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Autosomal dominant cerebellar ataxia with slow ocular saccades, neuropathy and orthostatism: A novel entity?

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Short title: Novel dominant cerebellar ataxia

Abstract

Background: We describe the clinical characteristics of a Swedish family with autosomal dominant cerebellar ataxia, sensory and autonomic neuropathy, additional neurological features and unknown genetic cause.

Methods: Fourteen affected family members were identified. Their disorder was characterized by neurological examination, MRI, electroneurography, electromyography, MIBG-scintigraphy, and tilt-testing.

Results: The disorder presented as a balance and gait disturbance starting between 16 and 47 years of age. Cerebellar ataxia progressed slowly over the course of decades, and MRI showed mild to moderate cerebellar atrophy. Sensory axonal polyneuropathy was the most prominent additional feature and occurred in all patients examined. Autonomic neuropathy caused pronounced orthostatic dysregulation in at least four patients. Several affected members showed muscle wasting, and mild upper or lower motor neuron signs were documented. Patients had no nystagmus but slow or hypometric horizontal saccades and ocular motor apraxia. Cognition remained unimpaired, and there were no non-neurological disease manifestations. The disorder affected men and women in successive generations in a pattern compatible with autosomal dominant inheritance without evidence of anticipation. A second family where 7 members had very similar symptoms was identified and its origin traced back to the same village in southern Sweden as that of the first family's ancestors. All relevant known genetic causes of cerebellar ataxia were excluded by a novel next-generation sequencing approach.

Conclusion: We present two probably related Swedish families with a characteristic and novel clinical syndrome of cerebellar ataxia and sensory polyneuropathy. The study serves as a basis for the mapping of the underlying genetic cause.

1. Background

Autosomal dominant cerebellar ataxias (ADCA) include a wide variety of subtypes, ranging from pure cerebellar syndromes to combinations of ataxia with pyramidal or extrapyramidal signs, cognitive impairment, bulbar, spinal or peripheral neurological dysfunction, or retinal degeneration [1-5]. The broad spectrum of clinical phenotypes reflects the genetic heterogeneity of the various ADCA subtypes. Known genetic causes include expansions of polyglutamine repeats or non-coding regions and conventional mutations. For a substantial number of ADCA subtypes the underlying genetic causes remain to be identified [4, 6]. We report a family from southern Sweden with autosomal dominantly inherited cerebellar ataxia, prominent sensory and autonomic polyneuropathy, and slow horizontal saccades. Extensive genetic testing has not revealed any of the known ADCAs. We suggest that this disorder represents a novel subtype of ADCA, and hope the present work will form the basis for the identification of the underlying genetic cause.

2. Patients and Methods

The patients described here were independently referred to KW, BB or AP for neurological evaluation. The patients expressed interest in research into the cause of their disease, and established contact between the authors and other family members. A pedigree was drawn from genealogical data provided by the families and, for the older generations, by genealogical research in public databases. With the family members' informed consent, medical records of affected family members were compiled and reviewed. Patients who were examined specifically for this study gave their written informed consent; patients shown in the

video that accompanies this article provided their informed consent to the publication of the video. The study was approved by the Regional Ethical Review Board. Examinations including electromyography, electroneurography, CT, MRI, tilt-test and I¹²³-metaiodobenzylguanidine (MIBG) scintigraphy and conventional genetic analyses were conducted in affected family members as part of the clinical neurological evaluation. For the purpose of this study, retrievable CT or MRI scans from 9 patients were reviewed by a neuro-radiologist (DvW). Cerebellar atrophy was graded subjectively on a scale from “+” to “++++”, with “+” indicating mild and “++++” indicating most severe degree of atrophy. White matter changes were graded according to Fazekas [7].

In addition, next-generation sequencing of 10 additional ADCA genes (Table 2) and 105 autosomal recessive or X-linked ataxia genes (esupp1) was performed. A sequencing library was constructed according to standard protocols. Following custom target enrichment for hereditary ataxia genes (HaloPlex, Agilent), a MiSeq next-generation sequencing instrument was used for analyses, yielding 1,18 million reads with 86,9% in the target regions (474kb). Reads were mapped against the hg19 standard reference genome to detect single nucleotide polymorphisms/variants, short deletions and insertions (SAMtools). The identified variants were compared to published data from dbSNP and the 1000Genomes project (Annovar). Details are available from PB (peter.bauer@med.uni-tuebingen.de) upon request.

3. Results

Fourteen affected individuals from three generations have been identified in Family 1 (figure 1A). Medical records were retrieved from a total of 10 affected family members, of whom 9 had been seen by neurologists, including 7 who had been examined personally by KW, BB

and/or AP. Patients had been followed at the Department of Neurology in Lund for up to 24 years. Three additional individuals in Generation I were affected according to family history and information in their relatives' medical records.

During the course of our study we identified a clinically identical disorder in a patient from another family, Family 2 (figure 1B). This patient (IV:1) was aware that he belonged to a family with autosomal dominant cerebellar ataxia that was published by Möller et al. in 1978 (described there as Family II)[8]. In that publication, six family members were known to be affected; IV:1 belongs to the generation following the pedigree published in 1978 and is thus the seventh known affected family member.

3.1 Clinical findings

This paragraph and Table 1 summarize clinical data on patients who have been evaluated by the authors (KW, BB, AP). Videos of 5 patients and detailed clinical information on these and the other affected family members can be found in the online supplement to this article (esupp2).

Family 1:

II:1

This female patient experienced numbness in her feet and balance problems at age 47. During the following years, dysarthria and upper limb ataxia developed, and the patient retired prematurely from her manual occupation at age 58. At 63 years, she used a walker for short distances, but was otherwise dependent on a wheelchair. She had urinary urge incontinence.

Neurological examination also revealed reduced sensibility for proprioception and vibration in lower legs. Dysphagia developed at age 66. When last evaluated at age 71, she also had moderate general muscular atrophy.

II:4

This woman started to experience balance disturbance at the age of 33 years. When last examined at age 67 (video segment 4), she scored 43 points in the ICARS ataxia scale [9]. Marked dysarthria made communication difficult at times. She was wheelchair-bound, had pronounced dystaxia and dysmetria in finger-to-nose test and heel-shin slide, as well as intention tremor. There was mild scoliosis, areflexia, normal muscle tone, and no cognitive deficit. Mild dystonic posturing of the feet was seen during movements. Vibration sense was absent in feet and lower legs. Horizontal saccades were markedly slowed; the patient turned her head rather than her eyes to look sideways.

III:1

This woman started noticing a balance and gait disturbance at age 37, and soon thereafter experienced reduced dexterity with manual fine motor tasks. At age 56 (video segment 3), she was only able to walk short distances with a walker and assistance, otherwise using a wheelchair. Writing and using cutlery had become very difficult. Speech was mildly dysarthric. Episodes of dizziness occurred when she was sitting, and she had very variable blood pressure ranging from 160/120mmHg in the morning to 55/44mmHg in the evening. The speed of horizontal saccades appeared mildly decreased and the patient displayed involuntary grimacing of the lower facial muscles when she was asked to turn her gaze sideways. She had some involuntary blinking when tested for ocular smooth pursuit.

III:3

This woman (proband, Family 1) developed a balance and gait disturbance at the age of 16. Symptoms worsened gradually, and in her late 20's, she also experienced reduced sensitivity in her fingers and reduced dexterity. By age 37, she was unable to work, perform household chores, to shop or drive a car. At age 38 (video segment 2), she scored 37 points in the ICARS scale [9]. There was bilateral upper eyelid retraction in neutral gaze position. Horizontal saccades were markedly hypometric, and the patient rapidly thrust her head in order to look sideways. The patient had hyporeflexia and some muscle wasting. During pronation-supination movements of one hand, mirror movements were observed in the contralateral hand, and there was dysdiadochokinesia. Heel-shin slide was jerky and with lateral movements; finger-to-nose test showed moderate dysmetria and moderate intention tremor. Muscle strength in hands, lower arms and feet was reduced. Tendon reflexes were weak or entirely absent. Sensation for pinprick, touch and vibration was reduced in the lower legs and feet. This patient had marked falls in blood pressure when erect and underwent a tilt test examination. Blood pressure dropped from 112/64 mmHg supine to 57/42 mmHg tilted to 70 degrees, with an increase in heart rate from 80 to only 85/min. This caused presyncope and was reproducible on repetition. Valsalva test was positive, indicating disturbance of the autonomic system. This patient also had severe postprandial diarrhea, which was responsive to loperamide but caused weight loss.

III:4

This female patient had wished to undergo electroneurography at age 24 when she had no overt neurological symptoms, as she knew that a familial disease had afflicted her mother. Already at the time of that examination sensory nerve action responses in the median, ulnar, or sural nerves were missing. Some motor units were enlarged. By age 31, the patient was

unable to ride a bicycle, and experienced tingling sensations in her fingers and decreased dexterity. At age 34 (video segment 1), she walked with a cane and had difficulty walking on uneven surfaces or in poorly lit areas. The patient reported dizziness when erect. Tilt-testing revealed a drop in blood pressure from 120/90 mmHg when supine to 73/47 mmHg at 70 degrees tilt. Nausea occurred after 5 minutes and heart rate increased to 125 after 10 minutes at 70 degrees. A 24 hour electrocardiogram showed sinus tachycardia (average heart rate, 107/min). Echocardiography was normal. ¹²³I-MIBG scintigraphy revealed a heart-to-mediastinum ratio of 1.2, suggesting cardiac sympathetic denervation (Figure 2 B).

Family 2

IV:1

This man (video segment 5) developed gait and balance problems at the age of 25. When examined at age 36 years, the patient was able to walk unassisted but his gait was markedly ataxic. Blood pressure was 130/95mmHg supine and 100/80 erect, but there was no dizziness. The clinical course was very similar to that of the other patients reported here.

Summary

The disorder presented as a balance and gait disturbance with onset between ages 16 and 47. In these families there are instances where the disease developed at an earlier age in the generation following that of the affected parent, but also instances when symptoms occurred at a later age; there was no pattern of anticipation. Sensory neuropathy was prominent and

neurography suggested an axonal type. Autonomic neuropathy caused pronounced blood pressure instability in three patients and additional signs and symptoms in others. In several patients, mild upper or lower motor neuron signs were observed on clinical and neurophysiological examination. Horizontal saccades appeared markedly slowed and were clearly hypometric in others. Patients with severe saccadic pathology exhibited compensatory head thrusts as in ocular motor apraxia, others grimaced involuntarily when gaze direction was changed. Vision and color vision was normal, as were other parts of the neuro-ophthalmological examination. Four patients had dystonic features including dystonic foot posturing during movement, involuntary oromandibular movements during (slow) saccades, and mirror movements. These dystonic features were mild and not bothersome to the patients. Two patients had bilateral upper eyelid retraction. None of the patients had pathological nystagmus, disturbance of smooth pursuit or gaze fixation. No family member had chronic psychiatric symptoms, behavioral abnormalities or obvious cognitive dysfunction. The neurological signs and symptoms were slowly progressive. Neuroradiological examinations (Figure 2 A) showed mild to moderate cerebellar atrophy. The degree of cerebellar atrophy was proportional to disease duration, but even two decades after clinical disease onset, cerebellar atrophy was mild. Possible mild brain stem atrophy on MRT was found in one patient with long disease duration.

3.2 Genealogical investigations

From a co-author of the publication on Family 2 from 1978 (J-E O) [8], we learnt that none of the original information or samples had been retained (personal communication, cited with permission). We were able to trace the ancestors of the oldest known affected persons from Family 1 back to the 1870s and from Family 2 to the 1780s. Both families had ancestors who

lived in a small village near the city of Malmö in southern Sweden; individuals from Generation I of Family 1 and Generation I of Family 2 lived in this village. As some historical records were missing in public registries, a complete genealogical link could not be established between the two families.

3.3 Genetic findings

Conventional genetic testing revealed no pathogenic mutations. Additional next-generation genotyping identified a total of 315 variants in 115 ataxia genes examined. Seven of these were non-synonymous, frameshift, truncating or splice-site mutations with an allele frequency of <1% in published reference databases. After comparison with our in-house variant database, no variants remained in the ADCA genes examined, and only one novel heterozygous variant each in the *SACS* and the *ABHD12* genes. These were not considered of relevance as they are associated with autosomal recessive ataxias. Details are provided in Table 2.

4. Discussion

We describe a Swedish family with autosomal dominant cerebellar ataxia, which we believe represents a novel disease entity, based on the clinical characteristics and the exclusion of all relevant known ADCA-genes through extensive conventional and next-generation genetic screening. The clinical features in members of a second family, published in 1978 [8], are very similar, and we traced ancestors of both families back to the same small village in

southern Sweden. Although the lack of records makes it impossible to establish a definitive genealogical link between the two families, we consider it highly probable that Family 2 represents a branch of Family 1.

The disorder described here presented with a combination of cerebellar ataxia and additional neurological symptoms, similar to the majority of the already characterized ADCAs [2, 4, 10]. Peripheral neuropathy was the key additional finding in this family and is a relatively common additional finding among the ADCAs [11]. Neuropathy in ADCA is frequently axonal. It may occur in the more frequent subtypes SCA1, 2, 3, or 6, that were excluded by genetic testing in this family. Pronounced peripheral neuropathy also occurs in SCA4 [12], SCA18 [13], and SCA25 [14], for which the causative genes are not known. In SCA4, symptoms such as diplopia, gaze-evoked nystagmus and auditory impairments have been described, none of which were present in the families reported here [12]. SCA18 is characterized by cerebellar ataxia in combination with axonal sensory neuropathy, and pyramidal tract signs, motor neuron dysfunction and proximal weakness have been described. However, the six described subjects with SCA18 had either horizontal jerk nystagmus or saccadic low gain smooth pursuit, and while sensory deficit starts at an average of 16 years, ataxia did not occur before 45 years [13]. The phenotypes expressed by patients of the only known SCA25-family were very variable, including not only sensory neuropathy, but also hypermetric saccades and paroxysmal gastric pain, which were not observed in our Swedish families. Co-occurrence of the clinical features of Friedreich's ataxia and of Charcot-Marie-Tooth neuropathy has been described in three families, but the affected individuals were distributed in a pattern compatible with X-linked inheritance [15]. Ataxia and sensory neuropathy also defines Autosomal dominant sensory ataxia, a disorder described in one family and linked to the *SNAX1* locus on chromosome 8, but neither cerebellar nor autonomic

symptoms occurred [16]. Mutations in *DNMT1* may cause autosomal dominant cerebellar ataxia, deafness, narcolepsy, neuropathies, and the original patients were described in Sweden [17]. However, none of our patients had hearing problems, narcolepsy, or the marked cognitive decline that is also part of *DNMT1*-associated disease.

There are rare reports of patients with SCA3 who had ataxia and orthostatism (reviewed in ref. [18]). Orthostatic hypotension and ataxia are also found in multiple system atrophy (MSA). Definite MSA with autosomal dominant inheritance has been described [19-22], but by convention a positive family history excludes this diagnosis. It has been discussed whether ADCA, Parkinsonism and orthostatic hypotension in an English family [23] may represent an unusual form of ADCA rather than familial MSA [18]. We noted head tremor in one member of the present Swedish families, but there was no parkinsonism. The slow progression in these Swedish families argues against MSA.

We consider the primary eye movement abnormality in this family to be hypometric saccades. It has been pointed out that clinical examination cannot always distinguish between slowing of saccades and series of hypometric saccades that have normal velocity and occur in rapid succession [24]. Hypometric saccades and ocular motor apraxia are well-known features in recessive ataxias, but are not usually encountered in ADCAs [24]. Slowing of horizontal saccades is a typical finding in SCA2 or 7, and may occur in SCA1 or 3 [1, 24, 25]. In Scandinavia, SCA7 may be relatively common [26], but all of these diagnoses were excluded by genetic testing in both families described here. A Scandinavian origin for a founder mutation in *POLG* has been postulated [28], and mutations in this gene may cause ataxia in progressive external ophthalmoplegia [29], but no mutation was found in this gene in the patients presented here. Furthermore, none of the patients described here had any visual deficit or external ophthalmoplegia, signs that frequently occur in SCA7 or in *POLG*-linked

ataxia [29, 30]. Recently described, SCA37 includes prominent eye movement abnormalities, but vertical abnormalities occur early in that disorder and the phenotype of SCA37 is otherwise that of pure cerebellar ataxia [27].

On clinical grounds, the disorder in these two most likely related families cannot be classified as any of the known subtypes of ADCA. The disorder affected men and women in successive generations in a pattern indicating monogenic autosomal dominant inheritance, and there was no evidence for anticipation. Genetically, it has not been possible to detect any known ADCA-mutation, despite extensive screening, including a newly developed next-generation sequencing approach targeted to 115 known ataxia genes. We therefore suggest that the patients described here present with a novel disease entity. It is to be hoped that the clinical characterization and the elucidation of the genetic cause will advance our understanding of mechanisms underlying the often devastating hereditary ataxias.

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Authors' roles

Klas Wictorin, MD, PhD: Conception, organization and execution of the research project, writing of the first manuscript draft and review and critique of subsequent manuscript versions.

Björn Brådvik, MD, PhD: Execution of the research project (clinical and genealogical analyses), review and critique of the manuscript.

Karin Nilsson, RN, PhD: Execution of the research project (genealogical research), review and critique of the manuscript.

Maria Soller, MD, PhD: Execution of the research project (genetic analyses), review and critique of the manuscript.

Danielle van Westen, MD, PhD: Execution of the research project (reading and analysis of MR images), review and critique of the manuscript.

Gunnel Bynke, MD, PhD: Execution of the research project (neuro-ophthalmological analysis), review and critique of the manuscript.

Peter Bauer, MD, PhD: Execution of the research project (genetic analyses), review and critique of the manuscript.

Ludger Schöls, MD, PhD: Execution of the research project (genetic analyses), review and critique of the manuscript.

Andreas Puschmann, MD, PhD: Conception, organization and execution of the research project, review and critique of the manuscript.

Relevant conflicts of interest/financial disclosures

None.

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Table Legends

Table 1: Overview of symptoms and signs

BD, balance disturbance; CA, cerebellar atrophy, graded as described in Methods; DD, disease duration; EPR, extensor plantar reflex; MIBG-scint, thoracic I¹²³-metaiodobenzylguanidine scintigraphy; M, motor neuropathy in EMG; NA, not assessed; OH, orthostatic hypotension; OMA, ocular motor apraxia; prop, proprioception; S, sensory neuropathy in EMG; temp, temperature; vib, vibration; WMC, white matter changes, graded acc. to Fazekas, noted where present [7].

Table 2: Genetic Analyses

Summary of the extensive genetic screening of relevant ataxia genes. A full list of all genes examined by NGS is provided in esupp1. No pathogenic mutations were detected; † denotes novel heterozygote sequence alteration (see text).

AR, autosomal recessive; Conventional, genetic testing performed on clinical basis with conventional methods, i.e. excluding next-generation sequencing approaches; EA, Episodic ataxia; FXTAS, Fragile X tremor/ataxia syndrome; NGS, next generation sequencing (see text for details); PEOA1, Progressive external ophthalmoplegia, autosomal dominant; PEOB, Progressive external ophthalmoplegia, autosomal recessive; PHARC, Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (autosomal recessive); ARSACS, Autosomal recessive spastic ataxia of Charlevoix-Saguenay.

Figure Legends

Figure 1 A and B: Pedigrees of Family 1 and Family 2.

Black symbol, affected; white symbol, not affected; circle, female; square, male. For reasons of confidentiality, gender was disguised for some unaffected individuals (diamond-shaped symbols), sibling order was altered in some instances and additional unaffected individuals were omitted.

Figure 2 A: MRI scans showing cerebellar atrophy of various degrees, proportional to disease duration. The degree of cerebellar atrophy was visually graded as “+” (mild) in Family 1, patient III:4, “+++” (marked) in III:1, and “++” (moderate) in Family 2, patient IV:1. Slight atrophy of the brainstem may also be present (not graded). From Family 1, MRI was available from five individuals and CT from three individuals, from Family 2, MRI was available from one individual; grading may have been biased due to larger slice thickness in CT and some MRIs. **Figure 2 B: MIBG scintigraphy** from patient III:4 (Family 1) at age 34, showing reduced radiotracer binding 4 hours after injection in the heart with a heart-to-mediastinum ratio of 1.2, indicating cardiac sympathetic denervation.

Appendix: Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/>:

esupp1: List of Genes examined by Next-Generation-Sequencing, coverage, individuals tested genetically

esupp2: Detailed clinical descriptions

Video: This video shows aspects of the neurological disease in four individuals from Family 1 and one patient of Family 2. The patient with the mildest symptoms and shortest disease duration (III:4, segment 1) is shown first, followed by III:3 (segment 2) and III:1 (segment 3) with increasing disease severity and duration, and II:4 (segment 4) who has severe disease. Finally, the eye movements and speech disturbance of patient IV:1 from Family 2 are shown (segment 5).

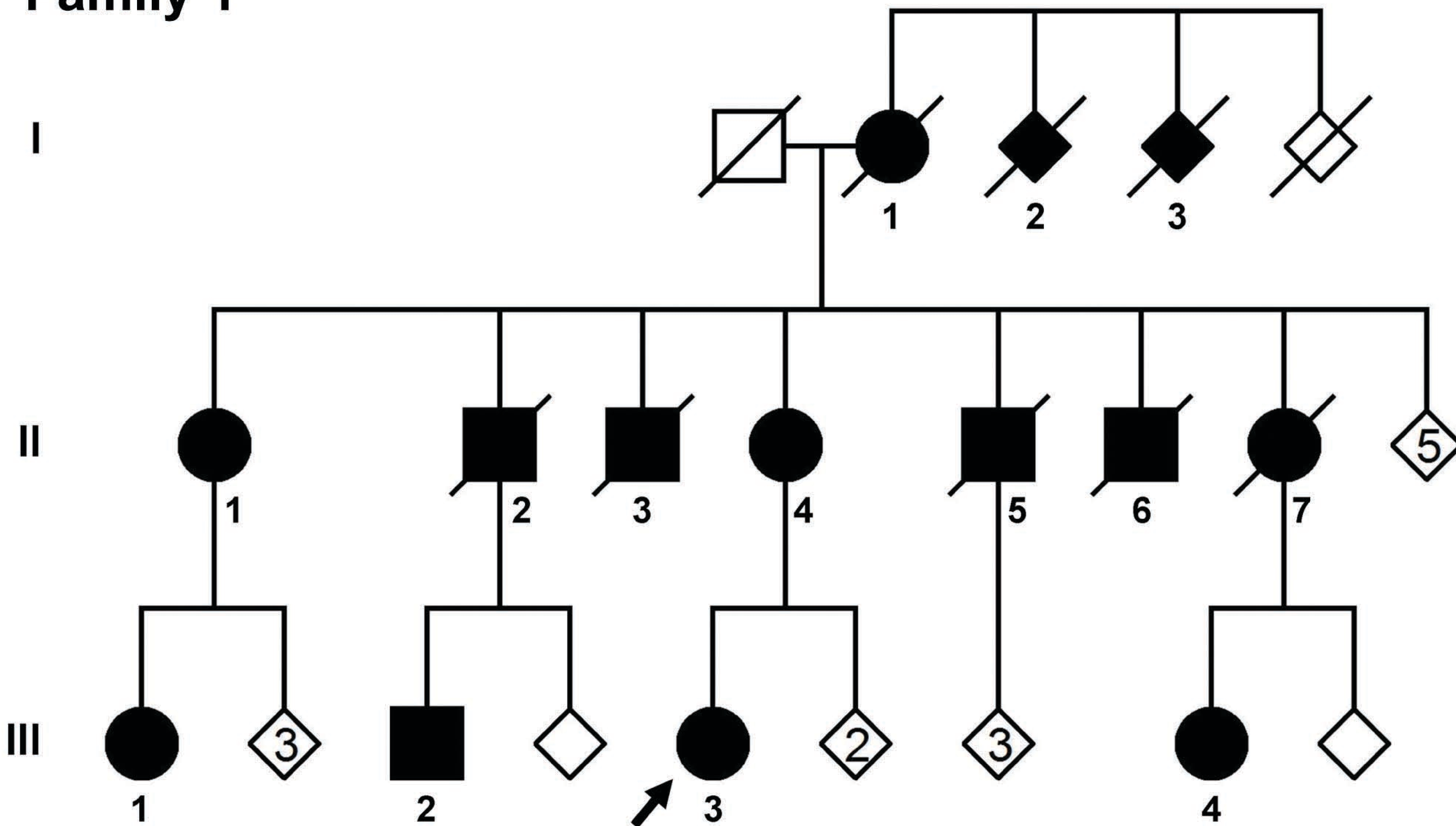
Table 1: Overview of symptoms and signs

	Family 1: II:1	II:2	II:4	II:5	III:1	III:3	III:4	Family 2: IV:1
Gender	Female	Male	Female	Male	Female	Female	Female	Male
Age of onset	47	36	33	32	37	16	31	25
Age at examination	78	70	67	60	56	37	35	37
Initial symptom(s)	BD, numbness in feet	BD, intention tremor	BD	BD	BD, impaired dexterity	BD	BD, difficulty to ride bicycle	BD
Gait ataxia	Wheelchair	Wheelchair	Severe	Wheelchair	Severe	Severe	Moderate	Moderate
Limb ataxia	Moderate	Moderate	Severe	Severe	Mild	Moderate	Mild	Mild
Dysarthria	Moderate	Moderate	Severe	Moderate	Mild	Moderate	Mild	Moderate
Horizontal saccades	NA	NA	Slow/ hypometric; head thrust (OMA)	NA	Slow/ hypometric	Hypometric; head thrust (OMA)	Slow/ hypometric	Hypometric
Reduced sensibility	++ (vib, prop)	++ (vib)	+++ (vib)	++ (touch, pain, vib, prop)	+++ (vib)	+++ (vib, pain)	++ (vib, pain, touch, temp)	+ (vib, temp)
Neurophysiology	NA	NA	S (axonal), mild M	NA	NA	S (axonal)	SM (axonal)	NA
Tendon reflexes	Absent	Absent	Absent	NA	Absent	Absent	Absent; EPR	Absent; EPR
Muscle wasting	Generalized	Pronounced, generalized	Not obvious	Pronounced	Not obvious	Not obvious	Moderate	Moderate
Dysautonomia	Urinary urge incontinence	None	None	Erectile dysfunction	Severe OH, abnormal blood pressure fluctuations	Severe Neurogenic OH	Neurogenic OH. Idiopathic sinus tachycardia. MIBG-scint: H/M ratio 1.2	OH
Additional symptoms, signs	Head tremor; dysphagia	Transient fasciculations	Mild foot dystonia	Paraparesis, reduced muscle strength and increased tone in arms; dysphagia	Involuntary grimacing during saccades	Mirror movements; postprandial diarrhea		Involuntary grimacing during saccades; postprandial diarrhea
CT/MRI (age in years)	CA +++, WMC 2 (CT 76)	CA ++ (CT 72)	NA	CA +++ (MRI 60)	CA +++, WMC 3 (MRI 57)	CA +++ (MRI 32)	CA + (MRI 33)	CA ++ (MRI 37)

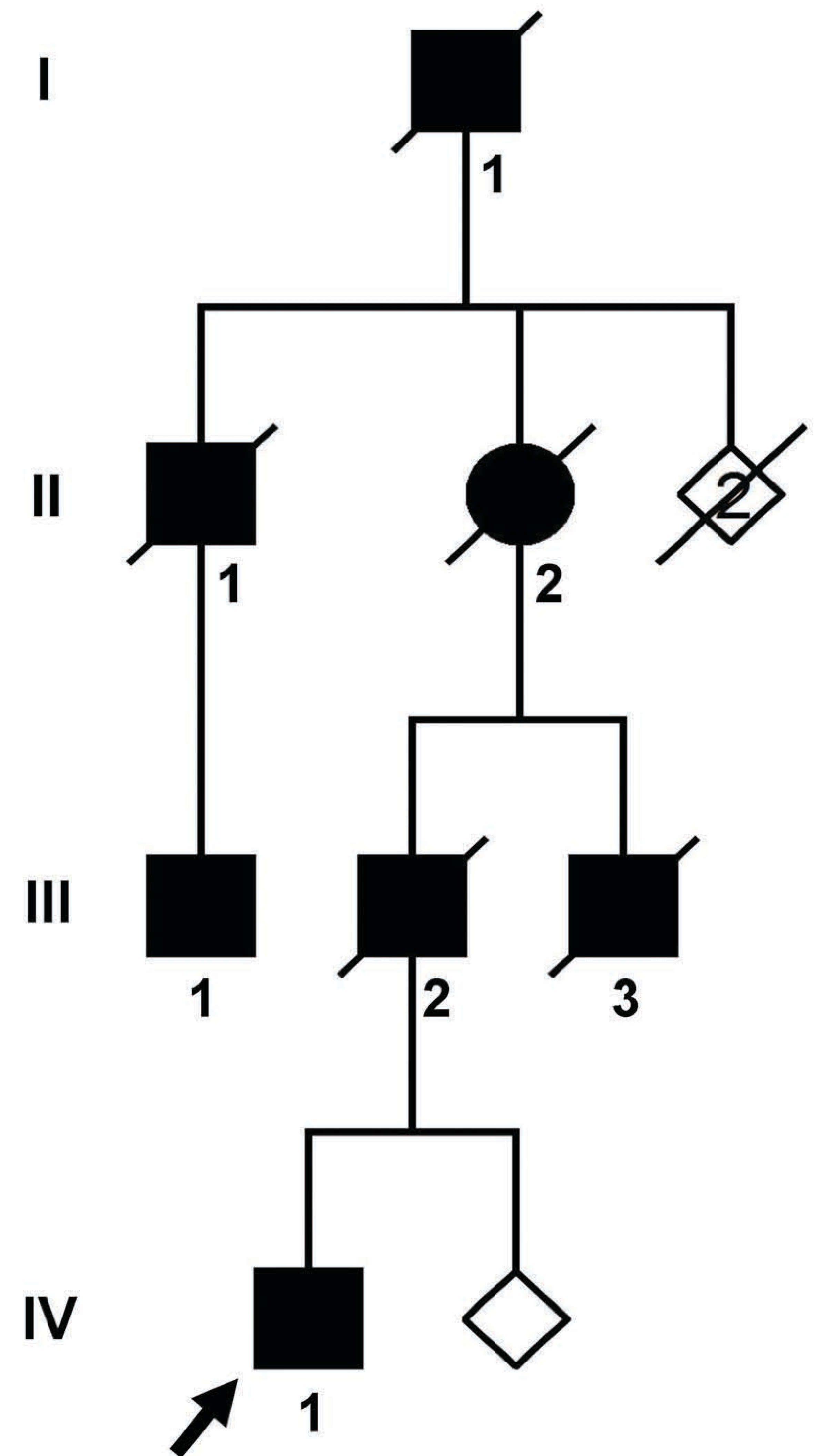
Table 2: Genetic Analyses

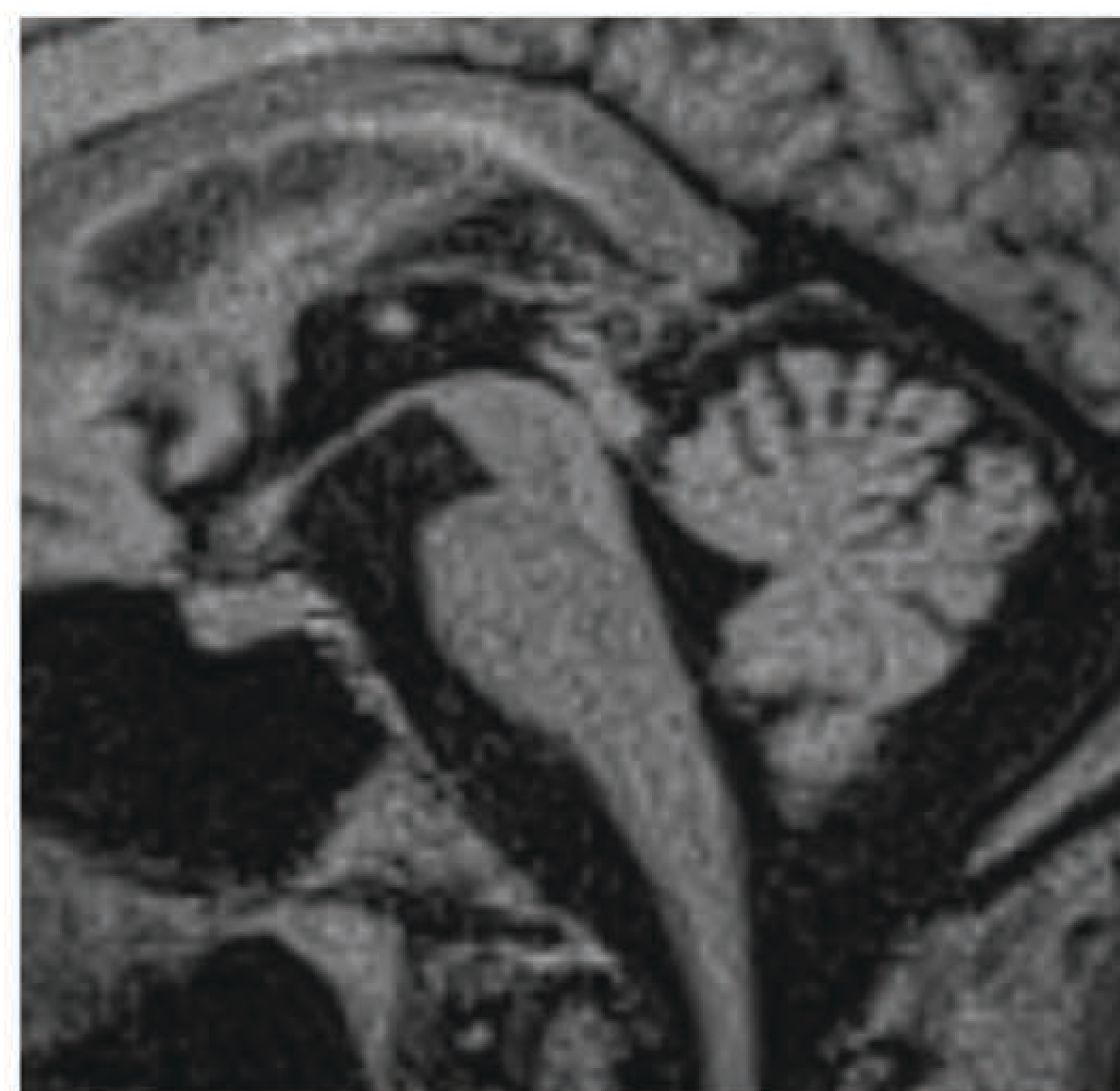
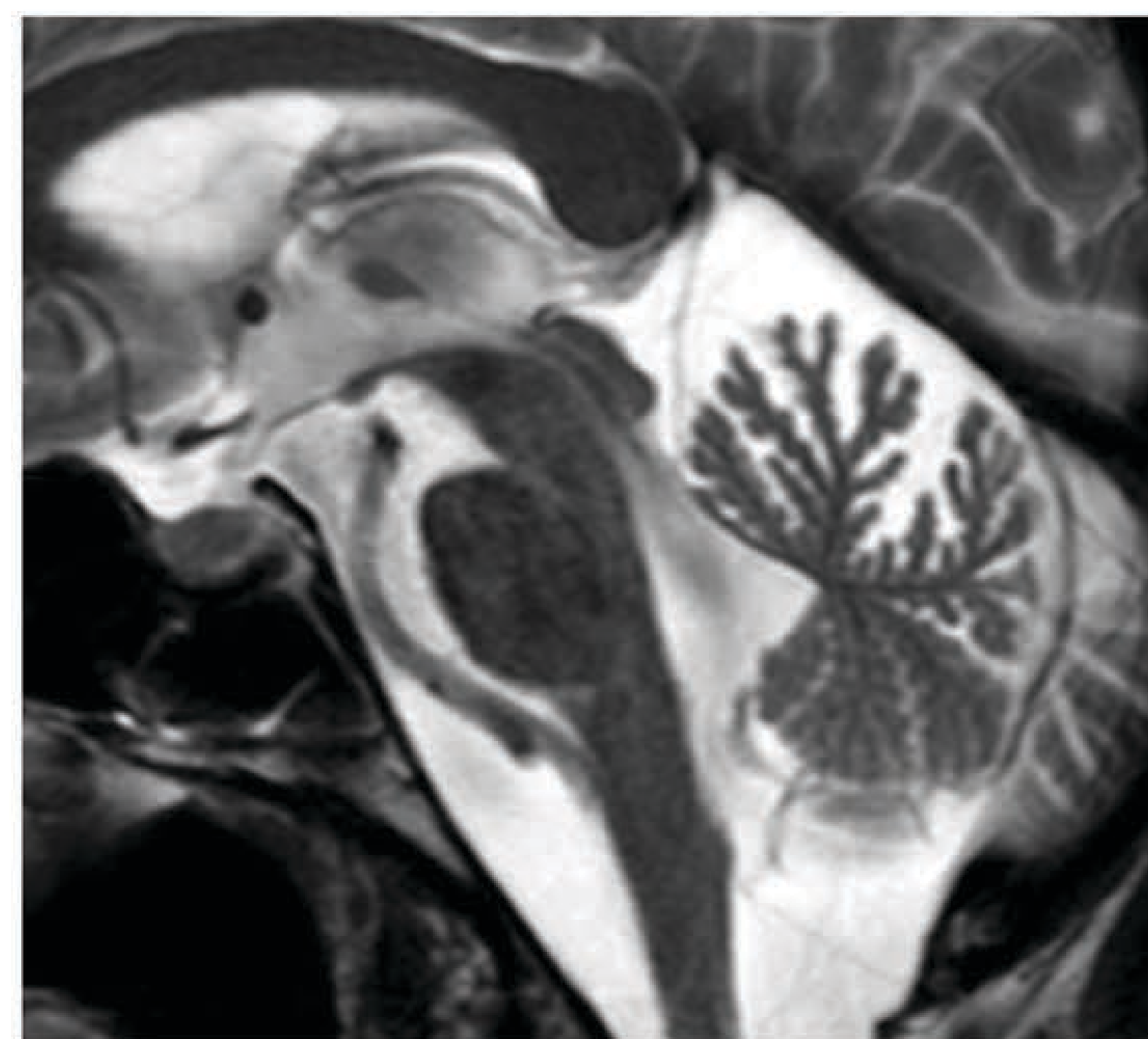
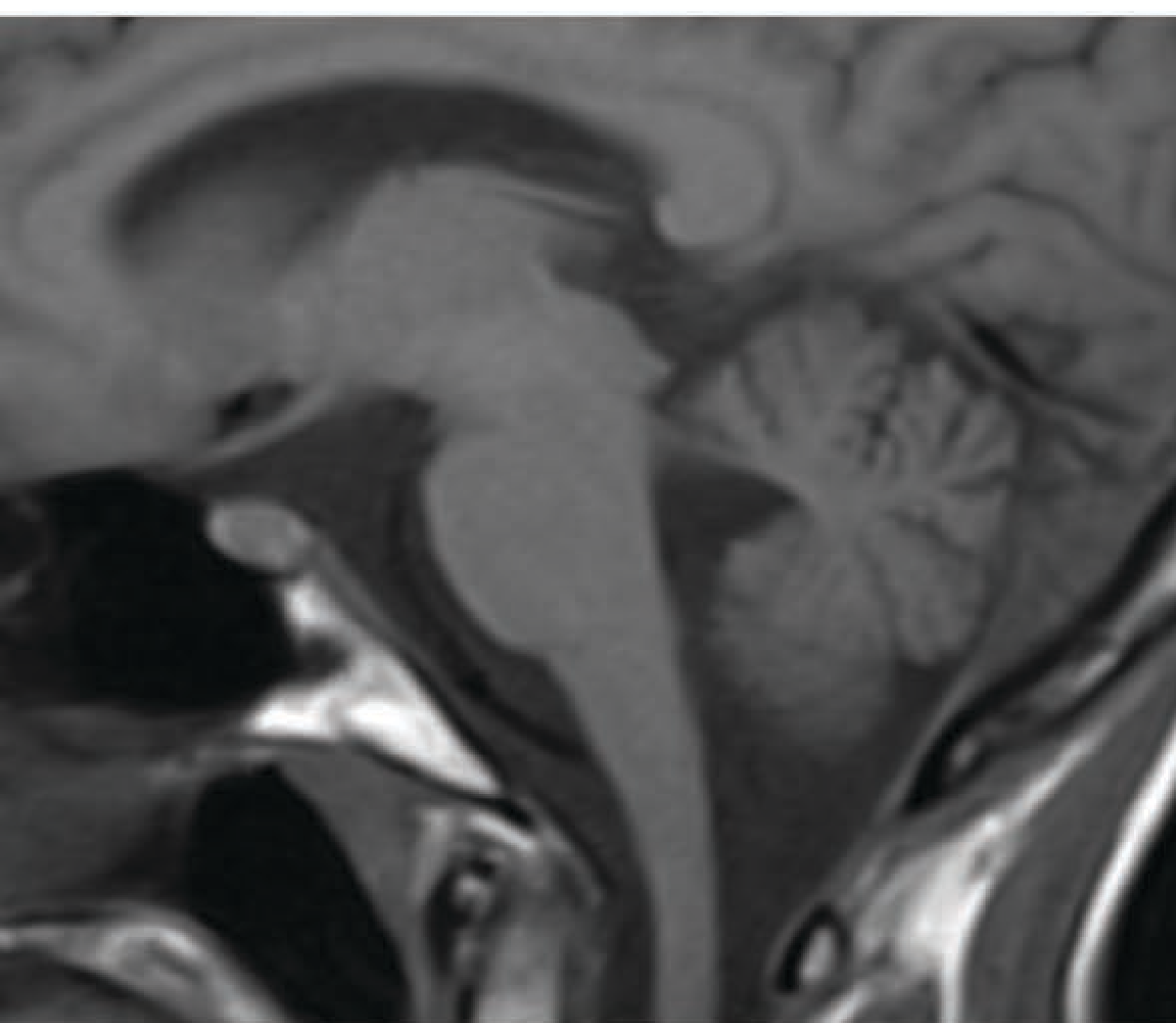
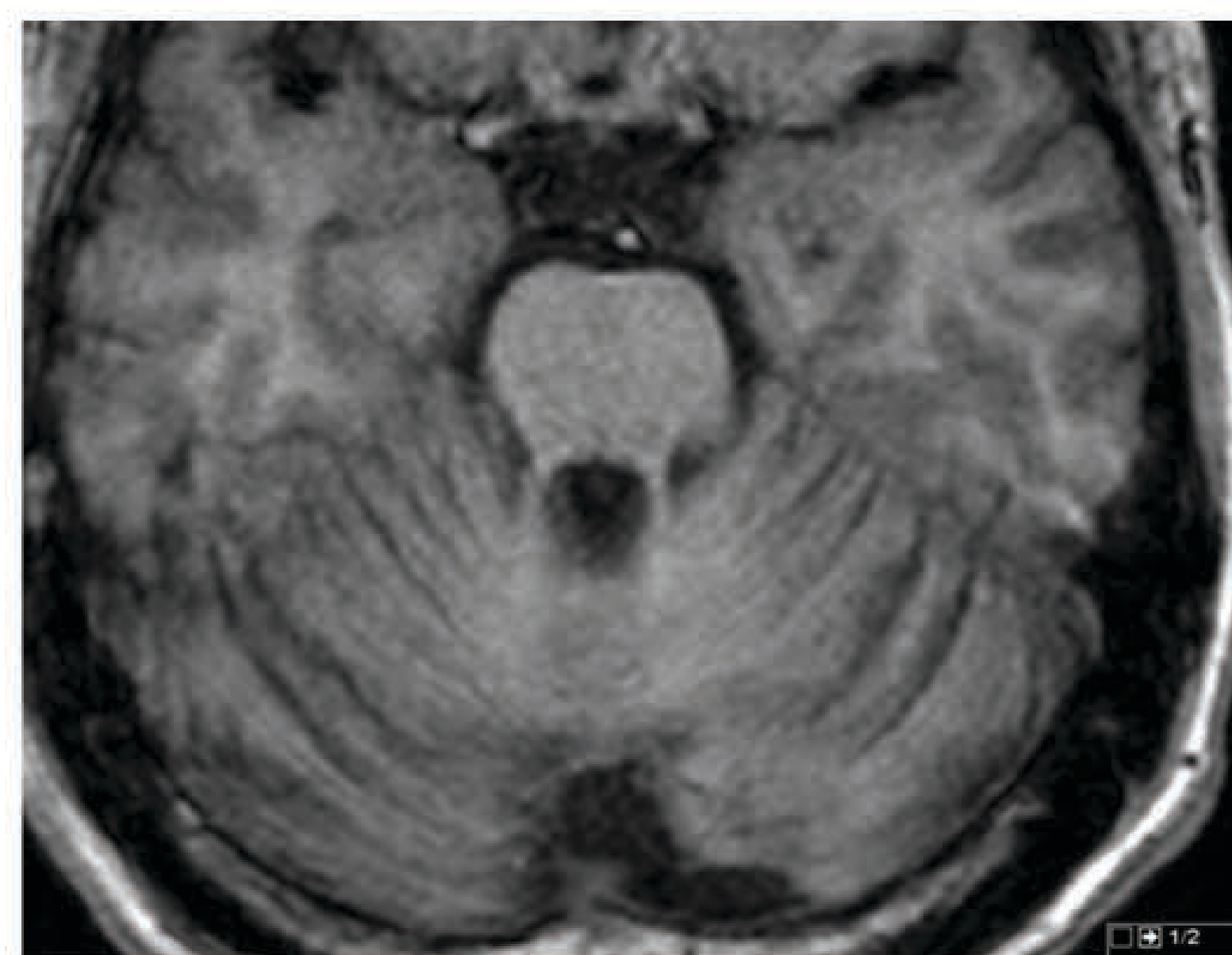
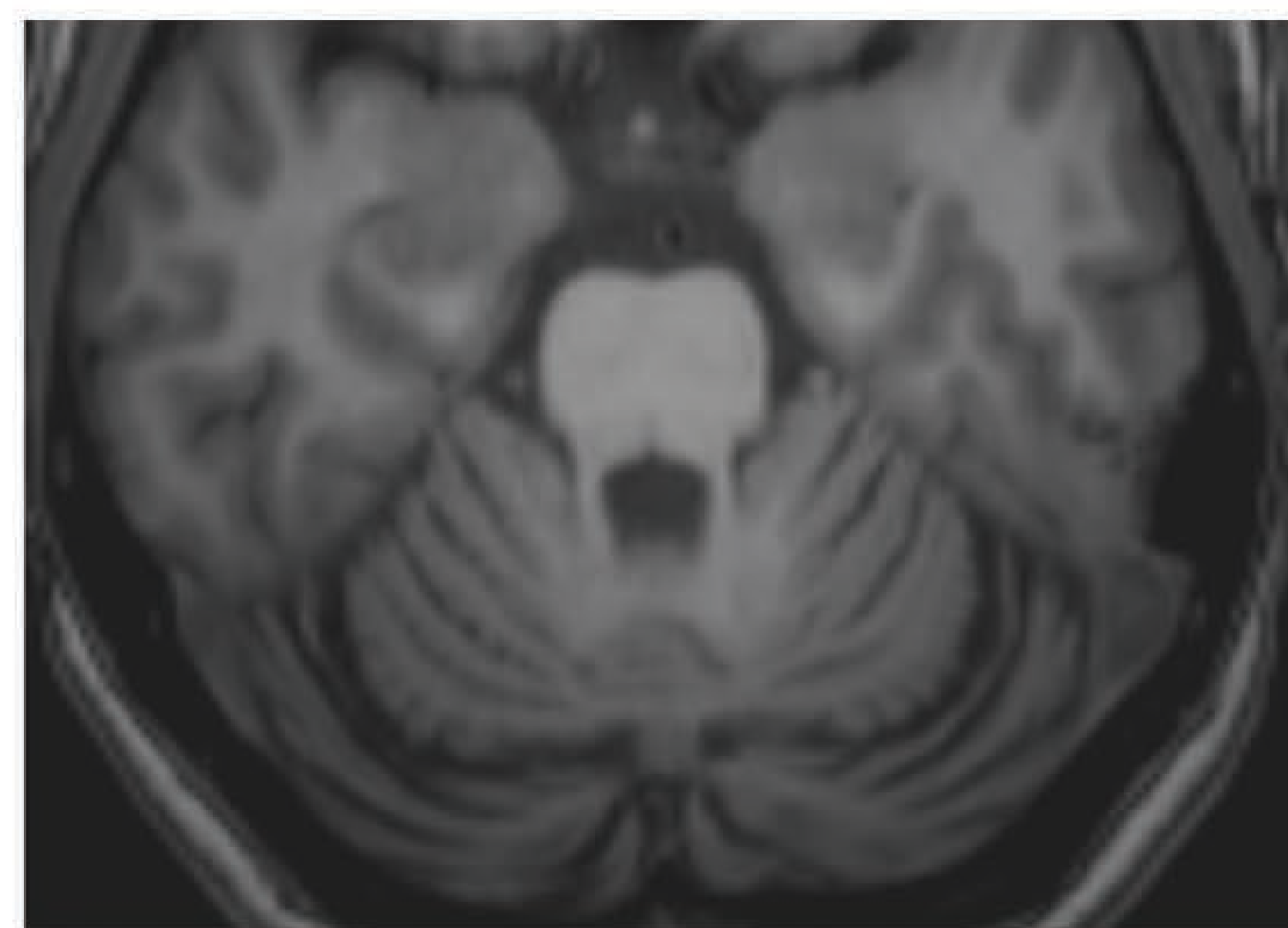
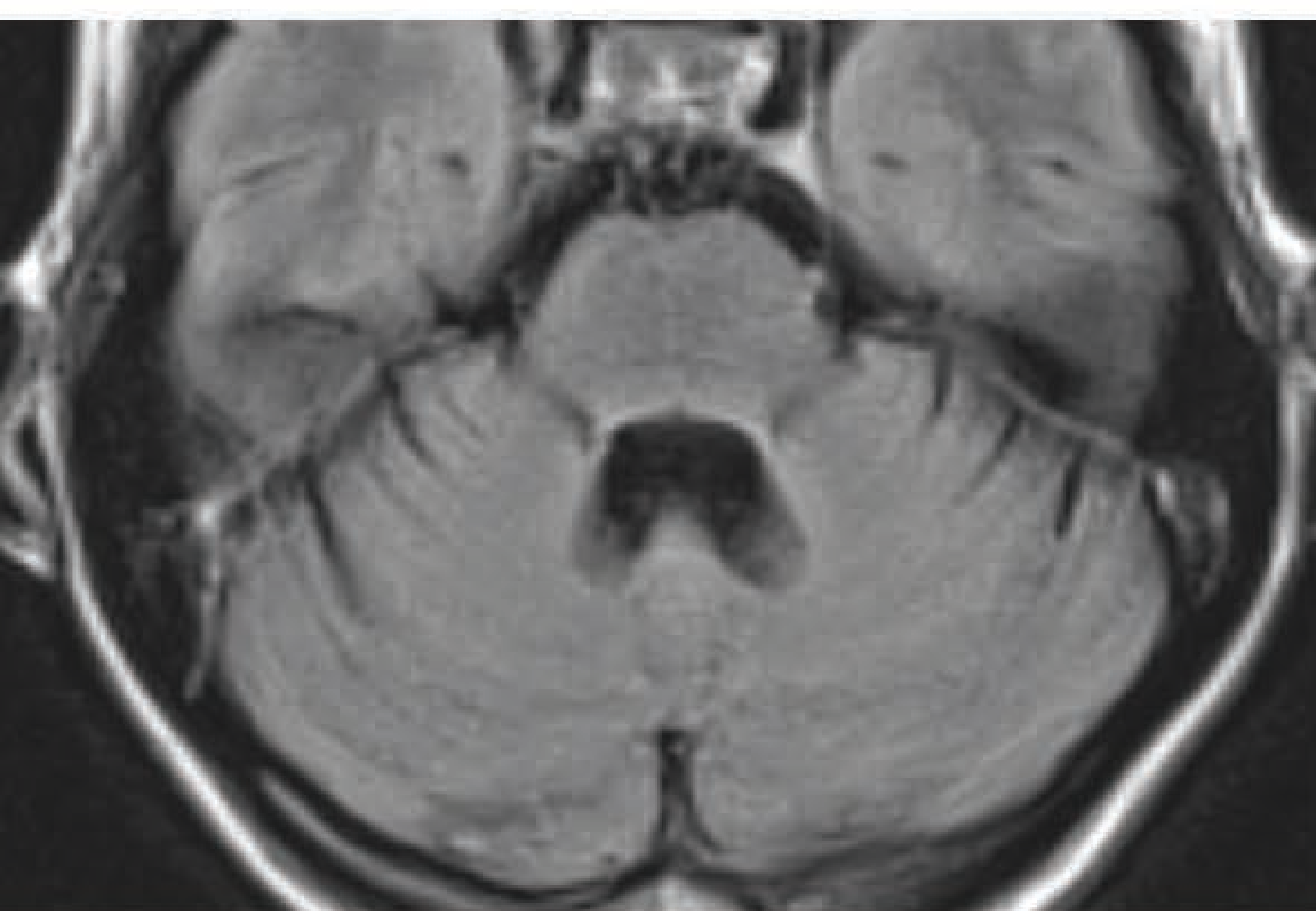
Ataxia subtype	Gene	Method
SCA1	<i>ATXN1</i>	Conventional
SCA2	<i>ATXN2</i>	Conventional
SCA3	<i>ATXN3</i>	Conventional, NGS
SCA5	<i>SPTBN2</i>	NGS
SCA6	<i>CACNA1A</i>	Conventional
SCA7	<i>ATXN7</i>	Conventional
SCA8	<i>ATXN8OS</i>	Conventional
SCA10	<i>ATXN10</i>	Conventional
SCA11	<i>TTBK2</i>	NGS
SCA13	<i>KCNC3</i>	NGS
SCA14	<i>PRKCG</i>	NGS
SCA15/16	<i>ITPR1</i>	NGS
SCA17	<i>TBP</i>	Conventional
SCA23	<i>PDYN</i>	NGS
SCA27	<i>FGF14</i>	NGS
SCA28	<i>AFG3L2</i>	NGS
EA1	<i>KCNA1</i>	NGS
EA2	<i>CACNA1A</i>	NGS
PEOA1, PEOB	<i>POLG</i>	Conventional
FXTAS	<i>FMR1</i>	Conventional
Friedreich ataxia	<i>FXN</i>	Conventional
PHARC	<i>ABHD12</i> [¶]	NGS
ARSACS	<i>SACS</i> [¶]	NGS
	<i>Additional 103 AR and X-linked ataxia genes (esupp1)</i>	NGS

Family 1



Family 2

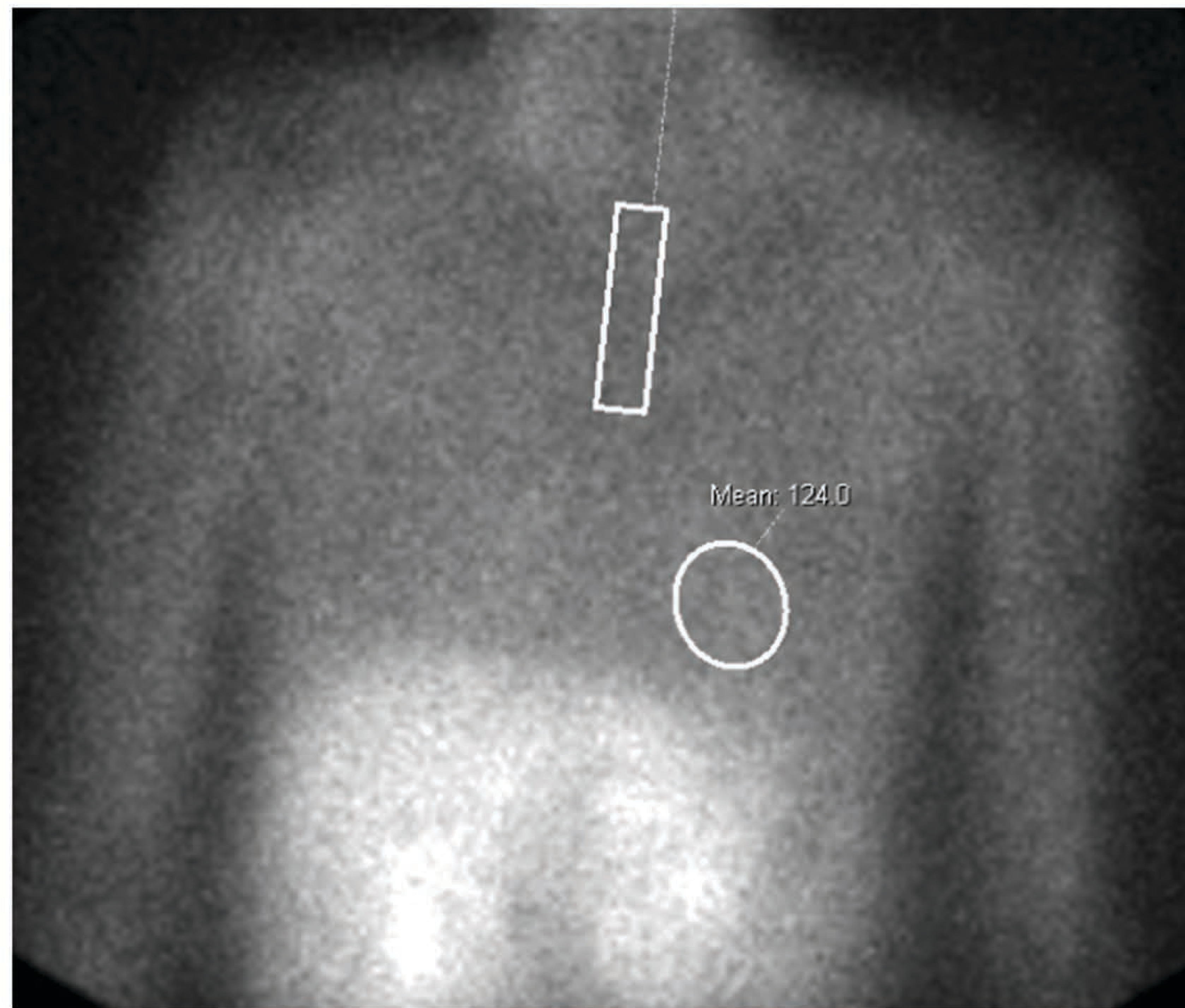


A

Family 1
III:4

III:1

Family 2
IV:1

B

Family 1
III:4

Autosomal dominant cerebellar ataxia with slow ocular saccades, neuropathy and orthostatism: A novel entity?

Klas Wictorin, Björn Brådvik, Karin Nilsson, Maria Soller, Danielle van Westen, Gunnel Bynke, Peter Bauer, Ludger Schöls, Andreas Puschmann

esupp 1: Genetic Analyses

A: List of Genes examined by Next-Generation-Sequencing:

ABCB7	ATXN7	DDB2	GBE1	MTTP	PNPLA6	SYNE1
ABHD12	BIVM, BIVM-ERCC5	DLAT	GCDH	NEU1	POLG	SYT14
ADCK3	BIVM-ERCC5, ERCC5	DNAJC19	GCLC	NPC1	POLH	TAPBPL, VAMP1
AFG3L2	C12orf29, CEP290	EEF2	GLB1	NPHP1	POLR3A	TDP1
AHI1	CA8	EIF2B1	GPR56	OPA1	POLR3B	TMEM67
ALAS2	CACNA1A	EIF2B3	GRM1	OPA3	PRKCG	TRPC3
ALG6	CACNB4	EIF2B5	HEXB	PAX6	RARS2	TSEN2
ANO10	CC2D2A	EPM2A, LOC100507557	HPRT1	PDHX	RELN	TSEN34
ARL13B	CELF6, HEXA	ERCC2	INPP5E	PDSS1	RPGRIP1L	TSEN54
ARSA	CEP290	ERCC3	ITPR1	PDSS2	RRM2B	TTBK2
ATCAY	CLN5	ERCC4	KCNA1	PEX10	SACS	TTPA
ATM	CP	FGF14	KCNC3	PEX7	SETX	VPS13A
ATM, C11orf65	CRAT	FLJ35024, VLDLR	KIAA0226	PHYH	SIL1	VRK1
ATP2B2	CSH1	FLVCR1	KIF5C	PIK3R5	SLC17A5	WFS1
ATP2B3	CSH2	FXN	L2HGDH	PLA2G6	SLC19A3	WWOX
ATP7B	CYP27A1	GALC	MRE11A	PLEKHG4	SPR	XPA
ATXN3	DARS2	GBAP1, GBA	MTPAP	PMM2	SPTBN2	XPC
					n/a (chr 19)	ZNF592

B: Coverage, tested individuals

Ataxia subtype	Gene	Method	Coverage	Individual tested	Result
SCA1	ATXN1	Conventional		F1 II:1, II:5; F2 IV:1	Normal number trinucleotide repeats
SCA2	ATXN2	Conventional		F1 II:1, II:5; F2 IV:1	Normal number trinucleotide repeats
SCA3	ATXN3	Conventional, NGS		F1 II:1, II:5; F2 IV:1	Normal number trinucleotide repeats
SCA5	SPTBN2	NGS	>99%	F1 III:3	No novel variant considered to be pathogenic*
SCA6	CACNA1A	Conventional		F1 II:1, II:5; F2 IV:1	Normal number trinucleotide repeats
SCA7	ATXN7	Conventional		F1 II:1, II:5; F2 IV:1	Normal number trinucleotide repeats
SCA8	ATXN8OS	Conventional		F1 II:1, II:2, III:3; F2 IV:1	Normal number trinucleotide repeats
SCA10	ATXN10	Conventional		F1 II:1, II:2	Normal number pentanucleotide repeats
SCA11	TTBK2	NGS	>92%	F1 III:3	No novel variant considered to be pathogenic*
SCA13	KCNC3	NGS	61%**	F1 III:3	No novel variant considered to be pathogenic*
SCA14	PRKCG	NGS	>98%	F1 III:3	No novel variant considered to be pathogenic*
SCA15/16	ITPR1	NGS	100%	F1 III:3	No novel variant considered to be pathogenic*
SCA17	TBP	Conventional		F1 III:3	Normal number trinucleotide repeats
SCA23	PDYN	NGS	100%	F1 III:3	No novel variant considered to be pathogenic*
SCA27	FGF14	NGS	100%	F1 III:3	No novel variant considered to be pathogenic*
SCA28	AFG3L2	NGS	100%	F1 III:3	No novel variant considered to be pathogenic*
EA1	KCNA1	NGS	100%	F1 III:3	No novel variant considered to be pathogenic*
EA2	CACNA1A	NGS	>95%	F1 III:3	No novel variant considered to be pathogenic*
PEOA1, PEOB	POLG	Conventional		F1 III:3	No pathogenic sequence alterations
FXTAS	FMR1	Conventional		F1 III:3	Normal number trinucleotide repeats
Friedreich ataxia	FXN	Conventional		F1 II:5	Normal number trinucleotide repeats
PHARC	ABHD12	NGS		F1 III:3	Novel heterozygote sequence alteration
ARSACS	SACS	NGS		F1 III:3	Novel heterozygote sequence alteration
Additional 103 AR and X-linked ataxia genes (see esupp 1A)		NGS		F1 III:3	No novel variant considered to be pathogenic*

Coverage rates are provided for >20 reads for every position of the gene's entire coding region.

**The KCNC3 gene is only partly covered due to extended homology regions in the human genome. F, Family.

Autosomal dominant cerebellar ataxia with slow ocular saccades, neuropathy and orthostatism: A novel entity?

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esupp 2: Detailed Clinical Descriptions

This supplement includes additional clinical details on patients described in the main text, as well as clinical data on family members not described in the main text.

Family 1:

I:1

This woman developed symptoms at an age of 40 years and was wheelchair-dependent at age 50. A diagnosis of *ataxia cerebellaris* was made at a medical hospital in the 1970's. She became confined to a wheelchair in her fifties and died in her seventies. Both of I:1's parents reportedly died at a young age during the 1918-1920 influenza pandemic.

I:2

This male individual was examined for neurological symptoms at a hospital.

II:1

This female patient was examined for the first time at the age of 48 years when she had experienced numbness in her feet and balance problems for one year. Neurography showed reduced nerve conduction velocity and probable cerebellar atrophy was seen on CT. She was again seen at age 54 when slight dysarthria and head tremor were present. She was unable to perceive passive upward or downward movements of her toes and lost equilibrium during Romberg's test. The patient developed clumsiness in her hands and at age 58 would drop objects she held. Alternating hand movements were slowed and there was dysmetria in finger-to-nose and knee-tibia tests. Because of her neurological symptoms she retired prematurely from her manual occupation at age 58. At 63 years, she used a walker for short distances, but was otherwise dependent on a wheelchair. She had urinary urge incontinence. Neurological examination revealed slight dysarthria, head tremor, action tremor in upper extremities, ataxia of gait and stance, reduced sensibility for proprioception and vibration in lower legs. At the age of 64 years, she was unable to perform household chores or selfcare due to ataxia. Dysphagia developed at age 66. At age 71 the patient had general muscular atrophy.

II:2

This man developed balance difficulties at the age of 36 years and dysarthria four years later. Neurological examination at the age of 45 years revealed generalized fasciculations in arms and legs, especially in proximal limbs. Musculature was hypotrophic and muscle tone was increased. There was intention tremor in both hands. Gait was broad-based and there was moderate ataxia with knee-tibia testing. Touch and vibration sense was reduced in both legs. At the age of 46 years, this patient was unable to continue with his manual work. At the age

of 65 years, the patient had become wheelchair bound but repeatedly fell from his wheelchair. There was no nystagmus.

II:4

This woman experienced balance disturbance at the age of 33 years. When last examined at age 67, she scored 43 points in the ICARS ataxia scale. Marked dysarthria made communication difficult at times. She was wheelchair-bound, had pronounced dystaxia and dysmetria in finger-to-nose test and knee-tibia test. There were involuntary movements in the limbs and head that were not rhythmic and were interpreted as manifestations of severe ataxia. Intention tremor was seen during finger-to-nose test. There was mild scoliosis, areflexia, normal muscle tone, and no cognitive deficit. Mild dystonic posturing of the feet was seen during movements. Vibration sense was absent in the feet and lower legs. Clinical examination of eye movements revealed marked slowing and hypometria of horizontal, but not of vertical, saccades. The patient rapidly turned her head to look sideways. There was no N.III, IV or VI palsy, nystagmus, or fixation instability. The patient had no symptomatic orthostatic hypotension. This patient confirmed that her mother and two of her mother's three siblings had had very similar symptoms. Electroneurography at age 50 revealed complete lack of sensory nerve action potentials; normal motor responses, and there were mild neurogenic changes in needle EMG.

II:5

This man noticed balance and gait disturbance at age 32. Thereafter, this progressed slowly. When examined at age 52, there was ataxia, sensibility for touch, pain, vibration and proprioception was reduced in extremities, moderate dysarthria, and mild to moderate dysphagia. He had bothersome numbness and tingling in the extremities, and urinary incontinence. At age 60, he had become wheelchair bound and needed the assistance of two persons to rise from a chair.

II:7

This woman had severe disease but never wished to undergo any neurological evaluation. She died at the age of 44 years due to complications of her neurological illness.

III:1

This woman started noticing a balance and gait disturbance when she was 37 years old. Soon thereafter she experienced reduced dexterity with manual fine motor tasks. These symptoms worsened slowly but steadily. At 45 years of age, she needed her husband's support to walk outside her home, had troublesome clumsiness in her hands and reduced skin sensitivity in her feet. She also experienced tingling sensations in her hands and was unable to walk in darkness. On examination, there was slight dysmetria in finger-to-nose testing, areflexia, and loss of vibration sense, tested with a tuning fork, from the patella and distally. There was mild (4/5) motor weakness in proximal leg and in hand muscles. Gait difficulties were obvious. Neurography showed lack of sensory responses in upper and lower extremity fibers but normal motor responses. She has been unable to work since age 46 because of her neurological symptoms. When examined at age 56, she was only able to walk short distances with a walker and assistance, otherwise needed to use a wheelchair. Writing and using cutlery had become very difficult. She had a mild dysarthria of cerebellar type. She had experienced episodes of dizziness that occurred when she was sitting, and she had very

variable blood pressure, ranging from 160/120mmHg in the morning to 55/44mmHg in the evening. However she did not report any episodes of syncope. She reported a certain decrease in her vision, but had good visual acuity on examination. She correctly identified 13 of 16 panels in an abbreviated version of the Ishihara Color Vision test, considered a normal result. There was mild atrophy of the musculature of feet and hands. There was no gaze-induced nystagmus and there were no gaze fixation abnormalities. The speed of horizontal saccades appeared mildly decreased and the patient displayed involuntary grimacing of the lower facial muscles when she was asked to direct her gaze sideways. Involuntary blinking occurred when testing for ocular smooth pursuit. There was only mild dysmetria in finger-to-nose test with open eyes; dysmetria was more pronounced with eyes closed. Mild dysdiadochokinesia was noted in the hands. With considerable support of one person, the patient was able to rise from the wheelchair and with continued support could go a few steps. Gait was very broad-based and there was risk for falling. There was no tremor or Parkinsonism. Sensibility for vibration was entirely absent in extremities and sternum. Proprioception, assessed by passive movements of her first toes or thumbs, was entirely absent. Pinprick sensibility was reduced in upper and lower extremities. The patient reported that she seems to experience warmth or cold with a latency, which has led to skin burns, but on examination was able to feel the temperature of a cool metal object placed on her hands or feet.

III:2

According to family history, this man had very similar symptoms, but contact with the investigators of this study was not established.

III:3

This woman developed a slight disturbance of balance and gait at the age of 16. This remained stable for several years. A neurography was performed during an educational activity in which the patient participated when she was in her early 20s. According to the patient this showed an abnormal result. At around the age of 25-30 years, she experienced gradually worsening symptoms with reduced sensitivity in her fingers, and problems with coordination and balance. Symptoms became more marked from age 37 years, and included ataxia, balance problems as well asymptomatic falls in orthostatic blood pressure. Her general physical condition was reduced and she was very easily fatigued; she had become unable to work, perform household chores, to shop or drive a car.

On examination at age 38, the patient had 37 points in the ICARS scale. In neutral gaze position, both upper eyelids appeared retracted, and during eye movements, the sclera became visible above the iris (Collier sign). There was a marked slowing of horizontal saccades and mild slowing of vertical saccades. Horizontal saccades were markedly hypometric, and this was even more evident when the patient was asked to rapidly alternate gaze direction between right and left. Instead, the patient rapidly turned her head in order to look sideways. Abnormalities of gaze fixation were not observed. The patient had hyporeflexia and amyotrophy. During pronation-supination movements of one hand, mirror movements were observed in the contralateral hand, and there was dysdiadochokinesia. Knee-tibia test was performed jerkily and with lateral movements; finger-to-nose test showed moderate dysmetria and moderate intention tremor. Slight dystonia may have been present in the feet during goal-directed movements or when changing body position, and during gait. Muscle strength in hands, lower arms and feet was reduced. Tendon reflexes

were weak or entirely absent. Sensation for pinprick, touch and vibration was reduced in the lower legs and feet.

This patient had marked falls in blood pressure when erect and underwent a tilt test examination. Blood pressure decreased from 112/64 mmHg supine to 57/42 mmHg tilted to 70 degrees, with an increase in heart rate from 80 to only 85/min. This caused presyncope and was reproducible on repetition. Valsalva test was positive, indicating disturbance of the autonomic system. MIBG scintigraphy could not be performed as the patient was not considered able to be without her treatment with etilefrin, and fludrocortisone. The patient had also tried midodrine and droxydopa alone and in various combinations but experienced side effects or lack of beneficial effect.

This patient also had several years of problems with partially severe postprandial diarrhea, occurring 5-15 minutes after meals. Loperamide tablets improved the situation, but nevertheless the patient had developed severe weight loss and anemia when last seen at 40 years of age. There was mild dysphagia.

III:4

This patient was aware that a familial disease occurred in her family and had afflicted her mother, II:7. She (III:4) wished to undergo neurography at age 24, when she had no overt neurological symptoms. This neurography showed a lack of sensory responses in the median, ulnar, or sural nerves. Some motor units were enlarged. Clinical neurological examination at the same age revealed generalized areflexia. When examining muscle strength, muscle cramps were noted. These initiated investigations at a unit for muscle disorders, but no diagnosis could be established.

At the age of 31, the patient had become unable to ride a bicycle and needed to watch her feet when walking to avoid missteps. She still reported frequent muscle cramping. On examination she showed clear signs of ataxia with knee-tibia test and a broad-based gait. She experienced tingling sensations in her fingers and decreased dexterity. She appeared amyotrophic and had lost weight. A neurologist observed muscle cramps directly after muscular activity. The patient's voice had become dysarthric and had a nasal sound. She had episodes with panic attacks at the time of her mother's death and again when she had developed neurological symptoms, but did not develop any longstanding psychiatric, or cognitive, symptoms. Renewed electrophysiological examination at age 32 showed axonal sensorimotor polyneuropathy. Denervation activity was not found, indicating that progress was slow.

At 34 years of age, she walked with a cane and had difficulty walking on uneven surfaces or in poorly lit areas. There was mild amyotrophy in lower arms and legs. Horizontal saccades appeared slow and/or hypometric, there was no nystagmus. There were involuntary contractions of facial muscles when the patient directed her gaze sideways or when executing unrelated movements such as hand grips. Visual acuity and color vision were normal (16/16 panels correct). Gait was broad-based. The patient performed finger- to-nose test with only mild dysmetria with eyes opened, but developed about 5cm hypermetria when closing her eyes. Similarly, she was able to stand with eyes open, but lost balance after a few seconds when closing her eyes. Knee-tibia test was gravely atactic. There was generalized ataxia, and the plantar reflex had now become extensor. Sensibility for light touch, pinprick, and temperature was absent below the level of the middle lower legs, proprioception and vibration sense was decreased in lower legs or feet. All modes of sensibility were normal in upper extremities. Tilt-testing was performed to further

characterize this patient's neuropathy, and as she reported a tendency to dizziness when standing up. Testing revealed a blood pressure of 120/90 mmHg when supine, and a sinus tachycardia of with a heart rate of 107 / min. When tilted to 70 degrees, the patient's blood pressure decreased to 73/47 mmHg with the patient not noticing any symptoms. Only after 5 minutes, when blood pressure remained low, did the patient report nausea. Heart rate increased to 125 after 10 minutes at 70 degrees. Echocardiography was normal, and the patient had sinus tachycardia during a 24 hours electrocardiogram registration (average heart rate, 107/min). ¹²³I-MIBG scintigraphy revealed a heart-to-mediastinum (H/M) rate of 1.2, suggesting cardiac sympathetic denervation.

Family 2

III:2

Limited information on this man was retrieved from family history and medical records. At age 52 he was described as very atactic and sensibility for touch and vibration was reduced bilaterally in hands, forearms, and feet. He broke the neck of his femur and afterwards used a wheelchair. There was cerebellar dysarthria, deep tendon reflexes were absent but plantar response was extensor. There was a tendency to diarrhea after meals. At 53 years of age he was wheelchair-bound and required help to move from the wheelchair to another chair. There was hyporeflexia and reduced sensibility in arms and legs.

IV:1

This man developed gait and balance problems at the age of 25. When examined at the age of 36, the patient was able to walk unassisted but his gait was markedly atactic and he sometimes had to hold on to walls or furniture. Alternating hand and forearm movements were slowed and irregular. Knee-tibia test showed dysmetria and decomposition of movements. There was moderate intention tremor in hands. Muscle tone was mildly increased. No tendon reflexes could be elicited. Sensibility to light touch, temperature and vibration was mildly reduced in hands and feet. Horizontal saccades were hypometric, and this was especially evident when the patient was asked to rapidly alternate gaze direction between right and left. Upper eyelids were retracted, and this increased during eye movements. There was mild amyotrophy in arms and legs and mildly reduced muscle strength with extension of feet and toes. Blood pressure was 130/95mmHg supine and 100/80 erect, but there was no dizziness. At the age of 37, the patient fell and fractured his femur. Shortly after orthopedic surgery, when treated with opioid analgetics, the patient had two episodes with bilateral cramping in arms and legs; an electroencephalogram was normal. Brain MRI showed moderate cerebellar atrophy (Figure 2), and there was mild calcification of the medial lentiform nuclei which was considered to not to be pathologic. Formal neuropsychological testing was performed on a routine basis and was entirely normal, which confirmed the clinical impression. MRI of the spinal cord was normal. For several years, this family member had chronic diarrhea after meals, which had led to weight loss, but could be controlled with loperamide (similar to Patient III:3, Family 1).

General remarks

Alternative causes of cerebellar ataxia, such as celiac disease, disturbance of cholesterol homeostasis, or autoimmune cerebellopathies, were excluded during routine clinical workup in several of the affected family members (both Families).

None of the patients had any cognitive dysfunction or psychiatric symptoms.