

SCA15 Due to Large *ITPR1* Deletions in a Cohort of 333 White Families With Dominant Ataxia

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Background: Deletions in *ITPR1*, coding for the inositol-triphosphate receptor type 1, have been recently identified in spinocerebellar ataxia type 15 (SCA15).

Objective: To determine the frequency and the phenotypical spectrum of SCA15.

Design: Taqman polymerase chain reaction (258 index cases) or single-nucleotide polymorphism genome-wide genotyping (75 index cases).

Setting: A collaboration between the Centre de Recherche de l'Institut de Cerveau et de la Moelle Epinière of the Salpêtrière Hospital (Paris, France) and the Molecular Genetics Unit of the National Institute of Aging (Bethesda, Maryland).

Patients: Index cases of 333 families with autosomal dominant cerebellar ataxia negative for CAG repeat expansions in coding exons.

Main Outcome Measures: Detection of *ITPR1* copy number alterations.

Results: A deletion of *ITPR1* was found in 6 of 333 families (1.8%), corresponding to 13 patients with SCA15. Age at onset ranged from 18 to 66 years (mean [SD] age, 35 [16] years). The symptom at onset was cerebellar gait ataxia, except in 1 patient with isolated upper limb tremor. Although families were tested irrespective of their phenotype, patients with SCA15 had a homogeneous phenotype and were characterized by a slowly progressive cerebellar ataxia. However, pyramidal signs (2 patients) and mild cognitive problems (2 patients) were occasionally present. Radiologic findings showed global or predominant vermian cerebellar atrophy in all patients.

Conclusions: In this series, *ITPR1* deletions were rare and accounted for approximately 1% of all autosomal dominant cerebellar ataxias. The SCA15 phenotype mostly consists of a slowly progressive isolated cerebellar ataxia with variable age at onset; an additional pyramidal syndrome and problems in executive functions may be present.

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AUTOSOMAL DOMINANT CEREBELLAR ATAXIAS (ADCAs) are a clinically and genetically heterogeneous group of progressive diseases characterized by cerebellar degeneration, often accompanied by degenerative changes in the brainstem, basal ganglia, cerebral cortex, spinal cord, and peripheral nervous system.¹⁻³ To date, 28 genetic loci have been linked to ADCAs, and, among these, 18 genes have been identified. However, the underlying cause of disease in up to 50% of patients with ADCAs remains unknown.^{2,4}

Based on the molecular mechanism, 3 major ADCA classes are considered: the so-called polyglutamine diseases, caused by translated CAG repeat expansions (spinocerebellar ataxia [SCA] type 1, SCA2,

SCA3, SCA6, SCA7, SCA17, and dentatorubral-pallidoluysonian atrophy); ADCAs due to repeat expansions falling outside the coding region of the respective genes (SCA8, SCA10, SCA12, and puratrophin); and ADCAs caused by conventional mutations (SCA5, SCA11, SCA13, SCA14, SCA20, SCA27, and SCA28).⁵

Recently, deletions in *ITPR1*, coding for the inositol-triphosphate receptor type 1 (*ITPR1*), have been identified in SCA15. Deletions were found initially in 3 SCA15-positive families and then in 2 Japanese families previously thought to have a distinct disease (SCA16)⁶⁻⁸; a missense mutation was identified in another Japanese family.⁷ Therefore, SCA15 and SCA16 are actually the same disease: any family with an *ITPR1* mutation should be regarded as

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having SCA15, whereas SCA16 should become a “vacant SCA.”⁹

The phenotype in the 10 SCA15-positive families described so far is that of an almost pure, slowly progressive cerebellar ataxia. Brain magnetic resonance imaging (MRI) showed marked, predominantly vermian, cerebellar atrophy.¹⁰⁻¹³ We report genetic and clinical data from 6 families with 13 patients carrying *ITPR1* deletions and estimate the relative frequency of this genetic entity.

METHODS

This study was approved by the local bioethics committee (Comité Consultatif pour la Protection des Personnes et la Recherche Biomedicale Paris-Necker). Written informed consent was obtained from all participating members of the families before blood samples were collected for DNA extraction. DNA was stored in the DNA and Cell Bank at the Pitié-Salpêtrière Hospital in Paris.

PATIENTS

We screened for *ITPR1* rearrangements in 333 unrelated index cases of ADCA. Age at onset ranged from 2 to 70 years (mean [SD] age, 43.7 [20] years). The study population included 86 index cases with pure cerebellar ataxia, 243 patients with a complex phenotype, and 4 individuals for whom the precise phenotype was not available.

Additional signs found in the index cases with complicated ADCA included in this series were alteration of vibration sense (n=79), pyramidal syndrome (n=72), cognitive impairment (n=72), dysphagia (n=55), electromyography-confirmed polyneuropathy (n=35), abnormal movements (n=26), ophthalmoplegia (n=25), parkinsonism (n=19), mental retardation (n=12), macular alterations (n=5), and optic atrophy (n=3). Most participants were of western European origin (n=307).

CAG repeat expansions in the *SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7*, *SCA17*, and dentatorubral-pallidoluysian atrophy (*DRPLA*) genes were excluded in all patients; repeat expansions responsible for SCA10 were excluded in 118 patients and for SCA12 in 243 patients. Also, SCA5 was excluded in 232 individuals, SCA11 in 61, SCA14 in 197, SCA13 in 202, and SCA28 in 238.

Individual 020 in family LYO-210 was initially referred as clinically affected, but molecular analysis did not find a deletion of *ITPR1*, despite identification of an *ITPR1* deletion in affected family members. This individual was subsequently re-examined by one of us (C.M.) and was diagnosed as having a generalized dystonic and hyperkinetic syndrome. Onset of dystonic symptoms was at age 46 years. Neurologic examination at age 60 years revealed orofacial dystonia with blepharospasm and facial grimaces, limb dystonic postures, and incessant hyperkinetic movements; except for mild difficulty in the heel/knee task, no other signs of cerebellar involvement were present, and the patient did not note gait disequilibrium or speech difficulties. Brain MRI, performed 14 years after disease onset, showed a very mild cerebellar vermis atrophy. He was treated with anticholinergic drugs and botulinum toxin injections in the orbicular muscles.

DETECTION OF COPY NUMBER ALTERATIONS AT THE *ITPR1* LOCUS

Two different techniques were applied to detect *ITPR1* gene dosage anomalies. Two hundred fifty-eight index cases of families

for which DNA from only 1 affected member was available were analyzed using a Taqman assay and an ABI 7900HT (Applied Biosystems, Foster City, California); gene dosage analyses were performed for exon 10 using β -globin as an endogenous reference gene, and positive results were confirmed using single nucleotide polymorphism (SNP) chips as per the manufacturer's protocol (Illumina 610-Quad; Illumina Inc, San Diego, California). Seventy-five index cases from families in which the DNA of more than 1 affected member was available were analyzed by genome-wide SNP genotyping⁶ using human genotyping chips (CNV370-Quad v3.0; Illumina Inc). Segregation analyses were performed using Taqman polymerase chain reaction in all available family relatives of index patients found to be carriers of *ITPR1* copy number changes.

RESULTS

We found 6 index cases harboring an *ITPR1* deletion. The availability of additional patients in 4 families allowed us to confirm cosegregation of the disease with the mutation. We collected and studied 13 patients with SCA15 (**Figure 1**).

The size of the deletion was studied by direct observation of SNP intensities in BeadStudio (Illumina Inc): it involved *ITPR1* and the neighboring gene *SUMF1* in families EPI-21 (approximately 390 kilobase [kb]), SAL-153 (approximately 420 kb), and MAR-588 (approximately 190 kb); it involved *ITPR1* and the neighboring genes *SETMAR* and *SUMF1* in family BOR-279 (approximately 590 kb); it was limited to *ITPR1* in families LYO-210 (approximately 250 kb) and BOU-698 (approximately 220 kb) (eFigure; <http://www.archneuro.com>).

The main clinical features of the 13 patients with SCA15 are given in the **Table**. All the families were of French origin. Age at onset ranged from 18 to 66 years (mean [SD] age, 35 [16] years); disease duration ranged from 3 to 43 years (mean [SD], 23 [13] years).

The main presenting symptom was cerebellar gait ataxia (12 of 13 patients) that was associated with upper limb postural tremor in 3 patients and with a pyramidal syndrome in 1 patient; 1 patient presented with isolated upper limb postural tremor. Almost all the patients subsequently developed a global cerebellar syndrome with gait and limb ataxia (13 of 13), ocular movement abnormalities (10 of 11), and dysarthria (11 of 12), which remains the main clinical finding at all stages of the disease. Ocular abnormalities were homogeneous and were characterized by horizontal gaze-evoked nystagmus and saccadic pursuit; saccadic velocity was preserved. Four patients (BOR-279-1, BOR-279-5, MAR-589-9, and MAR-589-11) reported an intermittent diplopia that disappeared in the following disease course in 3 patients. Postural tremor of the upper limbs was variably associated with disease progression: of the 4 patients with upper limb tremor at disease onset, only 2 still presented this sign at follow-up; in 1 patient, upper limb tremor appeared in a later stage of the disease. None of the patients had head tremor or titubation.

In addition to cerebellar ataxia, pyramidal signs with enhanced reflexes and the Babinski sign were observed

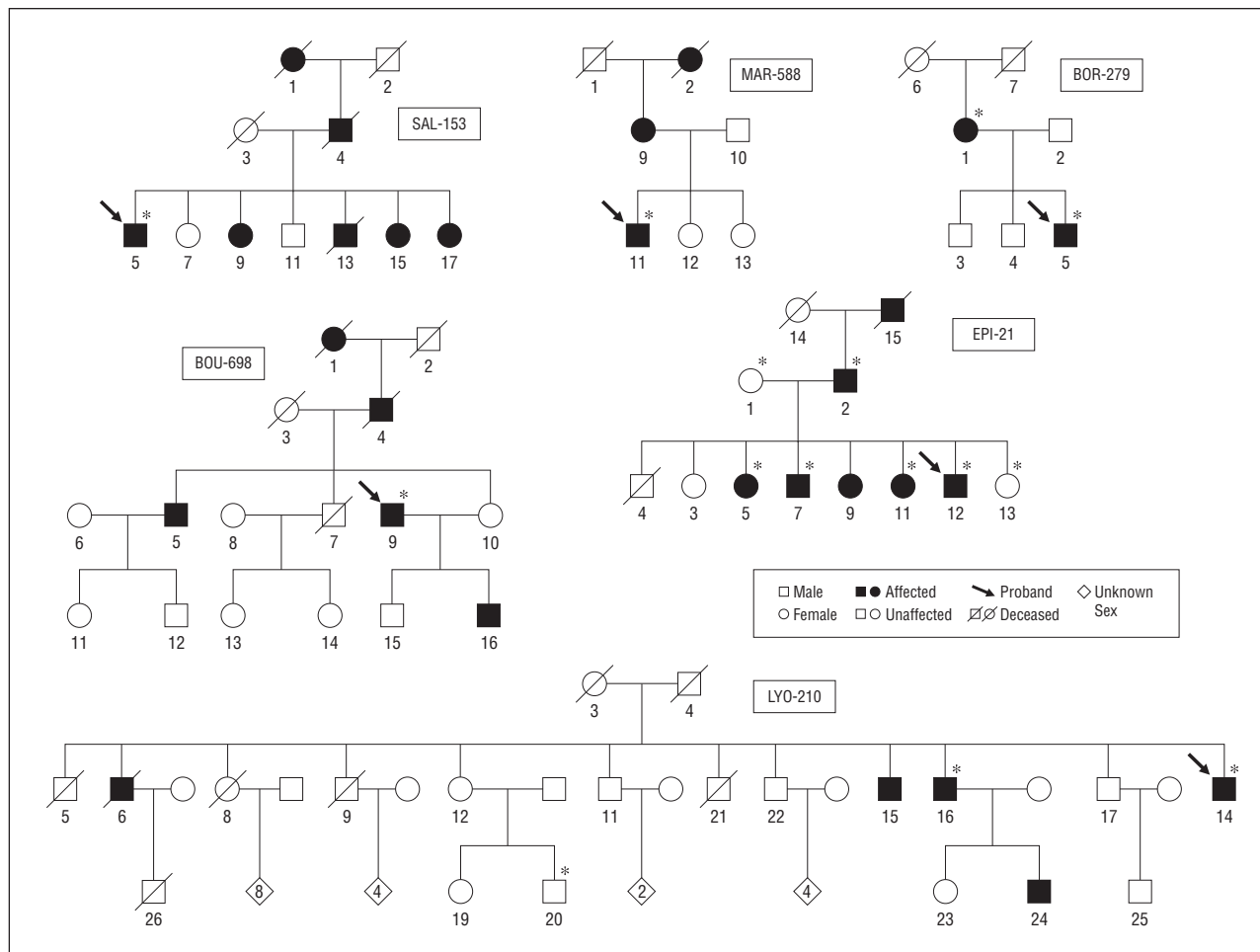


Figure 1. Pedigree of the 6 families with spinocerebellar ataxia type 15. *DNA was available for genetic analysis.

in the 2 patients from family LYO-210. Mild swallowing difficulties were reported by 2 other patients more than 30 years after onset of the disease. Although the Mini-Mental State Examination result was normal in 2 patients, it was slightly altered in 2 others (patients EPI-21-2 and EPI-21-7), with a score of 26 of 30 and 27 of 30 at ages 68 and 50 years, respectively, more than 25 years after disease onset. Moreover, patient EPI-21-7 had a low IQ using the Wechsler Adult Intelligence Scale (global IQ=84, verbal IQ=79, and performance IQ=93), and a further neuropsychological evaluation confirmed slightly worsened executive and attentive problems. Only 1 patient had a formal electromyographic examination, which had normal findings; in addition, none of the patients presented a deep sensory alteration or reduced or abolished reflexes, indicative of posterior column or peripheral nerve involvement. No urinary symptoms or extrapyramidal signs were found.

Progression of the disease was particularly slow, and disease severity was only moderate in most patients (disability score of 1-4 on a 1-7 scale); only the 2 patients with more than 40 years of disease duration needed help to walk (disability score=4), but they were still ambulatory.

Brain MRI was available for 11 patients showing cerebellar atrophy (**Figure 2**), with a predominant dorsal

vermis involvement in 2 patients (**Figure 3**). In 2 patients, only a brain computed tomographic scan was available, showing cerebellar atrophy.

COMMENT

Spinocerebellar ataxia type 15 is a rare form of ADCA. In this cohort of patients with ADCAs excluded for mutations in major ADCA genes, the frequency of *ITPR1* deletions is 1.8% (6 of 333), and it increases to 7.0% (6 of 86) considering the subgroup of families with pure cerebellar ataxia or minimal additional signs. Considering all ADCA cases and that known polyglutamine expansions cause approximately 50% of the ADCAs, the frequency of *ITPR1* deletions decreases to approximately 0.9%. The frequency we found is similar to the 2.7% recently reported in a series of 73 nonpolyglutamine ADCA-positive families.¹² In this latter study, *ITPR1* gene deletions were searched using the multiplex ligation-dependent probe amplification test, whereas in the present study, Taqman polymerase chain reaction was performed in the main subgroup of patients, with amplification limited to exon 10. An underestimation of SCA15 frequency could, therefore, have occurred because it is plausible that deletion may not extend to exon 10; ac-

Table. Clinical Characteristics of 13 Patients With *ITPR1* Deletions

Variable	Family													Frequency, No./ Total No. ^a
	LYO-210		EPI-21			BOR-279			MAR-588		SAL-153		BOU-698	
Patient No. /sex	14/M	16/M	2/M	5/F	7/M	11/F	12/M	1/F	5/M	9/F	11/M	5/M	9/M	NA
Age at onset, y	48	66	25	20	23	40	18	32	19	48	35	35	36	35 (16)
Symptoms at onset	Gait ataxia, stiffness	Gait ataxia	Ataxia	Gait ataxia	Gait ataxia	Gait ataxia, UL tremor	Ataxia	Gait ataxia, UL tremor	Gait ataxia, UL tremor	Ataxia	Gait ataxia	Ataxia	UL tremor	NA
Disease duration, y	24	14	43	31	27	6	14	31	13	17	19	42	10	23 (13)
Disability score ^b	ND	3	4	3	3	1	1	3	3	3	3	4	2	NA
Gait ataxia	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Limb ataxia	+	+	+	+	+	+	+	+	+	+	+	+	+	12/13
Dysarthria	+	+	+	+	ND	+	-	+	+	+	+	+	+	11/12
Nystagmus	ND	H, GE	+	+	H, GE	ND	-	H, GE	H, GE	H, GE	H, GE	H, GE	H, GE	10/10
Saccadic pursuit	ND	ND	+	+	ND	+	+	+	+	+	+	+	+	7/9
Postural tremor	ND	UL	ND	ND	ND	UL	ND	-	-	ND	ND	ND	UL	3/5
Swallowing problems	ND	-	+	ND	ND	ND	-	+	-	-	-	-	-	2/9
Pyramidal signs	+	+	-	-	-	-	-	-	-	-	-	-	-	2/13
EMG	ND	ND	ND	N	ND	ND	ND	ND	ND	ND	ND	ND	ND	0/1
MMSE	ND	ND	26/30	ND	27/30	ND	ND	30/30	ND	ND	ND	30/30	ND	NA
Cerebellar atrophy, MRI	ND ^c	Global	Global	Vermis	Global	Global	Vermis	Global	Global	Global	Global	Global	ND ^c	11/11

Abbreviations: EMG, electromyography; GE, gaze evoked; H, horizontal; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; N, normal; NA, not applicable; ND, not determined UL, upper limb; +, present; -, absent.

^aAge and disease duration are given as mean (SD).

^bDisability was assessed on a 7-point scale: 1, minimal disability; 2, unable to run but full autonomy; 3, moderate disability when walking; 4, unilateral support required to walk; 5, bilateral support required to walk; 6, wheelchair bound; and 7, bedridden.

^cTwo patients had computed tomographic evidence of cerebellar atrophy.

tually, in 1 of 6 families (family MAR-588) analyzed by genome-wide SNP genotyping, the deletion terminated at approximately exon 10 and failed to be detected by Taqman polymerase chain reaction during segregation analysis. Previous studies^{6-8,12} and the present genome-wide SNP genotyping on 75 families show that, up to now, large deletions almost constantly involve the first 10 exons of *ITPR1*. This rearrangement, predicted to involve the N-terminal inositol triphosphate-binding domain, has been, therefore, proposed as a minimal critical region for SCA15¹²; however, the case of family MAR-588 shows that careful attention should be taken in targeting it for diagnostic analysis.

We did not search for point mutations in *ITPR1*, although a Japanese family harboring a P1059L missense mutation and an individual with a V494I missense mutation have been described.^{7,12} In the Japanese family harboring a P1059L missense mutation, the mutation was located in exon 25 (*ITPR1* RefSeq AAB044947.2; GenBank) and involved the modulatory and transducing domain. In the individual with a V494I missense mutation, the mutation was in exon 15 (*ITPR1* RefSeq NM_001099952; GenBank), involving the inositol triphosphate-binding domain. Although in both cases the amino acids were highly conserved and located in important functional domains, the pathogenicity of the mutations has not yet been formally proved with functional studies.^{12,14}

Because we have not performed fine mapping of the breakpoints in the families described herein, it is difficult to comment on the mutational mechanism in these patients. Using PipMaker, Hara et al⁷ compared the 1-Mb genomic sequence surrounding *SUMF1* and *ITPR1* against

itself. Sequence analysis of the breakpoint junction of all patients with SCA15 reported at that time showed that distal breakpoints were scattered within an approximately 65-kb region and proximal breakpoints within an approximately 223-kb region.⁶⁻⁸ Moreover, in none of these families with SCA15 has significant homology been observed when comparing the reference sequence at the distal and proximal breakpoints. This suggests that non-allelic homologous recombination is unlikely to be the mechanism by which *ITPR1* mutations occur. However, overlap of 2 to 5 nucleotides between distal and proximal junction sequences has been identified in these families, suggesting that nonhomologous end joining may be the mutational mechanism in SCA15 cases.⁷

Although age at onset is highly variable, penetrance of SCA15 mutations seems to be complete; further studies are necessary to confirm this observation for genetic counseling. In this study, we chose to analyze a large cohort of patients with ADCAs irrespectively of their clinical presentation. Despite this, the global clinical and radiologic features of most patients with an *ITPR1* deletion were homogeneous and concordant with previous clinical studies describing an almost pure cerebellar ataxia. However, pyramidal involvement with the Babinski sign was present in 2 patients, in 1 at the onset of disease; because milder pyramidal signs were also described in 3 previously reported SCA15 cases,¹⁰⁻¹³ they could be considered part of the clinical spectrum of the disease in a few patients. On the contrary, peripheral neuropathy, previously reported in the SCA15-positive Japanese family with a missense mutation,^{7,15} was not present in any of the present patients. The occurrence of impairment of cognitive functions, possibly present in 2 patients on the

basis of Mini-Mental State Examination and Wechsler Adult Intelligence Scale scores, was confirmed in 1 patient showing progressive alteration of executive functions and was also recently reported in 2 other patients.¹⁴ We cannot, therefore, exclude possible mild cognitive involvement in a few patients with SCA15.

In the present series, ocular involvement is discrete and is characterized by the combination of gaze-evoked nystagmus and saccadic pursuit. An alteration of the vestibulo-ocular reflex has been reported in the original Australian family with SCA15.¹⁰ The combination of these ocular abnormalities points toward involvement of the flocculus-paraflocculus regions and of the dorsal vermis,¹⁶ which is in accord with MRI findings. Because diplopia had mostly disappeared at the last follow-up visit and was not associated with ophthalmoplegia, we considered it a subjective symptom due to a defect in stabilizing retinal images and not a sign of involvement of extracerebellar structures.

The boundaries between a pure and a complex cerebellar ataxia are not always simple to define. In SCA15, although we and other researchers¹³ show that other systems may be involved, this occurs in only a few patients, and cerebellar involvement largely predominates at clinical and radiologic levels. Compared with the constant and marked multisystemic involvement occurring in most polyglutamine ADCAs, SCA15 appears as pure cerebellar ataxia, sometimes associated with minimal extracerebellar signs. We did not find a correlation between the clinical phenotype and the extension of *ITPR1* deletion or the involvement of different contiguous genes.

The radiologic findings of the present patients with SCA15 were also homogeneous and showed cerebellar, predominantly vermian, atrophy without cortical or brainstem involvement. Serial MRIs were not performed, and we could not determine the progression of cerebellar atrophy and its correlation with clinical findings.

The pathogenesis of ataxia due to *ITPR1* deletions remains to be elucidated. *ITPR1* is highly expressed in Purkinje cells and mediates Ca²⁺ release from the endoplasmic reticulum in various neurons, including CA1, basal ganglia, and thalamic and Purkinje neurons.^{17,18} Homozygous *Itpr1* knockout mice develop severe ataxia and epilepsy and die early in development^{19,20}; a similar but less severe phenotype was found in the *opt* mouse, harboring a homozygous in-frame deletion of exons 43 and 44 of *Itpr1*,²¹ and in a mouse with a homozygous in-frame deletion of 18 base pairs in exon 36.⁶ A further mouse model, *Itpr1* heterozygous knockout, presented isolated late-onset mild ataxia.²² In these models, no apparent morphologic abnormalities were found. Note that none of the individuals with SCA15 due to *ITPR1* heterozygous mutations had epilepsy or abnormal electroencephalographic findings.

Evidence suggests that impairment of the inositol 1,4,5-triphosphate pathway is implicated in the pathogenesis of different types of ataxia. In 2 SCA1 mouse models, *itpr1* was among the neuronal genes downregulated at a very early stage in pathogenesis, and this downregulation required nuclear localization of the mutant ataxin-1.²³ The *ITPR1* seems to specifically interact also with the mutated form

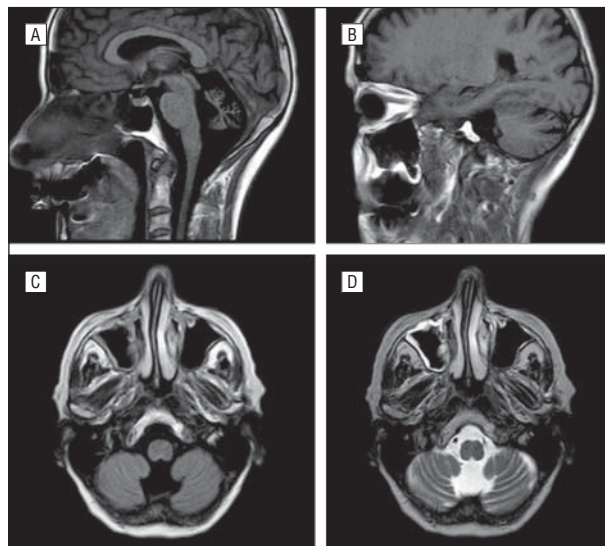


Figure 2. Brain magnetic resonance images of patient BOR-279-1 at age 63 years. Sagittal T1-weighted images (A and B) show global cerebellar atrophy, mainly involving cerebellar vermis; axial T2/fluid-attenuated inversion recovery-weighted (C) and T2-weighted (D) images show involvement of cerebellar hemispheres.

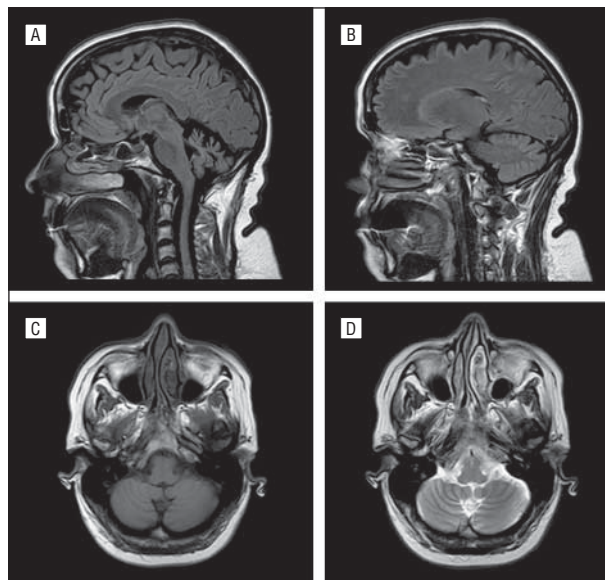


Figure 3. Brain magnetic resonance images of patient EPI-21-5 at age 51 years. Sagittal T1-weighted images show upper and dorsal cerebellar vermis atrophy with sparing of the pons (A) and cerebellar hemispheres (B); axial T1-weighted (C) and T2-weighted (D) images show relative sparing of cerebellar hemispheres.

of the proteins ataxin-3²⁴ and ataxin-2,²⁵ causing SCA3 and SCA2, respectively. Moreover, mutation in carbonic anhydrase-related protein 8, which inhibits the binding of inositol triphosphate to the *ITPR1*, has been recently shown to cause an autosomal dominant ataxia associated with mild mental retardation and predisposition to quadrupedal gait in humans.²⁶

Recently, the *ITPR1* receptor signaling cascade has been found to underlie the coincidence detection system in Purkinje cells, responsible for cerebellar plasticity; the dysfunction of this system has been proposed to be the unifying feature of the many genes that cause cerebellar ataxia

and interact with ITPR1.²⁷ Moreover, ITPR1 interacts with the huntingtin protein, mutated in Huntington disease, and it is, therefore, involved also in the pathogenesis of nonataxic neurodegenerative diseases.²⁸

In conclusion, SCA15 due to deletion in the *ITPR1* gene is uncommon; the relevance of SCA15 due to *ITPR1* point mutations remains to be determined. Although the main phenotype is a cerebellar ataxic syndrome associated with severe cerebellar atrophy, as seen by brain MRI, pyramidal signs and executive dysfunctions can also be rarely found and, therefore, should not be considered exclusion criteria. Disease progression is slow, and age at onset is remarkably variable. Moreover, it will be interesting to better understand the pathogenic mechanism of ataxia due to dysfunction of the ITPR1 pathway and cerebellar plasticity and to see whether other ataxias may also be due to impairment of the same signaling cascade.

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Announcement

Trial Registration Required. As a member of the International Committee of Medical Journal Editors (ICMJE), *Archives of Neurology* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as <http://ClinicalTrials.gov>). Trials must be registered at or before the onset of patient enrollment. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of *JAMA*. Also see the Instructions to Authors on our Web site: www.archneuro.com.