Supporting Information

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SI Text: Clinical Histories and Physical Examination Results

NG 1024-3. The neurological history is limited due to the parents being poor historians and the lack of records kept by them. The patient is a 34-y-old woman who is the eldest of six siblings. She is a product of an uncomplicated, term vaginal labor, and she reached early developmental milestones. The first abnormality was noticed by her parents at 5 y of age when she developed balance problems. At age 6, they recognized a decrease in her vision. When she started school at 7 y of age, her teachers noticed that she leaned over onto her notebooks while reading and writing and documented decreased vision. She first presented to a pediatric neurology clinic when she was 10 y of age. At that time, a full neurological examination was documented. She was awake, alert, cooperative, and oriented. Her IQ score was found to be 71. Visual acuity was 20/50 bilaterally, and optic atrophy and rotatory nystagmus were documented. Otherwise, the examination of cranial nerves was normal. Muscle strength was normal, although muscle tone was increased in the lower extremities, with hyperpatellar reflexes and bilateral positive Babinski response. Sensory examination was normal and her gait was ataxic. Her history is also remarkable for documented seizures, and she was found to have generalized 3.5- to 4-Hz spike activity on EEGs and was started on valproic acid, which she continues to take to date. Her last seizure was within 1 mo of this writing. Her current neurological examination is summarized in Table S1.

NG 1024-2. The patient is a 33-y-old woman who is the product of an uncomplicated, term labor through vaginal delivery. Similar to her older sister, she started to lean over close to her notebooks at 7 y of age. Over the next 2 y, she had progressive vision loss. Her first neurological examination was documented when she was 9 y of age. Her IQ was 74. She was awake, alert, cooperative, and oriented. Visual acuity was significantly diminished, and she could only count fingers from near distance. Bilateral optic atrophy and rotatory nystagmus were documented. Although muscle strength was normal, increased tone and hyperreflexia of her lower extremity were noticed. There was a positive Babinski response only on the right. She was found to have significant ataxia. All cerebellar tests were abnormal. Position sense in her lower extremities was found to be diminished, and the Romberg sign was borderline abnormal. Her current neurological examination is summarized in Table S1.

NG 1024-1. The patient is a 28-y-old man who is the product of an uncomplicated, term vaginal labor. His first neurological examination was documented when he was 4 y of age. Although the parents did not detect any abnormalities, when he was screened due to the findings in his two elder sisters, he was found to have early bilateral optical atrophy, nystagmus, and pyramidal tract abnormalities (not further documented). The findings of his current neurological examination are shown in Table S1.

Formal Visual Examination Results. In all patients, visual acuity was limited to light sense in both eyes. Intraocular pressure was 15 mmHg in both eyes (except that it was 16 mmHg for the left eye in NG 1024-1). Anterior segment examination was remarkable for vertical rotator nystagmus of both eyes, pupils were mid-dilated, and direct light response was weak; peripheral cortical annular type punctuate lens opacifications were noted. Fundus examination revealed bilateral optic atrophy; retinal vessels and macula were normal. Flash visual-evoked potentials revealed diminished response in both eyes. A full-field electroretinogram revealed normal photopic and scotopic responses of both eyes. The examinations were noted to be consistent with hereditary optic atrophy.

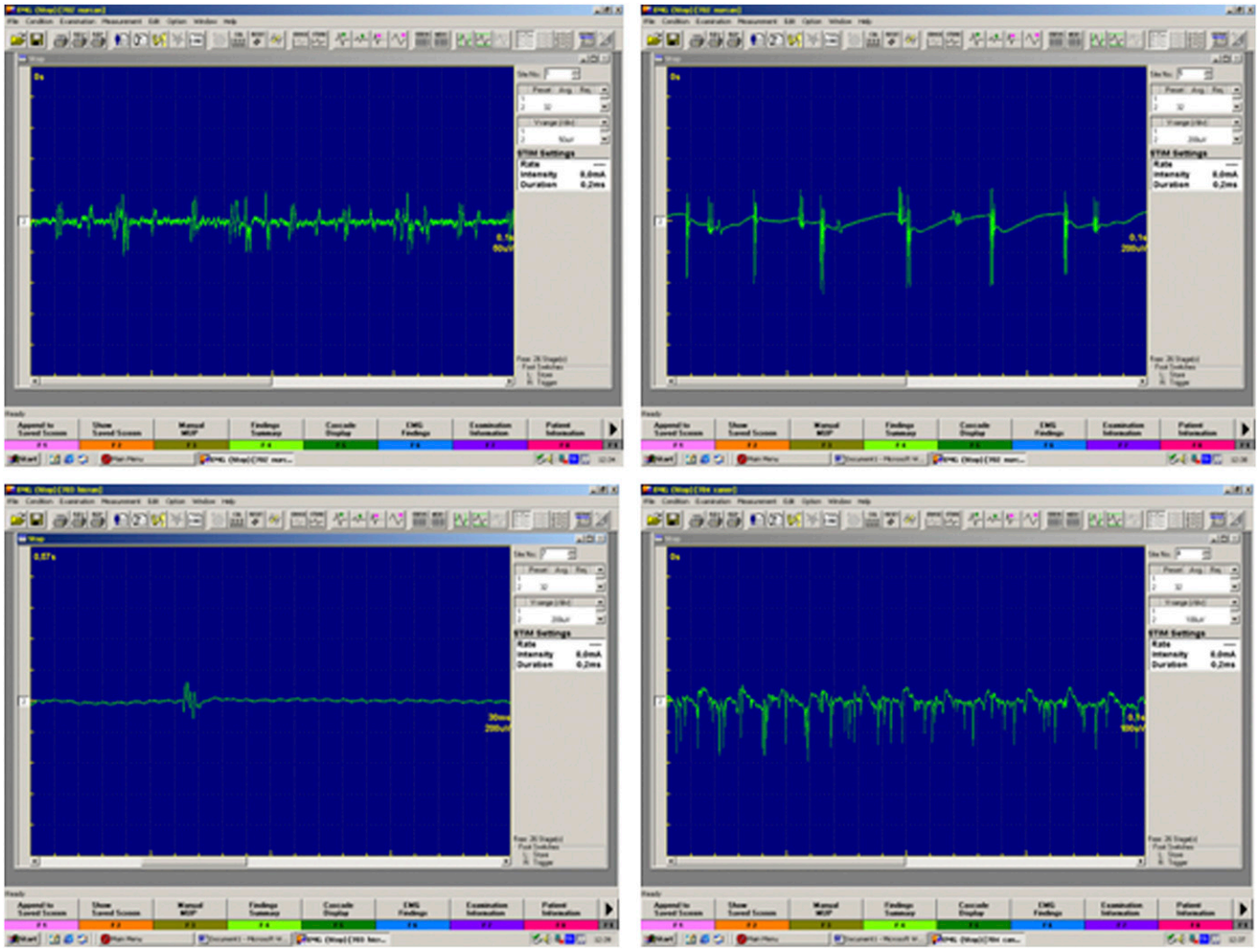

Fig. S1. EMG tests (*Upper*) Screen captures of right deltoid muscle EMG test in NG1024-2. Irregular single, double, or triple spontaneous 50- to 100-μV myokymic discharges that lead to visible muscle contractions are observed. (*Right*) Enlarged trace. (*Lower*) Screen captures of EMG tests in NG 1024-3 (*Left*) and NG 1024-1 (*Right*). For NG 1024-3, right deltoid muscle needle EMG shows infrequent, irregular spontaneous 100-μV myokymic activity. For NG 1024-1, the needle EMG of the gastrocnemius muscle is remarkable for frequent, repetitive fascilation-like 200- to 300-μV myokymic discharges For all three patients, upper and lower extremity motor (median, ulnar, and tibial) and sensory (median, ulnar, and sural) nerve conduction velocities and response amplitudes have been found to be within normal levels.

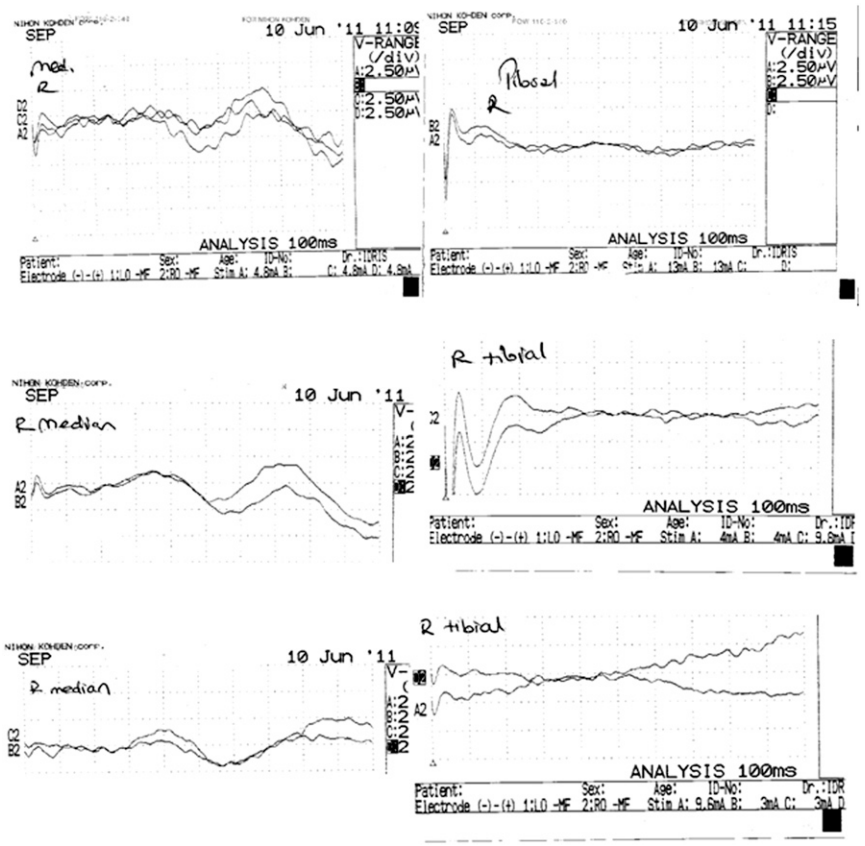

Fig. S2. Somatosensory-evoked potentials (SSEPs). SSEP results are shown for NG 1024-3 (*Top*), NG 1024-2 (*Middle*), and NG 1024-1 (*Bottom*). In all three patients, right median nerve stimulation results in diminished scalp evoked potential response (*Left*), whereas no response was elicited through right tibial nerve stimulation (*Right*).

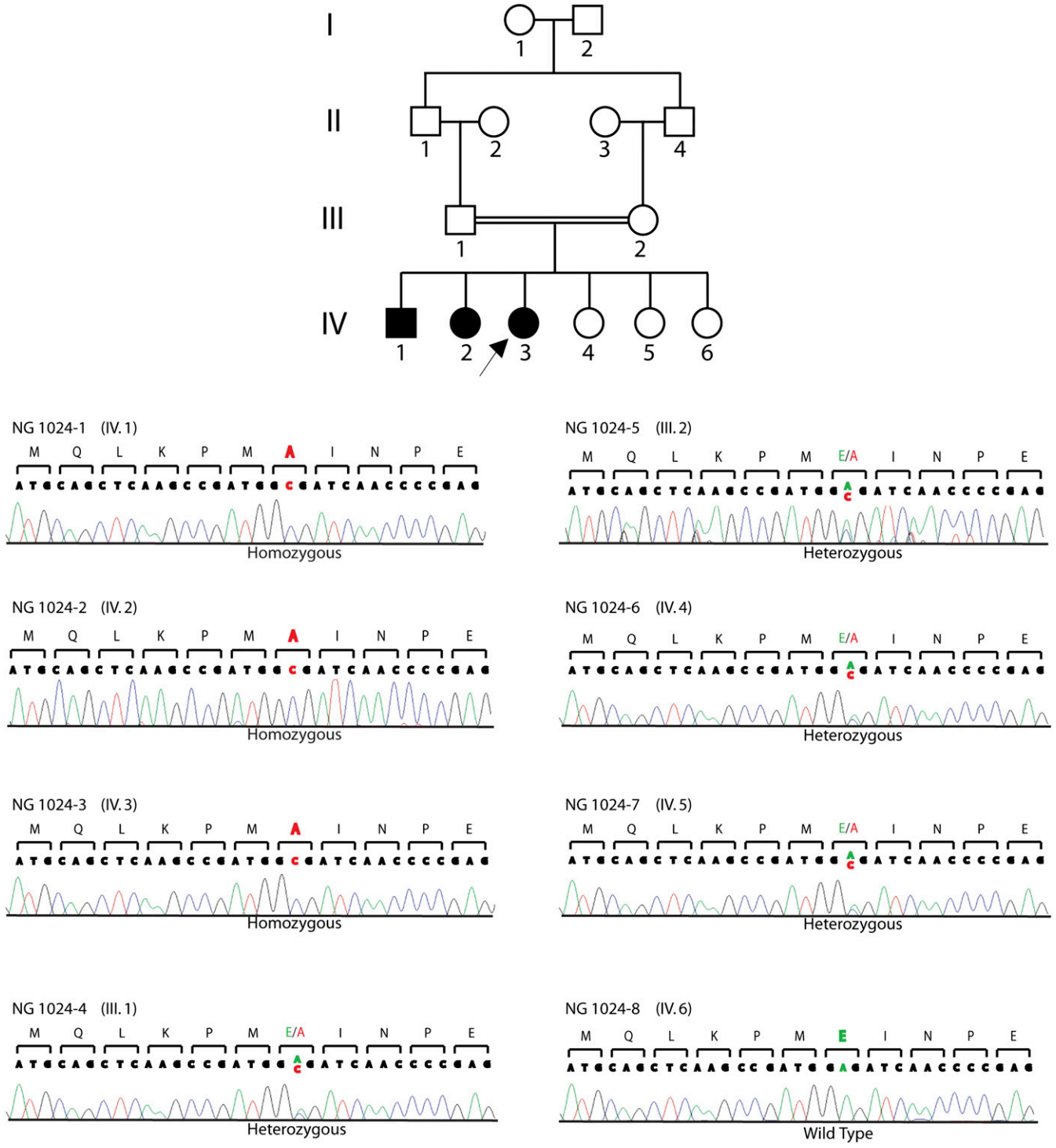

Fig. S3. Segregation of the GLU7ALA variant. The exons and exon-intron boundaries of *ubiquitin C-terminal hydrolase-L1* (*UCHL1*) were determined using the UCSC Genome Browser (http://genome.ucsc.edu); unique primers were designed using Sequencher 4.8 (Gene Codes) and were synthesized by Invitrogen. The fragments were amplified using standard PCR techniques and sequenced on 9800 Fast Thermocyclers (Applied Biosystems).

Table S1. Neurological examination findings

Clinical status	NG 1024-1	NG 1024-2	NG 1024-3
Age at exam/year born	28/1983	33/1978	34/1977
Vision	–	–	–
Standing without assistance	–	–	–
Nystagmus (all directions)	+	+	+
Titubation	+	+	+
Deep tendon reflexes	UE (++) LE (+++)	UE (++) LE (+++)	UE (++) LE (+++)
Babinski/Hoffman responses	+/+	+/–	+/–
Muscle strength	UE 5/5 LE 4/5	UE 5/5 LE 4/5	UE 5/5 LE 4/5
Clonus	–	–	–
Superficial sensation	Normal	Normal	Normal
Positional sense	Normal	Normal	Normal
Vibration (UE/LE, s)*	15/10	6/4	10/7
Spasticity	++	+++	+
Cerebellar tests, dysmetria	Abnormal	Abnormal	Abnormal
Myotonia	+	–	–

LE, lower extremity; UE, upper extremity; –, absent; +, present; ++, more present; +++, most present.
*Expected to last for 20 s; shorter responses associated with dorsal column dysfunction.

Table S2. DTI measurements of the optic pathways in patients versus age-matched controls

Subject	Value	Right optic tract	Left optic tract
NG 1024-1	ADC	0.99×10^{-3}	0.97×10^{-3}
	FA	0.478	0.505
	Number of voxels	251	211
NG 1024-2	ADC	1.01×10^{-3}	1.12×10^{-3}
	FA	0.446	0.414
	Number of voxels	556	401
NG 1024-3	ADC	0.91×10^{-3}	0.88×10^{-3}
	FA	0.525	0.565
	Number of voxels	389	350
Control 1	ADC	0.776×10^{-3}	0.787×10^{-3}
	FA	0.596	0.573
	Number of voxels	372	340
Control 2	ADC	0.813×10^{-3}	0.791×10^{-3}
	FA	0.589	0.569
	Number of voxels	342	298
Control 3	ADC	0.798×10^{-3}	0.787×10^{-3}
	FA	0.553	0.574
	Number of voxels	333	371

An increase in ADC and a decrease in FA is consistent with Wallerian degeneration of the optic tracts. ADC, apparent diffusion coefficient; FA, fraction anisotropy.

Table S3. Intervals of shared homozygosity between the three affected individuals of family NG 1024

Chromosome	Start*	End*	SNP start	SNP end	Number of SNPs	Length (cM)	Length (kb)
4	38,187,084	49,061,848	rs586844	rs12696828	905	9.75	10,874.76
6	44,575,446	53,593,569	rs472029	rs4493745	804	7.62	9,018.12
8	39,869,633	43,791,691	rs2981156	rs10958798	224	3.13	3,922.05
11	114,223,577	117,570,851	rs2852450	rs603377	351	5.44	3,347.27
Total					2,284	25.93	27,162.20

*NCBI37/hg19.

Table S4. Coverage distributions and error rates across the whole exome and shared exomic homozygosity intervals of NG 1024-3

Parameter	Value
Number of lanes	1
Read type	Single read
Read length	74
Total number of reads (millions)	37.96
Percent mapped to the genome	98.3
Exome	
Percent mapped to the exome	62.87
Mean coverage	51.84
Percent of bases covered at least four times	96.87
Mean error rate (%)	1.14
Second base error rate (%)	0.29
Last base error rate (%)	2.31
Shared exomic homozygosity intervals	
Interval size (kb)	297
Percent mapped to the interval	0.55
Mean coverage	51.85
Percent of bases covered at least four times	98.99
Mean error rate (%)	0.97
Second base error rate (%)	0.26
Last base error rate (%)	1.75

Table S5. Previously unreported homozygous variants identified within the shared exomic homozygosity intervals of NG 1024

Chromosome	Position*	Base change	Quality score	Coverage	Unique nonreference allele coverage	Unique reference allele coverage	Gene	Status	Amino acid change	Amino acid position	PhyloP
4	41,259,013	A to C	202	54	35	0	*UCHL1*	Missense	GLU7ALA	7/223	3.888
11	116,658,654	G to A	45	7	5	0	*ZNF259*	Missense	PRO18LEU	18/459	2.654

*NCBI37/hg1.

Table S6. Binding and thermodynamic parameters for UCHL1^{WT}, UCHL1^{GLU7ALA}, UCHL1^{CYS90SER}, and UCHL1^{ILE93MET}

Parameters	UCHL1^{WT}	UCHL1^{GLU7ALA}	UCHL1^{CYS90SER}	UCHL1^{ILE93MET}
K_d (nM)	85 ± 31	646 ± 288	32 ± 6	29 ± 5
n	0.77 ± 0.02	0.18 ± 0.03	0.65 ± 0.06	0.58 ± 0.01
ΔH (cal·mol^{-1})	−5,446 ± 498	−8,268 ± 1,812	−6,307 ± 539	−5,226 ± 200
ΔS (cal·mol^{-1}·deg^{-1})	14 ± 2	1 ± 7	13 ± 2	17 ± 1

K_d, dissociation constant; n, binding stoichiometry; ΔH, change in enthalpy; ΔS, change in entropy.