eTable 1: Lafora Disease Clinical Performance Scale.

Lafora Disease Clinical Performance Scale (0-18)	Score
Domain 1: Generalized tonic-clonic seizures	
None	3
Less than monthly (sporadic)	2
More than monthly but less than daily (frequent)	1
Daily or status epilepticus (constant or near constant)	0
Domain 2: Myoclonus	
Absent	3
Mild (patient can eat and drink, but not write or draw)	2
Moderate (patient cannot eat or drink)	1
Severe (continuous myoclonus at rest)	0
Domain 3: Ambulation	
Independent ambulation	3
Able to ambulate independently but gait clearly abnormal	2
Unable to ambulate without assistance	1
Unable to ambulate	0
Domain 4: Cognition (from school performance)	
No decline in school performance	3
Mild impairment; decline at school, but still in school	2
Moderate impairment: student requires special help at school or placement in an alternative learning environment	1
Severe impairment; patient no longer able to attend school	0
Domain 5: Speech	
Normal	3
Mild impairment: hesitates but remains fluent	2
Moderate impairment: diminished word production, difficult to understand	1
Severe impairment: no speech	0
Domain 6: Function	
Normal (preserved Activities of Daily Living [ADLs] listed below)	3
Mild impairment: has difficulty in 1 or 2 ADLs but remains independent	2
Moderate impairment: requires assistance in 3 or 4 ADLs	1
Severe impairment: requires assistance in all 5 ADLs	0
Total Score	Max. 18

Activities of Daily Living: Personal hygiene (bathing, grooming, brushing teeth), Dressing, Toilet hygiene, Ability to transfer (get in and out of bed/chair), and Ability to self-feed.

eTable 2: Clinical-genetic features and neurofilament light chain levels of patients with Lafora disease.

#	Sex	Genotype			Zyg.	Age at onset (years)	Time point	Disease duration (years)	Age at sampling (years)	LD stage	LDPS	cNfL (pg/ml)	sNfL (pg/ml)
		Gene	cDNA	Protein									
1	f	*EPM2A*	c.721C>T	p.Arg241*	Hom.	12	T1	3.8	15.8	2	9	-	7
							T2	5.0	17.0	2	8	-	6
2	m	*NHLRC1*	c.436G>A	p.Asp146Asn	Hom.	17	T1	18.6	35.6	3	7	-	10.3
3	f	*NHLRC1*	c.436G>A	p.Asp146Asn	Hom.	-	T1	-	36.9	0	18	502	6.2
							T2	-	40.3	0	18	-	8.3
4	f	*EPM2A*	c.269_275del; c.917A>T	p.Lys90Serfs*35; p.Asp306Val	Comp. het.	15	T1	9.1	24.1	4	4	-	19.8
5	m	*EPM2A*	c.259A>G	p.Lys87Glu	Hom.	9	T1	4.8	13.8	1	15	537	9.4
							T2	5.0	14.0	1	16	-	11.7
6	f	*EPM2A*	c.259A>G	p.Lys87Glu	Hom.	13	T1	11.7	24.7	4	6	-	25.5
7	f	*EPM2A*	c.259A>G	p.Lys87Glu	Hom.	10	T1	0.2	10.2	1	18	-	14.2
8	m	*NHLRC1*	c.436G>A	p.Asp146Asn	Hom.	16	T1	16.8	32.8	2	11	-	12.2
9	f	*NHLRC1*	c.436G>A	p.Asp146Asn	Hom.	16	T1	20.9	36.9	4	4	-	15.6
10	m	*NHLRC1*	c.205C>G	p.Pro69Ala	Hom.	14	T1	4.6	18.6	4	6	759	13.9
							T2	5.0	19.0	4	8	721	15.8
							T3	5.6	19.6	4	6	-	16.7
11	m	*NHLRC1*	c.436G>A	p.Asp146Asn	Hom.	11	T1	7.7	18.7	2	12	-	11.1
12	f	*NHLRC1*	c.436G>A	p.Asp146Asn	Hom.	16	T1	10.7	26.7	2	14	-	8.0
							T2	11.7	27.7	2	14	-	6.6
13	f	*EPM2A*	c.258C>G; c.301+1G>T	p.Tyr86*; p.?	Comp. het.	12	T1	7.9	19.9	4	2	-	16.1
14	m	*NHLRC1*	c.205C>G	p.Pro69Ala	Hom.	12	T1	6.0	18.0	2	11	-	6.1
							T2	6.5	18.5	2	12	-	5.8
15	m	*EPM2A*	c.787T>G	p.Tyr263Asp	Hom.	13	T1	2.0	15.0	1	13	643	8.6
16	m	*NHLRC1*	c.436G>A	p.Asp146Asn	Hom.	13	T1	9.0	22.0	3	7	468	18.3
17	f	*EPM2A*	c.473C>G; c.495G>A	p.Ser158*; p.Trp165*	Comp. het.	14	T1	3.0	17.0	2	10	-	12.2
18	m	*NHLRC1*	c.992del; c.698A>C	p.Glu331Glufs*3; p.Asp233Ala	Comp. het.	14	T1	3.0	17.0	3	3	747	36.8
19	f	*EPM2A*	c.323G>T	p.Arg108Leu	Hom.	11	T1	6.0	17.0	2	11	-	21.6
20	f	*EPM2A*	c.323G>T	p.Arg108Leu	Hom.	11	T1	13.0	24.0	4	1	311	20.4

21	m	*EPM2A*	c.721C>T; c.835G>A	p.Arg241*; p.Gly279Ser	Comp. het.	17	T1	2.0	19.0	1	12	1100	5.4
22	m	*NHLRC1*	c.436G>A; c.1133T>C	p.Asp146Asn; p.Leu837Pro	Comp. het.	16	T1	10.0	26.0	2	8	879	30.9
23	f	*NHLRC1*	c.260T>C	p.Leu87Pro	Hom.	11	T1	2.0	13.0	0	0	-	8.4
24	f	*NHLRC1*	c.162C>A; c.205C>G	p.Cys54*; p.Pro69Ala	Comp. het.	12	T1	7.0	19.0	2	9	-	22.4
25	m	*NHLRC1*	c.76T>G; c.1049_1050delAG	p.Cys26Gly; p.Glu350Glyfs*41	Comp. het.	14	T1	4.0	18.0	3	3	375	15.0
26	m	*EPM2A*	c.98_121del	p.Glu33_Arg41delins Gly	Hom.	15	T1	4.6	19.6	2	11	454	-
							T2	6.0	21.0	2	12	525	-
27	f	*EPM2A*	c.721C>T; c.487A>G	p.Arg241*; p.Asn163Asp	Comp. het.	14	T1	8.1	22.1	2	12	376	-
							T2	8.7	22.7	2	11	353	-
							T3	9.7	23.7	2	11	509	-
28	m	*EPM2A*	c.721C>T; c.487A>G	p.Arg241*; p.Asn163Asp	Comp. het.	15	T1	-1.3	13.7	0	18	344	-
							T2	0.3	15.3	0	18	554	-
29	f	*EPM2A*	c.302-1G>C	p.?	Hom.	12	T1	5.2	17.2	3	5	454	-
							T2	6.9	18.9	4	4	893	-
30	f	*NHLRC1*	c.656G>A; c.451G>T	p.Trp219*; p.Val151Phe	Comp. het.	13	T1	5.9	18.9	3	5	361	-
						13	T2	6.4	19.4	3	5	365	-
31	m	*EPM2A*	Deletion of exon 2; c.745 G>T	p.?; p.Val249Leu	Comp. het.	12	T1	3.2	15.2	2	12	353	-
							T2	3.7	15.7	2	11	509	-
							T3	4.8	16.8	2	9	401	-

#1-14 Ulm, Germany; #14-25 Bologna, Italy; #26-31 Dallas, USA. Patients #2-3, #5-7, #8-9, #19-20, and #27-28 are siblings each. Variants were annotated using the MANE transcript for each gene: *EPM2A* (NM_005670) and *NHLRC1* (NM_198586). Lafora disease clinical performance scale (LDPS), ranging from 0 (most severe) to 18 (asymptomatic). cNfL, CSF neurofilament light chain levels; sNfL, serum neurofilament light chain levels; zyg, zygosity.

eTable 3: Control probands examined in this study.

#	ID	Sex	Age at sampling (years)	Condition	sNfL (pg/ml)	cNfL (pg/ml)
1	12/2406-2	f	18.9	Unspecific sensory symptoms	5.4	175
2	12/2393-2	f	18.5	Migraine	5.4	167
3	12/2029-2	m	16.5	Lumboischialgia	12	260
4	12/1965-2	f	18.9	Neuropathia vestibularis	6.0	185
5	12/850-2	f	11.1	Condition unspecified	5.4	240
6	17/899-2	m	19.7	Cephalgia	6.0	237
7	17/846-2	f	36.0	Idiopathic facial paresis	8.0	409
8	17/988-2	f	36.9	Residual facial paresis after VZV infection	11.0	290
9	17/881-2	f	37.1	Idiopathic facial paresis	5.4	375
10	17/954-2	f	41.3	Peripheral facial palsy	10.0	281
11	17/968-2	f	20.2	Idiopathic facial paresis	5.4	295
12	17/945-2	f	21.2	Peripheral facial palsy	5.4	151
13	17/870-2	f	23.7	Idiopathic facial paresis	5.4	245
14	17/845-2	m	24.3	Idiopathic facial paresis	11.0	304
15	17/993-2	f	24.0	Facial palsy	10.0	810
16	17/872-2	m	33.0	Idiopathic facial paresis	7.0	336
17	17/930-2	f	27.4	Idiopathic facial paresis	10.0	348
18	17/943-2	f	27.6	Peripheral facial palsy	14.0	244
19	17/890-2	m	26.5	Facial palsy	6.0	301
20	12/2605-2	f	18.0	Suspected dopa-responsive dystonia	10.0	768
21	30/171-2	m	11.0	Cephalgia	-	344
22	30/56-2	f	12.9	Cephalgia	5.4	195
23	30/775-2	f	13.5	Tension headache	10.0	326
24	30/143-2	f	15.9	Cephalgia	6.0	176
25	30/860-2	m	16.1	Cephalgia	8.0	443
26	30/897-2	f	16.3	Second epileptic seizure	6.0	237
27	12/1884-2	f	16.6	Suspected paranoid schizophrenia	5.4	280
28	12/2408-2	f	17.0	Flu-like infection	9.0	170
29	30/1078-2	f	17.9	Migraine	7.0	228
30	12/2247-2	m	20.4	First epileptic seizure	6.0	443

eTable 4: Summary statistics of NfL measurements.

	Age at sampling (years)		sNfL (pg/ml)		cNfL (pg/ml)	
	con	**LD**	**con**	**LD**	**con**	**LD**
Number of values	30	46	30	32	30	25
25% Percentile	16.50	16.95	5.40	5.40	151.0	311.0
Median	19.20	18.95	5.40	8.09	228.0	372.5
75% Percentile	26.50	24.03	6.50	12.20	280.0	505.5
Maximum	41.30	40.30	10.00	17.90	344.0	727.5
Mean	21.86	20.97	7.72	13.95	306.8	576.9
Std. Deviation	7.96	6.79	2.49	7.61	150.8	276.2
Std. Error of Mean	1.43	1.00	0.45	1.34	27.09	54.17
Lower 95% CI	18.94	18.95	6.79	11.20	251.5	465.3
Upper 95% CI	24.78	22.98	8.65	16.69	362.2	688.5
Test	Mann-Whitney		Mann-Whitney		Mann-Whitney	
P value	0.74		<0.0001		<0.0001	