.
3	Requires mechanical equipment to eat, bathe, dress, or use the toilet independently.
4	Requires the help of another person to eat, bathe, dress, or use the toilet.
HUI Mark 3 - VISION	
1	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.
2	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses.
3	Able to read ordinary newsprint with or without glasses but unable to recognize a friend on the other side of the street, even with glasses.
4	Able to recognize a friend on the other side of the street with or without glasses but unable to read ordinary newsprint, even with glasses.
5	Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses.
6	Unable to see at all.
HUI Mark 3 - HEARING	
1	Able to hear what is said in a group conversation with at least three other people, without a hearing aid.
2	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at least three other people.
3	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, and able to hear what is said in a group conversation with at least three other people, with a hearing aid.
4	Able to hear what is said in a conversation with one other person in a quiet room, without a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
5	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
6	Unable to hear at all.
HUI Mark 3 - SPEECH	
1	Able to be understood completely when speaking with strangers or friends.
2	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know me well.
3	Able to be understood partially when speaking with strangers or people who know me well.
4	Unable to be understood when speaking with strangers but able to be understood partially by people who know me well.
5	Unable to be understood when speaking to other people (or unable to speak at all).
HUI Mark 3 - AMBULATION	
1	Able to walk around the neighbourhood without difficulty, and without walking equipment.
2	Able to walk around the neighbourhood with difficulty; but does not require walking equipment or the help of another person.
3	Able to walk around the neighbourhood with walking equipment, but without the help of another person.
4	Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood.
5	Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood.
6	Cannot walk at all.

HUI Mark 3 - DEXTERITY	
1	Full use of two hands and ten fingers.
2	Limitations in the use of hands or fingers, but does not require special tools or help of another person.
3	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person).
4	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools).
5	Limitations in use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools).
6	Limitations in use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools).
HUI Mark 3 - EMOTION	
1	Happy and interested in life.
2	Somewhat happy.
3	Somewhat unhappy.
4	Very unhappy.
5	So unhappy that life is not worthwhile.
HUI Mark 3 - COGNITION	
1	Able to remember most things, think clearly and solve day to day problems.
2	Able to remember most things, but have a little difficulty when trying to think and solve day to day problems.
3	Somewhat forgetful, but able to think clearly and solve day to day problems.
4	Somewhat forgetful, and have a little difficulty when trying to think or solve day to day problems.
5	Very forgetful, and have great difficulty when trying to think or solve day to day problems.
6	Unable to remember anything at all, and unable to think or solve day to day problems.
HUI Mark 3 - PAIN	
1	Free of pain and discomfort.
2	Mild to moderate pain that prevents no activities.
3	Moderate pain that prevents a few activities.
4	Moderate to severe pain that prevents some activities.
5	Severe pain that prevents most activities.

1B. HUI Single-Attribute Utility Functions

Level	Selfcare HUI 2	Vision HUI 3	Hearing HUI 3	Speech HUI 3	Ambulation HUI 3	Dexterity HUI 3	Emotion HUI 3	Cognition HUI 3	Pain HUI 3
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.85	0.95	0.86	0.82	0.83	0.88	0.91	0.86	0.92
3	0.55	0.73	0.71	0.67	0.67	0.73	0.73	0.92	0.77
4	0.00	0.59	0.48	0.41	0.36	0.45	0.33	0.70	0.48
5	n.a.	0.38	0.32	0.00	0.16	0.20	0.00	0.32	0.00
6	n.a.	0.00	0.00	n.a.	0.00	0.00	n.a.	0.00	n.a.

From Torrence GW *et al.*, Med Care 1996;34:702-722 and Feeny D *et al.*, Med Care 2002;40:113-128.

n.a.: not applicable

1C. HUI3 Multi-Attribute Utility Function

Level X_n	Vision b_1	Hearing b_2	Speech b_3	Ambulation b_4	Dexterity b_5	Emotion b_6	Cognition b_7	Pain b_8
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.98	0.95	0.94	0.93	0.95	0.95	0.92	0.96
3	0.89	0.89	0.89	0.86	0.88	0.85	0.95	0.90
4	0.84	0.80	0.81	0.73	0.76	0.64	0.83	0.77
5	0.75	0.74	0.68	0.65	0.65	0.46	0.60	0.55
6	0.61	0.61	n.a.	0.58	0.56	n.a.	0.42	n.a.

From Feeny D *et al.*, Med Care 2002;40:113-128.

Where x_n is the attribute level and b_n is the attribute utility score.

Formula (Dead - Perfect Health scale) $u^* = 1.371 (b_1 * b_2 * b_3 * b_4 * b_5 * b_6 * b_7 * b_8) - 0.371$

where u^* is the utility of a chronic health state on a utility scale where healthy has a utility of 1.00.

n.a.: not applicable

Supplementary Table 2. Guy's Neurological Disability Scale

1. Cognitive disability	
0	No cognitive problems.
1	Cognitive problems not noticeable to family or friends.
2	Cognitive problems noticeable to family or friends but not requiring help from others.
3	Cognitive problems requiring help from others for normal daily affairs; patient is fully orientated in time, place and person.
4	Cognitive problems requiring help from others for normal daily affairs; patient is not fully orientated.
5	Patient is completely disorientated in time, place and person.
2. Mood disability	
0	No mood problems
1	Asymptomatic on current drug treatment.
2	Mood problems present but not affecting the patient's ability to perform any of their usual daily activities.
3	Mood problems affecting the patient's ability to perform some of their usual daily activities.
4	Mood problems preventing the patients from doing all their usual daily activities.
5	Mood problems requiring inpatient management.
X	Unknown (scored as the mean of the cognitive and fatigue disability scores rounded the nearest integer).
3. Visual disability	
0	No visual problems.
1	Visual problems (blurred vision, diplopia, scotomas) but patient is still able to read ordinary newspaper print.
2	Unable to read ordinary newspaper print.
3	Unable to read large newspaper print.
4	Unable to count fingers if they hold their hand out in front of them.
5	Unable to see hand movement if they move their hand in front of them.
4. Speech and communication disability	
0	No speech problems.
1	Speech problems which does not require the patient to repeat themselves when speaking to strangers.
2	Speech problems which require the patient to repeat themselves when speaking to strangers.
3	Speech problems which require the patient to repeat themselves when speaking to their family and close friends.
4	Speech problems making speech difficult to understand; patient is able to communicate effectively by using sign language or the help of their carers.
5	Speech problems making speech difficult to understand, patient is unable to communicate effectively by using sign language or the help of their carers.
5. Swallowing disability	
0	No swallowing problems.
1	Needs to be careful when swallowing solids or liquids but not with most meals.
2	Needs to be careful when swallowing solids or liquids with most meals; patient is able to eat food of normal consistency.
3	Needs specially prepared food of modified consistency.
4	Tendency to choke with most meals.
5	Dysphagia requiring nasogastric or gastrostomy tube.
6. Upper limb disability – referred to as “Arm”	
0	No upper limb problem.
1	Problems in one or both arms, not affecting the ability to do any of the functions listed.
2	Problems in one or both arms, affecting some but not preventing any of the functions listed.
3	Problems in one or both arms, affecting all or preventing one or two of the functions listed.
4	Problems in one or both arms preventing three or all of the functions listed.
5	Unable to use either arm for any purposeful movements.

7. Lower limb disability - referred to as "Leg"	
0	Walking is not affected.
1	Walking is affected but patient is able to walk independently.
2	Usually uses unilateral support (single stick or crutch, one arm) to walk outdoors, but walks independently indoors.
3	Usually uses bilateral support (two sticks or crutches, frame, or two arms) to walk outdoors, or unilateral support (single stick or crutch, or one arm) to walk indoors.
4	Usually uses wheelchair to travel outdoors, or bilateral support (two sticks or crutches, frame, or two arms) to walk indoors.
5	Usually uses a wheelchair indoors.
8. Bladder disability	
0	Normal bladder problems.
1	Asymptomatic on current drug treatment.
2	Urinary frequency, urgency, or hesitancy with no incontinence.
3	Occasional urinary incontinence (once or more during the last month but not every week) or intermittent catheterisation without incontinence.
4	Frequent urinary incontinence (once a week or more during the last month but not daily) or occasional urinary incontinence despite regular intermittent catheterisation.
5	Daily urinary incontinence or permanent catheter (urethral/suprapubic) or penile sheath.
9. Bowel disability	
0	No bowel problems.
1	Asymptomatic on current drug treatment or constipation not requiring any treatment.
2	Constipation requiring laxatives or suppositories or faecal urgency.
3	Constipation requiring the use of enemas.
4	Constipation requiring manual evacuation of stools or occasional faecal incontinence (once or more during the last month but not every week).
5	Weekly faecal incontinence.
10. Sexual disabilities	
0	Normal sexual functions or persons who are voluntarily celibate.
1	Reduced sexual interest.
2	Problems satisfying oneself or sexual partner.
3	Physical problems interfering but not preventing sexual function.
4	Autonomic problems interfering but not preventing sexual function.
5	Physical or autonomic problems totally preventing sexual function.
X	Unknown or not applicable (scored as the mean of the lower limb, bladder, and bowel disability scores rounded to the nearest integer).
11. Fatigue	
0	Absent.
1	Occasional fatigue (present some days).
2	Frequent fatigue (present most days).
3	Fatigue affecting the patient's ability to perform some of their usual daily activities.
4	Fatigue preventing the patient from doing all their usual daily activities.
5	Fatigue preventing the patient from doing all their physical activities.
X	Unknown (scored as the mean of the cognitive and mood disability scores rounded to the nearest integer).
12. Other disabilities	
0	Absent.
1	Asymptomatic on current drug treatment.
2	Problems, present, but are not affecting the patient's ability to perform any of their usual daily activities.
3	Problems affecting the patient's ability to perform some of their usual daily activities.
4	Problems preventing the patient from doing all their usual daily activities.
5	Problems requiring hospital admission for assessment or treatment.

From Sharrack B *et al.*, *Mult Scler* 1999;5:223-233.

The GNDS is also known as the Neurological disability Scale (NDS) or the UK Neurological disability Scale (UKNDS)

Supplementary Table 3. Clinical characteristics classified by age of onset group

	Overall** <i>n</i> =296	<1 year (1) <i>n</i> =33	1 -<2 years (2) <i>n</i> =51	2 - <4 years (3) <i>n</i> =90	4 - <8 years (4) <i>n</i> =49	8 - <18 years (5) <i>n</i> =30	≥18 years (6) <i>n</i> =38	p-value
Disease onset								
Median age of clinical onset [quartiles]	3 y [22 mo-7 y] <i>n</i> =291	4 [2-7] mo <i>n</i> =33	18 [17-22] mo <i>n</i> =51	2 [2-3] y <i>n</i> =90	5 [4-6] y <i>n</i> =49	11 [8-15] y <i>n</i> =30	33 [23-42] y <i>n</i> =38	n.a.
Onset provoked by trigger	53% <i>n</i> =138/258	43% <i>n</i> =12/28	66% <i>n</i> =29/44	72% <i>n</i> =58/81	40% <i>n</i> =18/45	54% <i>n</i> =14/26	21% <i>n</i> =7/34	<0.001
Survival								
*Estimated median age of death	38 y <i>n</i> =102/296	9 mo <i>n</i> =28/33	10 y <i>n</i> =23/51	20 y <i>n</i> =31/90	n.a. <i>n</i> =7/49	n.a. <i>n</i> =5/30	n.a. <i>n</i> =6/38	<0.001
*Estimated median time to death (duration)	24 y <i>n</i> =100/291	8 mo <i>n</i> =28/33	8 y <i>n</i> =23/51	17 y <i>n</i> =31/90	n.a. <i>n</i> =7/49	n.a. <i>n</i> =5/30	n.a. <i>n</i> =6/38	<0.001
Median age of death [quartiles]	6 [1 - 13] y <i>n</i> =102	9 [6 - 14] mo <i>n</i> =28	4 [2 - 8] y <i>n</i> =23	9 [6 - 15] y <i>n</i> =31	13 [9 - 23] y <i>n</i> =7	29 [16 - 34] y <i>n</i> =5	37 [29 - 50] y <i>n</i> =6	<0.001
Median disease duration at death [quartiles]	3 y [9 mo - 9 y] <i>n</i> =100	7 [3 - 10] mo <i>n</i> =28	2 [1 - 6] y <i>n</i> =23	7 [3 - 13] y <i>n</i> =31	6 [5 - 17] y <i>n</i> =7	14 [4 - 22] y <i>n</i> =5	10 [4 - 14] y <i>n</i> =6	<0.001
Neurological development								
Abnormal cognitive development	14% <i>n</i> =31/221	63% <i>n</i> =10/16	21% <i>n</i> =7/33	9% <i>n</i> =6/65	9% <i>n</i> =4/44	11% <i>n</i> =3/28	3% <i>n</i> =1/35	<0.001
Achieved walking without support	94% <i>n</i> =237/253	0% <i>n</i> =0/4	74% <i>n</i> =34/46	100% <i>n</i> =88/88	100% <i>n</i> =48/48	100% <i>n</i> =30/30	100% <i>n</i> =37/37	<0.001
Ambulation***								
*Estimated median age of loss of walking without support	9 y <i>n</i> =174/235	8 mo <i>n</i> =4/4	2 y <i>n</i> =37/42	3 y <i>n</i> =65/81	14 y <i>n</i> =31/46	25 y <i>n</i> =16/27	44 y <i>n</i> =21/35	<0.001
*Estimated median time to loss walking without support (duration)	3 y <i>n</i> =174/235	0 mo <i>n</i> =4/4	2 mo <i>n</i> =37/42	1 y <i>n</i> =65/81	8 y <i>n</i> =31/46	15 y <i>n</i> =16/27	7 y <i>n</i> =21/35	<0.001
*Estimated median age of full wheelchair dependency	18 y <i>n</i> =125/229	8 mo <i>n</i> =4/4	3 y <i>n</i> =31/39	7 y <i>n</i> =47/79	18 y <i>n</i> =20/45	33 y <i>n</i> =11/27	56 y <i>n</i> =12/35	<0.001
*Estimated median time to full wheelchair dependency (duration)	8 y <i>n</i> =125/229	0 mo <i>n</i> =4/4	1 y <i>n</i> =31/39	4 y <i>n</i> =47/79	13 y <i>n</i> =20/45	20 y <i>n</i> =11/27	20 y <i>n</i> =12/35	<0.001

Other neurological functions								
*Estimated median time to start tube feeding (duration)	27 y n=75/219	5 mo n=16/22	3 y n=23/38	15 y n=21/65	n.a. n=7/42	n.a. n=5/24	n.a. n=3/28	<0.001
*Estimated median time to cognitive decline (duration)	4 y n=96/155	n.e.	2 y n=19/26	8 y n=22/45	17 y n=16/31	19 y n=11/22	0 y n=28/31	<0.001
*Estimated median time to first seizure (duration)	5 y n=103/173	6 mo n=17/22	2 y n=25/36	8 y n=30/50	9 y n=13/24	11 y n=11/21	n.a. n=7/20	<0.001
Disease course								
Exacerbating disease course	82% n=212/259	84% n=21/25	88% n=43/49	93% n=80/86	76% n=34/45	68% n=17/25	59% n=17/29	<0.001
Episode(s) of coma or reduced / altered consciousness	62% n=135/219	81% n=17/21	75% n=33/44	72% n=47/65	49% n=20/41	48% n=10/21	30% n=8/27	<0.001
Deterioration following febrile infection	64% n=154/239	61% n=14/23	77% n=36/47	83% n=65/78	58% n=23/40	35% n=8/23	29% n=8/28	<0.001
Deterioration following head trauma	46% n=106/228	0% n=0/19	34% n=14/41	67% n=48/72	57% n=25/44	52% n=12/23	24% n=7/29	<0.001

y; years, mo; months, n.a.; not applicable, n.e.; not evaluable

* Kaplan-Meier estimates

** for five patients the age of onset was unknown, therefore the numbers in the “overall” column do not always correspond to the sum of the numbers per age of onset group

*** only patients who achieved age ≥ 18 mo were included; patients who presented <18 mo and never achieved walking were scored as having lost ambulation at onset and patients who never achieved walking, but presented with signs of neurological deterioration later than 18 mo were score as having lost ambulation at 18 mo

Supplementary Table 4. Overview of presenting signs/symptoms in 288 patients

Presenting symptoms/signs	Frequency	Median age at presentation [range]	Provoked by trigger*
Gait problems	106	3y [14 mo - 45 y]	55 / 97
Ataxia / clumsiness	51	3 y [11 mo - 35 y]	28 / 45
Weakness / hypotonia	24	2 y [3 mo - 40 y]	17 / 23
Loss of motor skills following infection	24	22 mo [3 mo - 16 y]	24 / 24
Seizures	22	19 mo [2 mo - 25 y]	12 / 20
Loss of motor skills	21	2 y [2 mo - 33 y]	0 / 11
Cognitive / memory problems	20	11 y [18 mo - 54 y]	1 / 18
Loss of motor skills following head trauma	19	2 y [14 mo - 19 y]	19 / 19
Somnolence / coma following infection	16	2 y [8 mo - 14 y]	16 / 16
Developmental delay	11	18 mo [8 mo - 2y]	0 / 7
Spasticity/hypertonia	11	3 y [18 mo - 20 y]	6 / 9
Psychosis /confusion / behavioral change	10	19 y [2 - 43 y]	3 / 9
Irritability / encephalopathy	8	14 mo [8 mo - 14 yrs]	5 / 5
Antenatal signs	7	antenatally	0 / 7
Severe headache / migraine	7	13 y [3 - 33 y]	3 / 7
Speech problems / dysarthria	7	3 y [13 mo - 26 y]	3 / 6
Somnolence / coma following minor head trauma	6	6 y [23 mo - 19 y]	6 / 6
Fatigue / lethargy	6	2 y [8 mo - 33 y]	2 / 5
Dizziness / vertigo	5	8 y [2 - 45 y]	1 / 4
Depression	4	35 y [25 - 43 y]	0 / 4
Asymptomatic [incidental finding / affected sibling]	3	2 y [18 mo - 6 y]	2 / 3
Vision problems	3	31 y [4 - 33 y]	1 / 3
Amenorrhea / infertility	2	22 y [19 - 25 y]	0 / 2
Deterioration following vaccination	2	9 mo [5 - 14 mo]	2 / 2
Paresthesia	1	19 y	0 / 1

* the proportion among informative patients is presented; y, years; mo, months

Supplementary Table 5. Overview of presenting signs/symptoms per age of onset group

	<1 year (1) n=33	1 - <2 years (2) n=51	2 - <4 years (3) n=87	4 - <8 years (4) n=49	8 - <18 years (5) n=30	≥18 years (6) n=38
Presenting symptoms/signs						
Antenatal signs	21%	-	-	-	-	-
Irritability / encephalopathy	3%	8%	1%	-	3%	-
Seizures	21%	12%	2%	2%	7%	11%
Somnolence / coma / lethargy / fatigue	6%	16%	14%	4%	10%	5%
Deterioration following vaccination	3%	2%	-	-	-	-
Developmental delay	3%	16%	1%	-	-	-
Weakness / hypotonia	21%	6%	5%	6%	13%	8%
Gait problems	-	35%	49%	47%	33%	32%
Ataxia / clumsiness	3%	14%	25%	33%	7%	11%
Spasticity/hypertonia	-	10%	1%	6%	-	5%
Loss of motor skills	39%	35%	24%	10%	17%	8%
Speech problems / dysarthria	-	4%	2%	2%	-	5%
Cognitive / memory problems	-	2%	-	18%	3%	24%
Psychosis /confusion / behavioral change	-	-	2%	2%	3%	16%
Depression	-	-	-	-	-	11%
Severe headache / migraine	-	-	1%	-	17%	3%
Dizziness / vertigo / paresthesia	-	-	1%	-	7%	8%
Vision problems	-	-	-	2%	-	5%
Amenorrhea / infertility	-	-	-	-	-	5%
Asymptomatic (incidental finding / affected sibling)	-	2%	1%	2%	-	-

Supplementary Table 6. Phenotypic characteristics in groups of patients with similar genotypes

Genotype ¹	Number of informative patients (families)	Age of onset categories ² ; median age of onset ³ [range]	Median survival [age range]	Number of deaths [age range]	Number of patients who lost walking without support [duration range]	Median time (duration) to loss of walking without support ⁴
<i>EIF2B2</i>						
p.Gly200Val, p.Glu213Gly	9 (9)	[2] [3] 2 y [12 mo - 2 y]	11 y [4 - 34 y]	0	4 / 9 [0 - 4 y]	n.a.
p.Gly200Val, p.Pro291Ser	5 (3)	[1] 3 mo [ant. - 4 mo]	5 mo [3mo - 2 y]	5 [3 mo - 2 y]	no ambulation	no ambulation
p.Glu213Gly homozygous	12 (10)	[3] [4] 3 y [2 - 6 y]	22 y [6 - 38 y]	0	9 / 12 [0 - 24 y]	8 y
<i>EIF2B3</i>						
p.Ala87Val homozygous	3 (3)	[3] [5] [6] 17 y [2 - 22 y]	25 y [4 - 29 y]	0	2 / 3 [1 - 11 y]	11 y
<i>EIF2B5</i>						
p.Thr91Ala, homozygous	8 (6)	[3] [4] [5] 6 y [3 - 16 y]	37 y [16 - 46 y]	3 [16 - 29 y]	7 / 8 [0 - 19 y]	6 y
p.Thr91Ala, p.Arg113His	4 (3)	[3] [5] [6] 14 y [3 - 35 y]	21 y [6 - 47 y]	0	3 / 4 [1 - 7 y]	3 y
p.Thr91Ala, p.Arg339Trp	4 (3)	[2] [3] 23 mo [21 mo - 2 y]	8 y [4 - 14 y]	4 [4 - 14 y]	4 / 4 [0 - 2 mo]	0 mo
p.Leu106Phe homozygous	6 (4)	[2] [3] 22 mo [12 mo - 3 y]	6 y [4 - 16 y]	2 [6 - 16 y]	5 / 6 [0 - 1 y]	2 mo
p.Arg113His homozygous	36 (35)	[2] [3] [4] [5] [6] 17 y [18 mo - 54 y]	33 y [8 - 62 y]	4 [30 - 60 y]	16 / 32 [0 - 22 y]	16 y
p.Arg113His, p.Arg299His	5 (4)	[3] [4] [5] 6 y [3 - 9 y]	17 y [6 - 35 y]	4 [6 - 23 y]	5 / 5 0 - 10 y]	5 y
p.Arg113His, p.Arg315His	5 (5)	[3] [4] [5] 4 y [3 - 11 y]	16 y 12 - 22 y]	0	4 / 5 [0 - 10 y]	7 y
p.Arg113His, p.Arg339Gln	7 (6)	[2] [3] 2 y [18 mo - 3 y]	11 y [3 - 16 y]	2 [3 - 8 y]	6 / 6 [0 - 3 y]	1 y
p.Arg113His, p.Arg339Trp	3 (3)	[3] 2 y [2 - 3 y]	10 y [7 - 25 y]	1 [10 y]	3 / 3 0 - 2 y]	1 y
p.Arg113His, p.Ala403Val	3 (3)	[2] [3] 3 y [18 mo - 3 y]	8 y [7 - 10 y]	1 [10 y]	3 / 3 [0 - 4 y]	0 y
p.Arg136Cys homozygous	3 (3)	[2] [3] 23 mo [18 mo - 2 y]	6 y [5 - 6y]	1 [5 y]	1 / 1 [6 mo]	6 mo
p.Arg269Gln homozygous	5 (4)	[1] [2] 18 mo [6 - 18 mo]	2 y [15 mo - 10 y]	3 [15 mo - 2 y]	4 / 4 [0 - 8 mo]	2 mo (3x no ambulation)
p.Arg315Gly homozygous	5 (4)	[2] [3] 2 y [18 mo - 3 y]	4 y [2 - 26 y]	2 [4 - 26 y]	2 / 3 [0 y]	2 mo

¹ mutations are represented according to the following transcripts: *EIF2B2*: NM_014239.3, *EIF2B3*: NM_020365.3, *EIF2B5*: NM_003907.2

² (1) onset < 1 year, (2) onset 1 - < 2 years, (3) onset 2 - < 4 years, (4) onset 4 - < 8 years, (5) onset 8 - < 18 years, (6) onset ≥ 18 years

³ y, years; mo, months; ant., antenatally

⁴ calculated by Kaplan-Meier survival analysis

Supplementary Table 7. Overview of data on disability scales

7A. Overview of obtained HUI and GNDS scores per age of onset group

Age of onset group	number of patients (total: 291)	Deceased patients only included in HUI baseline + end scores* (total: 60)	Number of formal HUI scores (258 scores in 171 patients)				Number of formal GNDS scores (172 scores in 114 patients)			
			1	2	3	4	1	2	3	4
<1 y (1)	33	27	2	-	-	-	-	-	-	-
1 - <2 y (2)	51	13	19	7	1	-	3	2	-	-
2 - <4 y (3)	90	16	35	15	4	1	20	5	1	1
4 - <8 y (4)	49	2	20	10	7	2	21	6	6	2
8 - <18 y (5)	30	1	12	5	3	1	12	5	3	1
≥18 y (6)	38	1	20	6	1	-	19	6	1	-
Median disease duration [quartiles]			6 y [3-11]	10 y [5-18]	16 y [10-30]	23 y [16-28]	9 y [6-15]	16 y [9-24]	24 y [15-31]	23 y [16-28]

y = years

*In these patients no formal HUI scoring had been performed because of age younger than 2 years or because of nonresponse: they received scores for two time points (baseline score at onset and end score at death).

7B. Frequency distribution of HUI attribute levels

Level	HUI3 Cognition	HUI3 Emotion	HUI3 Vision	HUI3 Speech	HUI3 Hearing	HUI3 Dexterity	HUI3 Ambulation	HUI3 Pain	HUI2 Self-care
1 (normal)	77	150	136	134	238	66	46	134	71
2	46	65	72	47	4	51	31	72	45
3	10	20	3	29	2	8	18	32	3
4	46	15	10	9	4	30	30	17	139
5	31	8	17	39	0	33	30	3	n.a.
6 (most disabled)	48	n.a.	20	n.a.	10	70	103	n.a.	n.a.
Mean single-attribute score	0.65	0.89	0.85	0.76	0.95	0.53	0.39	0.90	0.43

The mode frequency is highlighted in gray

7C. Frequency distribution of GNDS score per disability domain

The mode frequency is highlighted in gray

Level	Cognitive	Mood	Visual*	Speech / Communication	Swallowing	Arm	Leg	Bladder	Bowel	Fatigue	Others**
0 (normal)	54	105	122	79	120	40	34	85	101	72	85
1	2	2	12	23	9	8	15	0	10	19	1
2	10	24	15	0	6	13	13	14	22	22	19
3	52	20	7	31	9	32	11	7	9	27	25
4	35	14	7	9	11	33	17	11	10	8	22
5 (total loss of function)	19	7	9	30	17	46	82	55	20	24	20
Mean domain score	2.40	1.17	0.79	1.76	1.03	2.86	3.21	2.14	1.28	1.72	1.76

* The discrepancy between the HUI and GNDS scores on visual function can be explained by the difference in rating systems, where the HUI does and GNDS does not consider wearing glasses/contact lenses as abnormal (Supplementary Tables 1A and 2).

** see Supplementary Table 7D

7D. Overview GNDS domain 'Other' problems

Reported problem	n=
muscle spasms / cramps	24
pain limbs	15
Headache/migraine	14
Dizziness	9
Seizures	9
Spasticity	5
Osteoporosis	3
Rigidity	3
Balance problems	1
Autonomic neuropathy	1
Scoliosis	1
Aggression	1
Gastroparesis	1
Decubitus	1