Supplemental data

Autosomal dominant optic atrophy and cataract "plus" phenotype including axonal neuropathy

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Tables e-1 to e-6

Table e-1. Reported *OPA3* mutations and associated phenotypes

Inh.	*cDNA variant**	*Protein variant**	*Exon / Intron*	*Phenotype*	*Comments*	*Refs.*
AR	c.[1A>G];[142+5G>C]	p.[(Met1?)];[0]	Exon 1; Intron 1	MGA3	c.1A>G appeared homozygous on cDNA sequencing, suggesting that the c.142+5G>C allele is degraded; MAF c.142+5G>C = 0.00041%	[e1]
	c.[143-1G>C];[143-1G>C]	p.[0];[0]	Intron 1	MGA3	Founder mutation in the Iraqi-Jewish population (rs80356523); no mRNA detected on Northern blot analysis	[e2-e4]
	c.[320_337del];[320_337del]	p.[(Gln108_Glu113del)];[(Gln108_Glu113del)]	Exon 2	MGA3	Private mutation (one family)	[e5]
	c.[415C>T];[(415C>T)]	p.[(Gln139*)];[(Gln139*)]	Exon 2	MGA3	Private mutation (one family); presumed homozygous but DNA from mother not available for co-segregation analysis	[e6]
AD	c.10_11insCGCCCG	p.(Val3_Gly4insAlaPro)	Exon 1	Optic atrophy ± cataracts ± hearing loss	Private mutation (one family)	[e7]
	c.235C>G	p.(Leu79Val)	Exon 2	Optic atrophy + cataracts + additional neurological and systemic features	Private mutation (*de novo*, sporadic)	[e8]
	c.277G>A	p.(Gly93Ser)	Exon 2	Optic atrophy + cataracts ± additional neurological features	Private mutation (one family)	[e9]
	c.313C>G	p.(Gln105Glu)	Exon 2	Optic atrophy ± cataracts ± additional neurological or systemic features	Seven unrelated cases/families	[e7, e9-e11]
Other	c.[32T>A];[32T>A]	p.[(Leu11Gln)];[(Leu11Gln)]	Exon 1	Optic atrophy + extrapyramidal signs (dystonia, chorea and myoclonus) ± ataxia ± pyramidal signs	Private mutation (one family); the heterozygous mother had adult-onset bilateral hand dystonia (but was not available for detailed assessment); other heterozygous carriers were reported as unaffected	[e12]

	c.[1A>G(;)209C>T]	p.[(Met1?)(;)(Pro70Leu)]	Exon 1; Exon 2	Optic atrophy	DNA from parents was not available for co-segregation analysis; MAF c.209C>T = 0.00041%	[e13]

*NCBI Reference Sequence NM_025136.3; NP_079412.1.

Inh. = mode of inheritance; MAF = minor allele frequency in the gnomAD dataset (http://gnomad.broadinstitute.org/); MGA3 = 3-methylglutaconic aciduria type III; Refs. = references.

Table e-2. Clinical features in reported individuals with dominant *OPA3*-related disease

OPA3 protein variant	*No. of reported individuals / families*	*Optic atrophy (n)*	*Cataracts (n)*	*Hearing loss (n)*	*Complex phenotype (n)*	*Other features (n)*	*Refs.*
p.(Val3_Gly4insAlaPro)	5 / 1	5	4	4	-	Scheuermann's disease (1)	[e7]
p.(Leu79Val)	1 / 1	1	1	1	Nystagmus, cerebellar and extrapyramidal signs, sensory neuropathy confirmed by NCS (plus proximal weakness and chronic neurogenic changes on EMG), dysautonomic features, abdominal pain and constipation alternating with diarrhea, adipose tissue abnormalities (1)	-	[e8]
p.(Gly93Ser)	7 / 1	6	7	-	Postural and resting tremor, extrapyramidal rigidity in UL, LL areflexia, pes cavus (1) Postural tremor, pes cavus (1) Postural tremor, poliomyelitis sequelae (1)	-	[e9]
p.(Gln105Glu)	23 / 7	23	17	3	Nystagmus, cerebellar ataxia, positive sensory symptoms, LL areflexia, pinprick and light-touch hypoesthesia, pes cavus, severe constipation alternating with diarrhea; normal NCS; abnormal SSEPs; mild cerebellar atrophy on brain MRI (1) Nystagmus, generalized areflexia, severely reduced vibration sense in LL (1)	Intestinal pseudo-obstruction (1) Chiari malformation type 1 (1) Ocular hypertension (1) AVM in frontal lobe (1) Nystagmus (3)	[e7, e9-e11]

AVM = arteriovenous malformation; EMG = electromyography; LL = lower limbs; MRI = magnetic resonance imaging; NCS = nerve conduction studies; Refs. = references; SSEP = somatosensory evoked potentials; UL = upper limbs.

Table e-3. Nerve conduction studies in patients AII-2, BIII-2, BII-1 and CII-1

Patient	*AII-2*			*BIII-2*				*BII-1*	*CII-1*					*Normal values*
Age at exam	20 y	67 y		30 y		40 y	53 y	65 y	16 y	23 y		26 y	32 y	
Right / left side	R	R	L	R	L	R	R	L	R	R	L	L	L	
Motor NCS														
Median nerve, APB														
DML, ms	3.5	3.4	-	3.7	-	3.5	4.0	3.4	-	-	-	-	-	≤4.4
CMAP, mV	8.0	9.5	-	11.3	-	12.5	9.5	5.3	13.9	8.6	7.3	9.2	6.8	≥4.0
MNCV, m/s	57	58	-	55	-	58	51	52	49	52	53	**44**	50	≥49
F wave, ms	26.6	25	-	26.4	-	-	28	29	-	-	-	-	-	≤31
Ulnar nerve, ADM														
DML, ms	2.9	3.0	-	-	-	**3.5**	**3.9**	**3.5**	-	-	-	-	-	≤3.3
CMAP, mV	9.5	8.4	-	-	-	11.7	8.0	6.3	10.5	10.5	9.0	8.3	**4.8**	≥6.0
MNCV, m/s	58	56	-	-	-	58	57	50	**46**	53	50	51	49	≥49
F wave, ms	26.2	28	-	-	-	29.9	29	31	-	-	-	-	-	≤32
Peroneal nerve, EDB														
DML, ms	4.5	4.3	-	4.9	5.1	4.2	**6.6**	**6.9**	-	-	-	-	-	≤6.5
CMAP, mV	5.5	4.7	-	3.6	2.7	2.8	2.0	**0.6**	-	-	-	-	-	≥2.0
MNCV, m/s	49	48	-	**42**	**43**	**43**	**40**	48	-	-	-	-	-	≥44
F-wave, ms	43.7	44	-	53.5	-	-	**0**	**59**	-	-	-	-	-	≤56

Tibial nerve, AH													
DML, ms	-	4.0	-	3.7	-	3.8	4.6	4.4	-	-	-	-	-	≤5.8
CMAP, mV	-	5.2	-	11.4	-	6.4	5.4	4.4	**0.5**	-	-	-	-	≥4.0
Sensory NCS														
Radial nerve														
SNAP, µV	-	**7**	**6**	18	-	**13**	**9**	-	**0**	-	-	**0**	**0**	≥15.0
SNCV, m/s	-	58	57	56	-	61	53	-	-	-	-	-	-	≥50
Median nerve, D2/3														
SNAP, µV	**0**	-	-	13	-	8	**6**	**6.5**	**0**	-	-	-	-	≥8.0
SNCV, m/s	-	-	-	52	-	53	51	54	-	-	-	-	-	≥50
Ulnar nerve, D5														
SNAP, µV	**0**	**0**	-	-	-	**2**	**0**	**2**	**0**	-	-	-	-	≥7.0
SNCV, m/s	-	-	-	-	-	**45**	-	**41**	-	-	-	-	-	≥50
Sural nerve														
SNAP, µV	**0**	**0**	-	**1**	**1**	**1**	**0**	**3**	**0**	-	-	-	-	≥6.0
SNCV, m/s	-	-	-	**37**	**39**	**34**	-	50	-	-	-	-	-	≥40

ADM = abductor digiti minimi; AH = abductor hallucis; APB = abductor pollicis brevis; CMAP = distal compound muscle action potential; D2/3 = second or third finger; D5 = fifth finger; DML = distal motor latency; EDB = extensor digitorum brevis; F wave = minimal F wave latency; MNCV = motor nerve conduction velocity; NCS = nerve conduction studies; SNAP = sensory nerve action potential; SNCV = sensory nerve conduction velocity; 0 = no response; - = not assessed. Numbers in bold indicate abnormal values.

Table e-4. Exome sequencing and variant filtering of patients AII-2, BIII-2 and CII-1			
Patient	*AII-2*	*BIII-2*	*CII-1*
Sequencing platform	Illumina HiSeq 2000	Illumina HiSeq 2500	Illumina HiSeq 2500
Target enrichment system	Illumina TruSeq Exome	Agilent SureSelect Focused Exome	Agilent SureSelect Human All Exon Kit
Alignment tool	NovoAlign	NovoAlign	Burrows-Wheeler
Variant calling tool	SAMtools	GATK	Freebayes
Total no. of reads	120,684,958	75,972,282	101,065,612
30x coverage	85.54%	95.16%	77,83%
20x coverage	89.67%	97.60%	84.89%
10x coverage	93.13%	99.29%	91.10%
2x coverage	96.25%	99.91%	93.72%
Exonic variants	23,307	7,743	35,338
Synonymous variants excluded	12,086	3,750	22,053
MAF <0.1% in the ExAC dataset	875	255	5356
In optic atrophy / inherited neuropathy genes (AD inheritance)	3	1	4
Known pathogenic variants	0	1	1

AD = autosomal dominant; MAF = minor allele frequency; ExAC = Exome Aggregation Consortium (http://exac.broadinstitute.org).

Table e-5. Variants in optic atrophy and inherited neuropathy-related genes detected in patient AII-2

Gene	*Location*	*Sequence variant*	*Zyg*	*AF*	*MIM*	*Gene-associated phenotype*	*Inh*	*Comments*	*Variant class*
OPA3	19q13.32	NC_000019.9: g.46088000A>G	Het	n/a	258501 165300	3-methylglutaconic aciduria type III Optic atrophy 3 with cataract	AR AD	Consistent with phenotype and mode of inheritance; absent from public and in-house databases; *in silico* analyses and evolutionary conservation are shown in table e-6 and figure e-1	VUS
PRX	19q13.2	NC_000019.9: g.40900054G>A	Het	n/a	614895	Charcot-Marie-Tooth disease type 4F	AR	Monoallelic variant in gene associated with autosomal recessive demyelinating Charcot-Marie-Tooth disease	VUS
INF2	14q32.33	NC_000014.8: g.105173884_105173889delCACCCC	Het	n/a	614455 613237	Dominant intermediate Charcot-Marie-Tooth disease type E with focal segmental glomerulosclerosis Focal segmental glomerulosclerosis 5	AD AD	Low read depth in WES; adjacent to g.105173863_105173868delCCCCAC (allele frequency of 8.65% in ExAC but possible low quality site); both variants lead to p.Pro427_pro428del within a polyproline segment in exon 8	VUS

AD = autosomal dominant; AF = allele frequency; AR = autosomal recessive; ExAC = Exome Aggregation Consortium dataset (http://exac.broadinstitute.org); Het = heterozygous; Inh = disease mode of inheritance; Low-quality site = covered in <80% individuals in ExAC dataset; Variant class = sequence variant classification according to ACMG recommendations (reference e14); VUS = variant of uncertain significance; WES = whole-exome sequencing; Zyg = zygosity.

Table e-6. *In silico* analysis of the heterozygous missense variants c.23T>C (p.Met8Thr) and c.313C>G (p.Gln105Glu) in *OPA3*.

		c.23T>C		*c.313C>G*	
		Score	*Interpretation*	*Score*	*Interpretation*
Amino acid change	Grantham	81	Moderately conservative	29	Conservative
Conservation scores	GERP++	5.77	Conserved nucleotide	3.74	Conserved nucleotide
	phyloP	2.32	Conserved nucleotide	2.653	Conserved nucleotide
Predictive algorithms	LRT	0.000	Deleterious	n/a	n/a
	SIFT	0.184	Tolerated	0.159	Tolerated
	PANTHER	176*	Probably benign	176*	Probably benign
	Align-GVGD	C65*	Most likely to interfere with function	C25*	Less likely to interfere with function
	Mutation Assessor	1.905	Low functional impact	1.64	Low functional impact
	Mutation Taster	0.999*	Disease causing	0.002*	Disease causing (automatic)
	PolyPhen-2	0.346	Benign	0.248	Benign
	FatHMM	-1.62	Damaging	-1.65	Damaging
	CONDEL	0.543	Deleterious	0.542	Deleterious
	CADD	21.3	Probably deleterious†	15.38	Probably deleterious‡

*Scores for *OPA3* transcript variant 2 (NCBI RefSeq NM_025136.3). †Predicted to be within the 1% most deleterious substitutions in the human genome. ‡Predicted to be within the 10% most deleterious substitutions in the human genome.

Align-GVGD = Align-GVGD class (http://agvgd.iarc.fr/); CADD = Combined Annotation Dependent Depletion v1.3 Phred score (http://cadd.gs.washington.edu/); CONDEL = Consensus Deleteriousness v.2 calculated score (http://bbglab.irbbarcelona.org/fannsdb/); FatHMM = Functional Analysis through Hidden Markov Models v2.3 Weighted score (http://fathmm.biocompute.org.uk/inherited.html); GERP++ = Genomic Evolutionary Rate Profiling RS score (https://genome.ucsc.edu/); Grantham = Grantham Matrix score (reference e15); LRT: Likelihood Ratio Test P-value (http://www.genetics.wustl.edu/jflab/lrt_query.html); Mutation Assesor = Mutation Assessor r3 Functional Impact combined score (http://mutationassessor.org/r3/); Mutation Taster = Mutation Taster-2 probability value (http://www.mutationtaster.org/); PANTHER = PANTHER Position Specific

Evolutionary Preservation time (http://www.pantherdb.org/tools/csnpScoreForm.jsp?); phyloP = phyloP base-wise conservation score derived from multiple sequence alignment of 46 vertebrate species (https://genome.ucsc.edu/); PolyPhen-2 = Polymorphism Phenotyping v2 HumVar score (http://genetics.bwh.harvard.edu/pph2/); SIFT = Sorting Intolerant From Tolerant algorithm score (http://sift.jcvi.org/).

Figure e-1

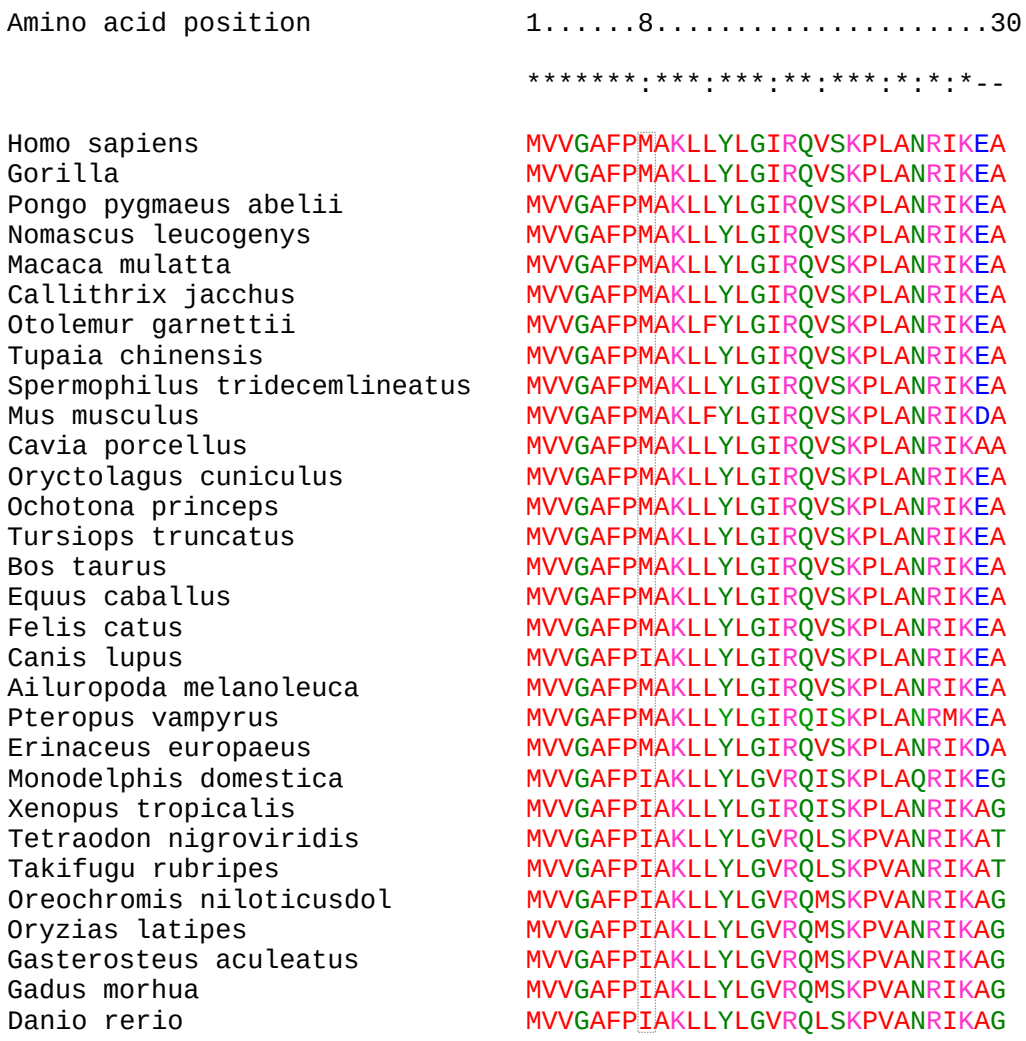

Figure e-1. Multiple sequence alignment of OPA3 amino acids 1–30 from 30 different species. There is conservation of amino acids with similar physicochemical properties at position 8 (methionine [M] and isoleucine [I], with nonpolar, aliphatic R groups) from *Homo sapiens* to *Danio rerio* (grey box). Amino acids are colored according to their physicochemical properties (https://www.ebi.ac.uk/seqdb/confluence/display/THD/Help++Clustal+Omega+FAQ). Asterisk (*) = positions with fully conserved amino acids; colon (:) = positions with conservation between amino acids of strongly similar properties.

e-Methods

Sanger sequencing

Validation and co-segregation analysis of OPA3 variants in families A and B were performed by Sanger sequencing using the Applied Biosystems BigDye Terminator v3.1 protocol on an ABI3730XL automatic DNA sequencer using the following primers (5'–3'): exon 1 TGCGCCTCTGAAGTTTCCCT (forward), TCGGGCTGTGATTGGTCGTA (reverse); exon 2 TGCATTCCCTGGGTGAGAG (forward); CCTATTTCTTGGACGCAGGC (reverse). Sanger sequencing of the OPA3 variant in family C was performed by Eurofins Genomics with the following primers (5'–3'): exon 2 GGAAGAAGGCCACGTTAGGT (forward) and GCAGTGTATCACTGGGTGGA (reverse).

Computational analyses

DNA and protein sequence variants are described in accordance with the recommendations of the Human Genome Variation Society (http://varnomen.hgvs.org/). Evolutionary conservation of nucleotides was assessed using phyloP (46 vertebrate species) and GERP++ scores,[e16,e17] which were accessed through the UCSC Genome Browser (https://genome.ucsc.edu/) using genomic coordinates from human genome assembly GRCh37 (hg19). *In silico* analysis of DNA or protein sequence variants was performed using the following pathogenicity prediction tools: LRT,[e18] SIFT,[e19,e20] PANTHER,[e21] Align-GVGD,[e22,e23] Mutation Assessor,[e24,e25] Mutation Taster,[e26] PolyPhen-2,[e27,e28] FatHMM,[e29] CONDEL,[e30] and CADD.[e31] Multiple sequence alignment of OPA3 homologs from 30 different vertebrate species was performed using Clustal Omega v1.2.4 with the default settings (https://www.ebi.ac.uk/Tools/msa/clustalo/).[e32,e33] Prediction of mitochondrial targeting sequences and cleavage sites of the OPA3 protein was performed with MitoProt (https://ihg.gsf.de/ihg/mitoprot.html),[e34] TargetP (http://www.cbs.dtu.dk/services/TargetP),[e35,e36] and MitoFates (http://mitf.cbrc.jp/MitoFates/cgi-bin/top.cgi).[e37]

e-Results

Case reports

Family A. The proband and six relatives belonging to three generations were affected in this family (figure 2)**.**

Proband AII-2. This patient had past history of bilateral cataract surgery at age 6 and left tarsorrhaphy for ptosis in her mid-30s. She also had symptoms of intestinal dysmotility since her 30s, including an erratic bowel habit with intermittent constipation. Her main complaint, however, was numbness in both feet since her late 40s, which she felt was aggravated after an acute left L5 radiculopathy at age 49. Over the following years she also developed gait imbalance and mild hearing loss. She had no sensory symptoms in her hands but complained of dropping objects involuntarily. She described episodes of dizziness or lightheadedness that were sometimes related to posture. She denied cognitive decline, visual symptoms, weakness, neuropathic pain, urinary disturbances, or diabetes.

Neurological examination at age 49 showed mildly reduced visual acuity and altered colour vision in both eyes. She had bilateral pes cavus. Muscle bulk, strength and tone were normal. Deep tendon reflexes (DTRs) were present in the upper limbs (ULs) and absent in the lower limbs (LLs). Plantar responses were flexor. Light touch and pinprick were symmetrically reduced from the wrists and knees distally, vibration sense was absent at the first metatarsophalangeal joints, and joint position sense was normal. No limb ataxia or tremor were observed. Stance and gait were normal. Romberg test was negative. There was no postural drop in blood pressure. Her examination at age 57 confirmed progression of the pinprick hypoesthesia to two inches above the wrists and mildly impaired joint position sense at the toes. Additional findings on subsequent examinations until age 67 included mild bilateral ptosis, hypoactive DTRs in the ULs, mild weakness of big toe dorsiflexion (4+/5 bilaterally), and unsteadiness on tandem walking.

Routine blood tests, including lactate and creatine kinase, were normal. Urine excretion of 3-methylglutaconate and 3-methylglutarate was within reference values. Brain MRI was normal. Whole spine MRI showed narrowing of the left L5 neural foramen, but the remaining neural foramina and the vertebral canal were well preserved, and the spinal cord was normal. The patient underwent neurophysiological studies at ages 20 and 67 (table e-3). Motor NCS and EMG were normal. On sensory NCS, radial responses had reduced amplitudes (6-7 µV) with normal conduction velocities; median, ulnar and sural responses were absent. These findings were indicative of a severe, chronic axonal sensory neuropathy. Thermal thresholds at the left hand and foot were within normal limits at age 49. Autonomic testing at age 56 did not show evidence for postural hypotension but, on head-up tilt, there was orthostatic tachycardia up to 148 bpm after 10 minutes.

Neuro-ophthalmological exam at age 49 revealed visual acuity of 6/9 binocularly but no optic atrophy. She was able to read only 2/14 Ishihara plates and colour vision testing showed elevation of protan, deutan and tritan thresholds. At age 67, visual acuity was 6/15 binocularly and there was evidence of optic atrophy on fundoscopy and optic coherence tomography (figure 3B-C). Neuro-otological investigations between ages 49 and 67, including brainstem auditory evoked potentials, were consistent with bilateral auditory neuropathy; no vestibular or oculomotor involvement was observed.

Genetic analysis to exclude 17p11.2 chromosome region rearrangements and direct sequencing of *GJB1*, *TTR*, *POLG* and targeted regions of *TWNK* revealed no pathogenic variants.

Patient AI-1. The mother of the proband was considered affected based on the history provided by relatives. She developed cataracts before age 5 and hearing loss in her 50s. She was reported to suffer from intestinal subocclusion, muscle atrophy in her LLs and pes cavus.

Patient AII-1. The sister of the proband was considered affected based on the history provided by relatives. She developed cataracts before age 5. She had gastrointestinal problems from

her 40s, including gastroparesis and constipation, and required surgery for intestinal occlusion. She was reported to have muscle atrophy in her LLs.

Patient AIII-1. The eldest son of AII-1 had past history of surgery for congenital cataracts at age 3. He had symptoms of gastrointestinal dysmotility from his teens, including intestinal pseudo-obstruction, for which he required parenteral nutrition from his mid-20s. Pes cavus and distal muscle weakness and atrophy were noted in his teens and he was diagnosed with peripheral neuropathy in his early 20s. NCS/EMG had been reported as consistent with an axonal motor and sensory neuropathy. Previous examinations had also confirmed bilaterally reduced visual acuity and bilateral hearing loss. Neurological examination at age 31 revealed signs of past cataract surgery but optic fundi were not well visualized. In his limbs, there was marked distal-predominant muscle wasting and weakness and sensory loss, more severe in the LLs than in the ULs. DTRs were absent and plantar responses were unobtainable. Limb coordination was normal but gait was unsteady. There was no postural drop in blood pressure.

Patient AIII-2. The middle son of AII-1 was considered as affected based on the history provided by relatives. He had mild intestinal symptoms. He had abnormal neurophysiological studies and was told to have a mild form of the disease.

Patient AIII-3. The youngest son of AII-1 was considered affected based on the history provided by relatives. He had early-onset cataracts, mild intestinal symptoms, and a peripheral neuropathy confirmed by neurophysiological studies.

Patient AIII-4. The daughter of the proband was considered affected based on the history provided by relatives. She had surgery for cataracts at ages 14 and 22. She was diagnosed with peripheral neuropathy, and suffered from constipation.

Family B. The proband and three relatives belonging to three generations were affected in this family (figure 2)**.**

Proband BIII-2. This patient developed impaired vision at age 5. Neuro-ophthalmological examination at age 16 revealed bilateral visual acuity of 6/18, temporal pallor of both optic

discs on fundoscopy, and red-green deficiency on colour vision testing. Her vision progressively deteriorated and she was declared legally blind by age 40. Bilateral cataracts were detected in adulthood and surgically removed at age 44. She also suffered from symptoms of gastrointestinal dysmotility since age 5, sometimes requiring hospital admission and attributed to intestinal pseudo-obstruction or gastroparesis; she required emergency bowel resection for intussusception in her 50s. In her 20s, she developed abnormal sensation in her feet that interfered with walking. Sensory symptoms progressed over the following years and, on her last appointment, she complained of reduced sensation up to her knees but denied neuropathic pain or weakness. On questioning, she also described mild hearing loss, urinary urgency and stress incontinence, and episodes of lightheadedness as a result of which she had been previously diagnosed with orthostatic hypotension. She denied cognitive symptoms or diabetes.

Neurological examination at age 52 revealed reduced visual acuity limited to light perception in the right eye and to finger counting in the left eye, and bilateral optic atrophy on fundoscopy. She had nystagmus with a vertical and rotatory component on lateral gaze and upgaze. There was mild wasting of first dorsal interosseous on the right hand and extensor digitorum brevis in both feet, but muscle strength and tone were intact. DTRs were present in the ULs but absent in the LLs. Plantar responses were flexor. Pinprick sensation was reduced to 3 inches below the knees distally. Vibration sense was reduced in her hands and wrists and below the sternum in the trunk and LLs. Joint position sense was preserved. Her gait was broad based and she could not tandem walk. Romberg test was positive. Additional findings on subsequent examinations until age 55 included mild hip flexion weakness (4+/5 bilaterally), generalised areflexia, reduced pinprick sensation above the elbows and knees, abnormal joint position sense at the great toes, and mild dysmetria of the LLs.

Routine blood tests were normal. At age 52, MRI of the neuraxis was normal except for an incidental meningioma. Three neurophysiological studies were performed between ages 30 and 53 (table e-3). Serial sensory NCS revealed a progressive and length-dependent reduction

in the amplitude of the sensory responses, with normal or mildly reduced conduction velocities. Motor NCS showed a decrease in the right peroneal compound muscle action potential (CMAP) amplitude from 3.6 mV at age 30 to 2 mV at age 53; minor changes in distal motor latencies and motor nerve conduction velocities (MNCV) were also noted. EMG revealed chronic partial denervation in distal muscles of the ULs and LLs. These findings were consistent with a chronic axonal sensorimotor neuropathy with predominant sensory involvement.

Gene panel testing to exclude mutations in genes involved in mitochondrial DNA maintenance revealed no pathogenic variants.

Patient BI-1. The grandmother of the proband was considered affected based on the history provided by relatives. She developed visual loss from age 10 and was only able to perceive light by age 30.

Patient BII-1. The father of the proband developed impaired vision from age 10 and he was only able to perceive light by age 40. He also suffered from recurrent gastrointestinal symptoms, including severe bouts of diarrhoea and abdominal pain without vomiting, that had been attributed to irritable bowel syndrome, but no further details were available on this point. He had no hearing loss. His exam at age 65 revealed bilateral cataracts and bilateral optic atrophy. There was no muscle wasting or weakness in his limbs. DTRs were all absent except for the biceps reflexes. Plantar responses were flexor. Vibration sense was reduced in all fingers and distally to the ankles. The remainder of the neurological examination was unremarkable. NCS performed at age 65 y were consistent with an axonal motor and sensory neuropathy (table e-3).

Patient BII-2. The paternal aunt of the proband was considered affected based on the history provided by relatives. She developed visual loss from age 7 and was only able to perceive light by age 30. She also suffered from gastrointestinal symptoms that had been attributed to irritable bowel syndrome.

Family C. The proband (CII-1) was the only affected individual in this family (sporadic case) (figure 2).

Patient CII-1 was referred for evaluation at age 16 by a physical therapist who suspected a peripheral neuropathy during treatment for a fracture of her left foot. Prior to that, she had frequent ankle sprains as a child. Her prior medical history was remarkable for two hospitalizations for pancreatitis at age 11 and 14, and bilateral cataract surgery at age 14. Her exam at age 16 showed normal muscle strength except for possible mild weakness of intrinsic hand muscles and weakness of ankle dorsiflexion (4/5) and big toe dorsiflexion (3/5). She was areflexic. Vibration sense was diminished in the feet but not quantified. At age 18, her intrinsic hand muscles were weak (4/5), and vibration sense was absent in the toes. At age 22, ankle plantar flexion weakness was noted (4+/5), and neuropathic pain had appeared. At age 23, she had another severe bout of pancreatitis. At age 26, ankle plantar flexion (4/5) and intrinsic hand muscles (4 to 4-/5) were weaker. Pinprick was normal in legs and hyperpathic in the feet, and vibration sense was absent at knees and thumbs. At age 32, wrist extensors (4+/5) and hamstrings (4+/5) were also weak, and severe bilateral optic neuropathy was found by optical coherence tomography. Between the ages of 16 and 32, she has had many bouts of nausea, vomiting, and abdominal pain, some requiring hospitalization. She became hypertensive during some of these episodes, to the point that she developed posterior reversible encephalopathy syndrome (PRES) on one occasion. Her CMT Exam score (CMTES) and neuropathy score (CMTNS) worsened from age 26 (CMTES/CMTNS = 15/19) to age 32 (CMTES/CMTNS = 21/26).

The patient underwent four neurophysiological exams between ages 16 and 32 (table e-3). All of the sensory responses were absent at age 16. Tibial CMAP was severely reduced in amplitude by age 23. The median and ulnar CMAP amplitudes and MNCV were still normal at age 32, but EMG showed severe, chronic denervation in the same muscles, and moderate, chronic denervation in proximal arm muscles. These findings were consistent with a severe,

chronic axonal sensorimotor neuropathy. Gene panel testing to exclude mutations in *GJB1*, *MPZ*, *NEFL*, *GDAP1* and *MFN2* revealed no pathogenic variants.

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