

Clinical Features and Neuropathology of Autosomal Dominant Spinocerebellar Ataxia (SCA17)

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Autosomal dominant spinocerebellar ataxias (SCAs) are a group of neurodegenerative disorders clinically characterized by late-onset ataxia and variable other manifestations. Genetically and clinically, SCA is highly heterogeneous. Recently, CAG repeat expansions in the gene encoding TATA-binding protein (TBP) have been found in a new form of SCA, which has been designated SCA17. To estimate the frequency of SCA17 among white SCA patients and to define the phenotypic variability, we determined the frequency of SCA17 in a large sample of 1,318 SCA patients. In total, 15 patients in four autosomal dominant SCA families had CAG/CAA repeat expansions in the *TBP* gene ranging from 45 to 54 repeats. The clinical features of our SCA17 patients differ from other SCA types by manifesting with psychiatric abnormalities and dementia. The neuropathology of SCA17 can be classified as a “pure cerebellar” or “cerebello-olivary” form of ataxia. However, intranuclear neuronal inclusion bodies with immunoreactivity to anti-TBP and antipolyglutamine were much more widely distributed throughout the brain gray matter than in other SCAs. Based on clinical and genetic data, we conclude that SCA17 is rare among white SCA patients. SCA17 should be considered in sporadic and familial cases of ataxia with accompanying psychiatric symptoms and dementia.

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Neurodegenerative disorders caused by the expansion of CAG trinucleotide repeats are increasingly recognized. To date, at least six autosomal dominant spinocerebellar ataxias (SCAs)^{1–4} as well as Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), and spinal and bulbar muscular atrophy (SBMA)⁵ are known to be caused by this type of mutation. For the group of SCAs, further heterogeneity has been shown, and we currently recognize 21 genetically distinct subforms.⁶ In most SCAs, the expanded CAG repeats encode polyglutamines (poly-Q) in otherwise unrelated proteins.⁵ Recently, Koide and colleagues⁷ identified a polyglutamine expansion in the transcription factor TATA-binding protein (TBP) in a patient with ataxia, short stature, pyramidal signs, and mental deterioration with negative family history. Subsequently, CAG repeat expansions in the *TBP* gene were identified in two German,⁸ four Japanese,⁹ and one Belgian¹⁰ SCA family, establishing this repeat expansion as the underlying mutation in SCA17.

To determine the frequency and to examine the phe-

notypic variability of SCA17, we investigated 1,318 white SCA patients for whom CAG repeat expansions in the SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA12 genes and the GAA repeat expansion in Friedreich's ataxia gene were excluded. We identified four autosomal dominant SCA families with CAG/CAA expansions in the *TBP* gene. One of the pathological hallmarks of poly-Q diseases is the presence of nuclear aggregates of mutant proteins. Accordingly, we used immunocytochemistry to study neuronal intranuclear inclusions in the postmortem brain tissues of three SCA17 patients in one pedigree.

Subjects and Methods

Patients

With informed consent, we studied 1,318 patients with sporadic and familial ataxia and gait disturbances for whom repeat expansions in the SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA12 genes and the GAA repeat expansion in the Friedreich's ataxia gene were excluded.^{11,12} Six hundred eighty-four white control subjects were genotyped: 155 peo-

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Table. Summarized Clinical and Radiological Findings in SCA17 Patients

Family/ Gender	CAA/CAG Repeat Size		Onset (age, yr)	Follow-up (yr)	CCT/MRI	Ataxia ^a	Psychiatric Symptoms	Other Signs
	NA	AA						
1-I.1/ Female	37	49	Depression (38)	22	Unremarkable (45 yr)	None	Schizophrenia (Hallucination at 40yr, sui- cide attempts)	Moderate parkinsonian signs at 60yr (drug- induced?)
1-II.1/ Female	36	49	Cognitive decline (16) Gait ataxia (18)	22	Severe cerebellar at- rophy (at 18 yr)	Gaze-evoked nystag- mus (+) Dysarthria (++) Dysphagia (++) Gait ataxia (++) Limb ataxia (++) Intention tremor (+)	Dementia IQ 68 (21 yr) Mutism (30 yr)	Hypogonadotropic hypogonadism Underweight
1-II.2/ Female	n.d.	n.d.	Cognitive decline (16) Gait ataxia (18)	22 (died at 36)		Gaze-evoked nystag- mus (+) Dysarthria (++) Dysphagia (++) Gait ataxia (++) Limb ataxia (++) Intention tremor (+)	Dementia IQ 62 (21 yr) Mutism (24 yr)	Hypogonadotropic hypogonadism Monocytic twin to 1-II.2
2-III.1/ male	37	54	Gait ataxia (36) Psychiatric signs (38)	12	Severe atrophy with prominence in the cerebellum (Fig 2B,C)	Dysarthria (+++) Dysphasia (++) Gait ataxia (+++) Limb ataxia (+++)	Dementia Aggression Paranoia Severe mutism	Epilepsy Chorea (+) Dystonia (+) Increased DTR
2-III.2/ male	37	54	Ataxia (18) Dementia (22)	26	General atrophy with prominence in the cerebellum	Dysarthria (++) Dysphagia (+) Gait ataxia (++) Limb ataxia (+++)	Disoriented Dementia (++) Apraxia (+++)	Increased DTR
2-III.3/ Female	37	54	Hallucinations (23)	19	General atrophy, more prominent in cerebellum and occipital cortex	Dysarthria (+++) Dysphagia (+) Gait ataxia (+) Limb ataxia (++)	Disoriented Dementia (+) Mania Apraxia (+++)	Slow saccades (+) Chorea (+) Dystonia (+) Increased DTR Bladder dysfunction Slow saccades (+)
2-IV.1/ male	34	54	Slight dysarthria (18)	2	No atrophy in MRI	Dysarthria (+)	None	
3-I.1/ Female	39	45	Slight dysarthria, depression (30)	38	Distinct general at- rophy	Dysarthria (+) Gait ataxia (+)	Depression	Moderate parkinsonian signs at 66yr
3-II.1/ male	37	45	Gait ataxia (43)	2	No atrophy in MRI	Gait ataxia (+) Dysphagia (+)	Depression	Slow saccades (+)
3-II.2/ female	37	45	Psychiatric symp- toms with de- pression ac- companied by slight psy- chotic symp- toms (30)	17	General atrophy, more prominent in cerebellum and occipital lobe	Dysarthria (+++) Dysphagia (+) Gait ataxia (+) Limb ataxia (+)	Deficit in time orientation MMS 20/30 aggression paranoia con- structive apraxia	Slow saccades (+) Chorea (+) Dystonia (+) Postural tremor (+) Increased DTR
3-III.1/ male	36	45	Dysarthria (23) Gait ataxia (26)	3		Dysarthria (+) Gait ataxia (+)	None	Slow saccades (+) Increased DTR (+)
4-II.3/ Female	n.d.		Ataxia (33)	8 (died at 41 yr)		Ataxia Dysmetria	Dementia	Dystonia Athetoid posture Parkinsonian gait
4-II.6/ Female	n.d.		Ataxia (33)	18 (died at 51 yr)		Ataxia Dysmetria	Dementia	Akathisia Dystonia
4-II.9/ Female	n.d.		Mental retarda- tion (8)	24 (died at 32 yr)		Ataxia Dysmetria	Aggressive be- havior Self-mutilation	Slow saccades Blepharospasm Choreiform move- ments
4-III.12/ male	36	54	Ataxia (18)	33	Cerebellar and oli- vary atrophy	Ataxia Dysmetria	None	Dystonia

NA = normal allele; AA = affected allele; MRI = magnetic resonance imaging; (+) slight; (++) moderate; (+++) severe; n.d. = not done (no DNA samples were available); CCT = cranial computed tomography scan; DTR = deep tendon reflexes.

ple older than 60 years with no neurological signs, 250 patients with dystonia, 81 patients with genetically confirmed Huntington's disease (HD), and 198 ataxic patients with pathological genotypes of SCA1, SCA2, SCA3, SCA6, or SCA7.

Subjects with repeat expansions in the *TBP* gene underwent standardized neurological and psychiatric examination including neurophysiological analyses and computed tomography scans/magnetic resonance tomography scans.

Polymerase Chain Reaction Analysis of the *TBP* Gene

As a first step, a nonradioactive polymerase chain reaction (PCR) amplification of the CAG repeat region in the *TBP* gene was performed for all DNA samples in a 20µl reaction volume containing the primer pair TATA-BF (5'-GACCCACAGCCTATTCAGA-3') and TATA-BR (5'-TTGACTGCTGAACGGCTGCA-3'). A 203bp-long PCR fragment corresponds to 38 CAG/CAA repeats.⁷ Optimal

PCR conditions were obtained by including 10% dimethyl-sulfoxide and in 30 cycles of 1 minute at 94°C, 1 minute of 56°C, and 1 minute of 72°C, respectively. PCR fragments were subsequently separated by electrophoresis on a 2% agarose gel. DNA samples with enlarged alleles were PCR amplified incorporating radioactively labeled [$\alpha^{32}\text{P}$]-dCTP (Amersham, Arlington Heights, IL) and subjected to electrophoresis on 6% denaturing polyacrylamide gels and using a radioactively labeled M13 sequence as marker for size determination.

Neuropathological Studies

Autopsy tissues were available from three sisters in Family 4. They died at the respective ages of 41 years (4-II.3), 51 years (4-II.6), and 32 years (4-II.9). Routine histological stains of selected sections and immunocytochemistry with a polyclonal antiserum to neuron-specific enolase, and monoclonal antibodies to antiubiquitin, TBP, and polyglutamine (1C2¹³) was accomplished on 6 μm -thick paraffin sections. For immunocytochemical visualization of ubiquitin, TBP, and polyglutamine, two antigen-enhancing methods were tried: microwave irradiation in 0.1M citrate buffer at pH 6.0 and incubation for 5 minutes in concentrated formic acid.⁹ They gave comparable results though monoclonal anti-TBP yielded more intense reaction product with formic acid incubation. Immunocytochemical reaction product was visualized in analogy to the avidin-biotin-peroxidase complex method.¹⁴ The avidin-biotin-peroxidase complex was replaced by horseradish peroxidase-labeled streptavidin. Antisera and antibodies were purchased from Accurate Chemical and Scientific Corp. (Westbury, NY; polyclonal anti-human neuron-specific enolase); Zymed (South San Francisco, CA; prediluted monoclonal antiubiquitin); QED Bioscience (San Diego, CA; monoclonal anti-TBP); and Chemicon (Temecula, CA; 1C2). Polyclonal anti-neuron-specific enolase was diluted 1 to 1,000. The protein concentration of monoclonal antibody solutions was adjusted to 0.1 $\mu\text{g}/\text{ml}$.

Statistics

Sample proportion Student's *t* test, linear regression, and correlation coefficients were calculated by standard techniques.

Results

Analysis of the CAG/CAA Repeat in the TBP gene in Ataxia Patients and Controls

In an initial analysis, we separated the PCR-amplified CAG/CAA repeat alleles of the *TBP* gene of 1,318 ataxia patients, of 155 normal controls, 250 patients with dystonia, and of 81 patients with genetically confirmed Huntington's disease by agarose gel electrophoresis. Large alleles are being easily identified by this method. To determine the respective exact CAG/CAA repeat sizes, we performed a radioactive PCR, and the labeled fragments were separated by polyacrylamide gel electrophoresis. Using this approach, we identified repeat expansions in the *TBP* gene ranging from 45 to 54 repeats in a total of four autosomal dominant SCA families. The allele with 45 CAG/CAA repeats coseg-

regated with the disease in the family (Family 3, Table). In 486 controls consisting of 155 normal subjects older than 60 years, 250 patients with dystonia and 81 patients with genetically confirmed HD, the largest allele consisted of 42 combined CAG/CAA repeats. Four alleles of 43 CAG/CAA repeats were found in the *TBP* gene in SCA patients with repeat expansions in the SCA1, SCA2, SCA3, SCA6, and SCA7 genes, respectively. We therefore consider 43 CAG/CAA repeats as the largest normal and 45 CAG/CAA repeats as the smallest expanded allele defining a small nonoverlapping region. As calculated by a sample proportion Student's *t* test (two-sided, assuming four pathogenic genotypes in our cohort), this threshold dissected pathogenic and irrelevant alleles significantly ($p < 0.05$).

In total, we identified 15 patients with expanded SCA17 alleles in four families. All families displayed autosomal dominant inheritance of the neuropathological or psychiatric phenotype. The median age at onset was 23 years, the median follow up for disease progression was 18.5 years (see Table). Four patients died during follow-up after a disease course of 8, 18, 20, and 24 years, respectively. By age of 43 years, all patients with pathological SCA17 alleles showed neurological or psychiatric dysfunction, and complete penetrance of the genotype can be assumed in our families. Overall, we studied 10 meiotic transmissions in our families: no meiotic instability was observed of the expanded CAG/CAA tracts. According to Zühlke and colleagues, meiotic repeat instability is associated with loss of CAA interruptions, being rather seldom at the TBP locus.⁸ In contrast with other types of SCA, correlation between length of the CAG/CAA tracts and age at onset was weak (correlation coefficient $r^2 = 0.429$; Fig 1).

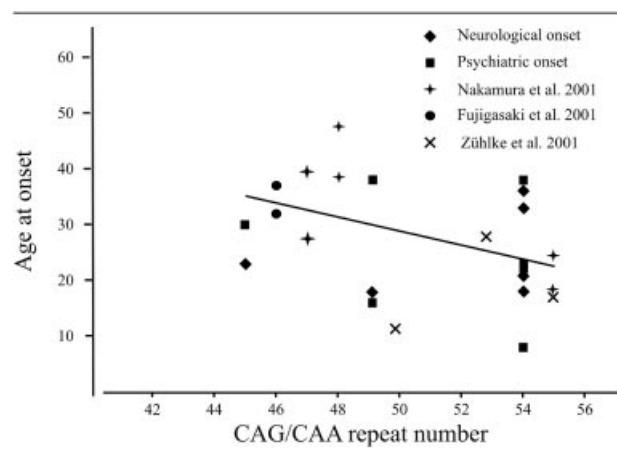


Fig 1. Correlation between combined CAG/CAA repeats and age at onset. In the chart, we integrate our data together with the reports of Nakamura and colleagues,⁹ Fujigasaki and colleagues,¹⁰ and Zühlke and colleagues.⁸ Linear regression analysis resulted in a correlation coefficient of $r^2 = 0.429$.

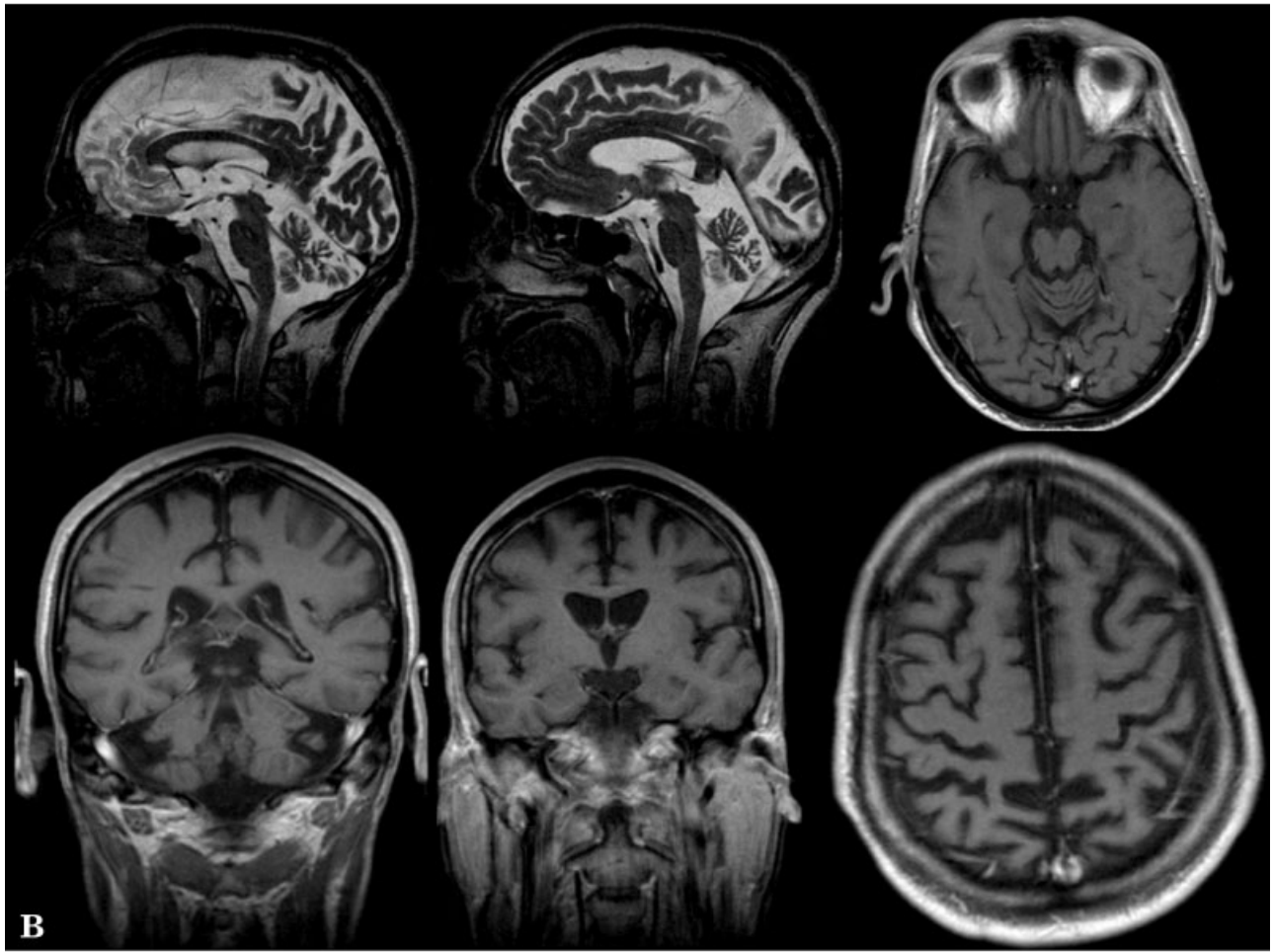
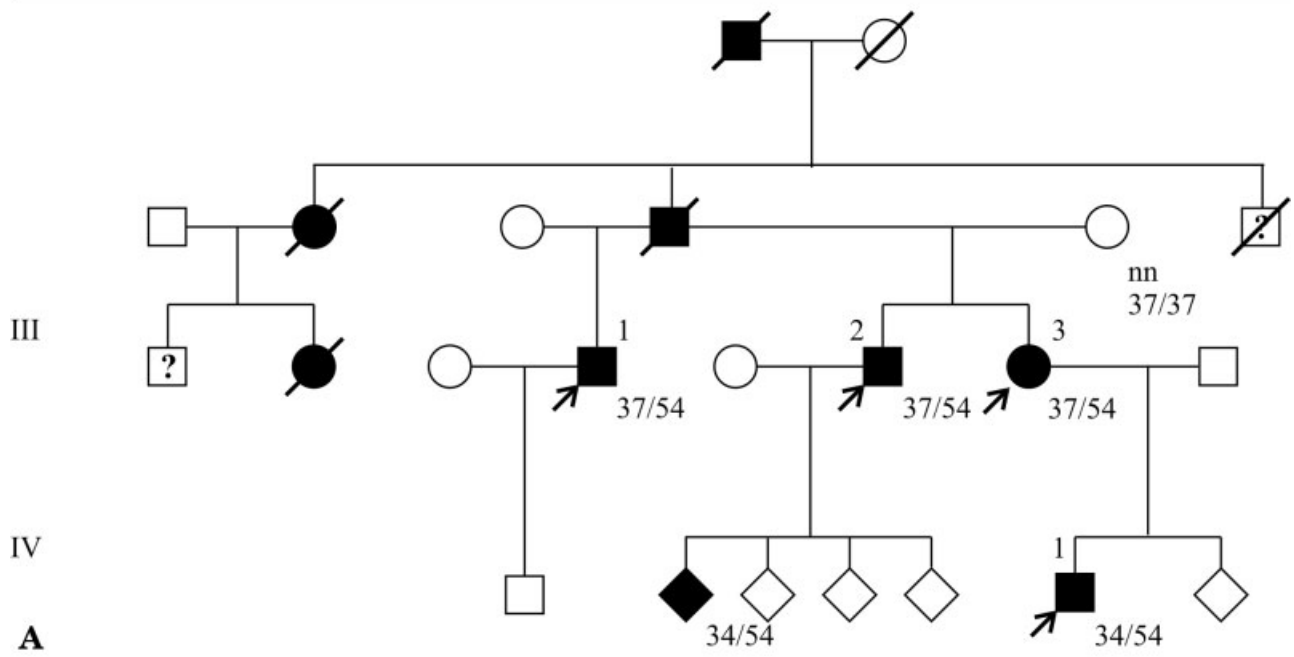


Fig 2. Figure and legend continue.

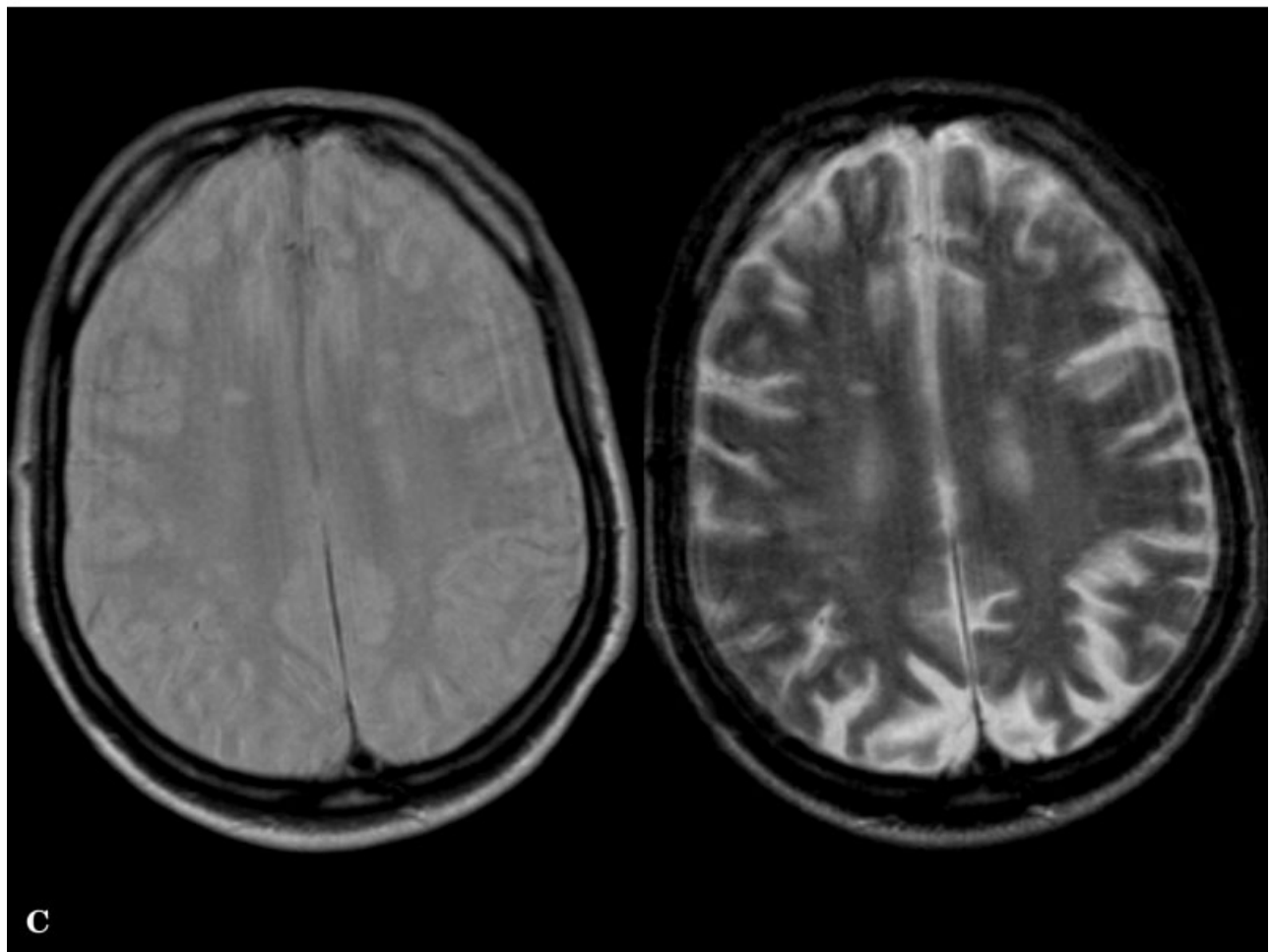


Fig 2. (continued.) (A) Simplified pedigree of a large German family (Family 2) with 54 expanded CAG/CAA repeats. (solid symbols) affected members; (open symbols) unaffected members; (squares) male subjects; (circles) female subjects; (question marks) no clinical data available; (arrows) probands. For reasons of confidentiality, parts of the pedigree have been masked. (B) Brain magnetic resonance imaging images of a representative patient (Family 2, 2-III.1) showing diffuse cortical and cerebellar atrophy. Cerebellar atrophy is pronounced. Moreover, diffuse subcortical white matter lesions of unknown cause have been detected in this patient (C).

The Clinical Features and the Course of SCA17

A summary of clinical and diagnostic milestones of our SCA17 patients is given in the Table. In Family 1, index Patient 1-II.1 with 36 normal and 49 expanded CAG/CAA repeats, (CAG/CAA)_{36/49}, experienced difficulties in tandem walking at age 18 years. Mental problems became obvious at age 16 years. Cognitive function declined progressively and, at age 21 years her IQ was 68. Her monozygotic twin sister 1-II.2 had a similar course and died at the age of 36 years. The mother of the index patient (1-I.1 [CAG/CAA]_{37/49}) suffers from schizophrenic symptoms. Mild psychiatric features presented first at the age of 38 years and initially were interpreted as depression. Problems increased at the age of 40 years with auditory hallucination of threatening and insulting voices. Neurological abnormalities were restricted to moderate parkinsonian signs, but there were no signs of cerebellar dysfunction.

A computed tomography scan at the age of 45 years was reported as unremarkable and especially cerebellar atrophy was excluded.

In Family 2 (see Fig 2A), three members of one generation (2-III.1, 2-III.2, and 2-III.3) and the son (2-IV.1) of 2-III.3 showed 54 CAG/CAA expanded repeats in the *TBP* gene. Subject 2-III.1 developed a slowly progressive gait ataxia at the age of 36 years. Two years later, he had a rapidly progressive dementia with impulsivity and paranoid periods. Three years later, slow saccades and choreiform movements with dystonia and hyperreflexia were described. At this time (12 years after the first clinical signs), the patient demonstrated dementia with severe mutism, a stupor-like state, marked cerebellar ataxia of limbs and trunk, and dysphagia. On magnetic resonance imaging, severe brain atrophy was accompanied by dilatation of the lateral and fourth ventricle (see Fig 2B, C). At the age of

18 years, 2-III.2 developed a rapidly progressive gait ataxia, which was followed by dementia 4 years later. Subject 2-III.3 developed progressive disorientation and auditory hallucinations at age 23 years. The psychiatric course of the disease was characterized by manic symptoms over a period of 12 years. Eleven years after onset of first psychiatric symptoms, she developed progressive dysarthria, gait and limb ataxia, and dysphagia. Subject 2-IV.1 developed moderate signs of cerebellar dysarthria and saccadic eye movements at age 18 years.

In Family 3, the grandmother 3-I.1 had (CAG/CAA)_{39/45} repeats. At the age of 30 years, she developed rapidly progressive disorientation regarding time and place. She had aggressive periods, intellectual decline, and hallucinative episodes. Two years later, she developed cerebellar dysarthria, truncal ataxia with postural tremor, spasticity, and muscle weakness. Subject 3-II.1, the son of 3-I.1, had (CAG/CAA)_{36/45} repeats. He presented with moderate gait ataxia when he was 43 years old, whereas his sister 3-II.2, also with (CAG/CAA)_{36/45} repeats, had an earlier onset at 30 years of age with depression. Over time, she developed remarkable dysarthria, gait ataxia, and intellectual decline. Subject 3-III.1, the son of 3-II.2, also had (CAG/CAA)_{36/45} repeats. He demonstrated moderate signs of cerebellar dysarthria with abnormal saccades at 23 years. Three years later, he developed moderate spasticity with hyperreflexia and gait disturbance but no intellectual deterioration. There were no sensory disturbances, autonomic dysfunction, or muscle weakness.

Clinical features and the pedigree of Family 4 were published previously, and the designations refer to Figure 2 in the cited reference.¹⁵ An additional family member developed symptoms and signs of progressive ataxia (III,12 in the same figure). His lymphocyte DNA was found to contain (CAG/CAA)_{36/54} repeats in the *TBP* gene. The clinical features in three sisters of generation II were similar though the youngest (II.9) had an

early onset at 8 years. Her original diagnosis was postinfectious encephalitis after measles. The other two sisters had adult-onset ataxia with a relentlessly progressive course that included ataxia, athetoid postures, the "thalamic hand," anxiety, and cognitive decline.

The Neuropathology of SCA17

Three sisters in Family 4 have been investigated. They died at the ages of 41 years (4-II.3), 51 years (4-II.6), and 32 years (4-II.9). Gross observations were similar in the three specimens and are summarized here as follows. The overall size of the brain was reduced (brain weights 1,125, 930, and 1,100gm, respectively). Brainstem and cerebellum were smaller than normal, but the spaces between the cerebellar folia were not dilated. Serial coronal slices disclosed hydrocephalus of the lateral ventricles. Transverse slices of the brainstem suggested atrophy of the substantia nigra in 4-II.9 but not in the other two cases. The white matter surrounding the dentate nuclei appeared reduced in thickness.

Histological results are illustrated in Figure 3. The molecular layer of the cerebellum was greatly thinned because of subtotal loss of Purkinje cells (see Fig 3A). Silver stains showed empty baskets (B, C), an axonal torpedo (B), and an unusual dendritic expansion (C) (Bodian stain). (D) Inferior olivary nucleus. There is subtotal loss of neurons in the chief olivary nucleus (hematoxylin and eosin). (E) Dentate nucleus. The neurons of the dentate nucleus are preserved (immunocytochemical stain for neuron-specific enolase). (F) Basis pontis. A pontine neuron contains an intranuclear inclusion body (immunocytochemistry for ubiquitin). (G) Dorsomedian nucleus of the thalamus. Two neurons show pan-nuclear reaction product and dense intranuclear inclusion bodies (immunocytochemistry for TBP). (H) Basis pontis. Many nerve cells of the basis pontis show dense pan-nuclear reaction product (immunocytochemistry for TBP). (I) Betz cells. One of two Betz cells contains pan-nuclear reaction product (immunocytochemistry for TBP). (J) Cerebellar cortex. The nuclei of two basket cells and one stellate neuron (arrows) show immunoreactivity (immunocytochemistry for TBP). (K) Basis pontis. Several neurons display intranuclear reaction product (immunocytochemistry with monoclonal antibody 1C2). (L) Betz cell. The nucleus of this large pyramidal cell shows pan-nuclear reaction product. The plasma membrane of the neuron is indicated by the arrowheads (immunocytochemistry with monoclonal antibody 1C2). (M) Basis pontis of a patient with SCA2. An immunoreactive nucleoliform intranuclear inclusion body is present (immunocytochemistry with 1C2). (N) Basis pontis of a patient with SCA3. An immunoreactive intranuclear inclusion (arrow) is distinct from the nucleolus (arrowhead) (immunocytochemistry with 1C2). Markers: A, 1mm; B and C, 50μm; D, 1mm; E, 100μm; F and G, 25μm; H, 50μm; I–L, 50μm; M; and N, 25μm.

Fig 3. (A) Cerebellar cortex. The height of the molecular layer is greatly reduced, and there is subtotal loss of Purkinje cells (hematoxylin and eosin). (B, C) Cerebellar cortex. Silver impregnation shows empty baskets (B, C), an axonal torpedo (B), and an unusual dendritic expansion (C) (Bodian stain). (D) Inferior olivary nucleus. There is subtotal loss of neurons in the chief olivary nucleus (hematoxylin and eosin). (E) Dentate nucleus. The neurons of the dentate nucleus are preserved (immunocytochemical stain for neuron-specific enolase). (F) Basis pontis. A pontine neuron contains an intranuclear inclusion body (immunocytochemistry for ubiquitin). (G) Dorsomedian nucleus of the thalamus. Two neurons show pan-nuclear reaction product and dense intranuclear inclusion bodies (immunocytochemistry for TBP). (H) Basis pontis. Many nerve cells of the basis pontis show dense pan-nuclear reaction product (immunocytochemistry for TBP). (I) Betz cells. One of two Betz cells contains pan-nuclear reaction product (immunocytochemistry for TBP). (J) Cerebellar cortex. The nuclei of two basket cells and one stellate neuron (arrows) show immunoreactivity (immunocytochemistry for TBP). (K) Basis pontis. Several neurons display intranuclear reaction product (immunocytochemistry with monoclonal antibody 1C2). (L) Betz cell. The nucleus of this large pyramidal cell shows pan-nuclear reaction product. The plasma membrane of the neuron is indicated by the arrowheads (immunocytochemistry with monoclonal antibody 1C2). (M) Basis pontis of a patient with SCA2. An immunoreactive nucleoliform intranuclear inclusion body is present (immunocytochemistry with 1C2). (N) Basis pontis of a patient with SCA3. An immunoreactive intranuclear inclusion (arrow) is distinct from the nucleolus (arrowhead) (immunocytochemistry with 1C2). Markers: A, 1mm; B and C, 50μm; D, 1mm; E, 100μm; F and G, 25μm; H, 50μm; I–L, 50μm; M; and N, 25μm.

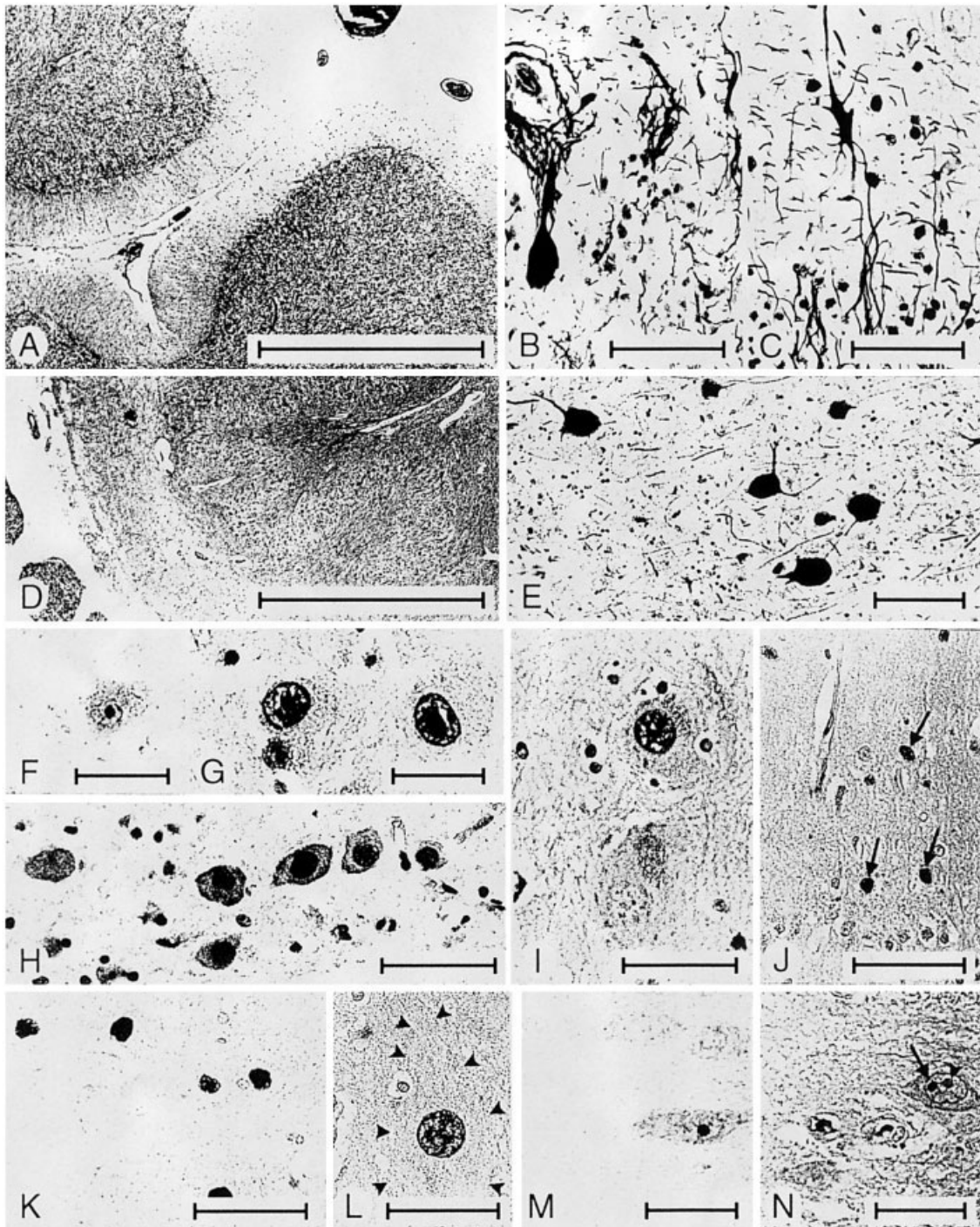


Figure 3

the basis pontis (see Fig 3F) and the thalamus showed immunoreactivity with antiubiquitin. In contrast, anti-TBP and 1C2 yielded intense reaction product in the neuronal nuclei of the thalamus (see Fig 3G), the basis pontis (see Fig 3H, K), Betz cells (see Fig 3I, L) and other pyramidal neurons of the frontal lobe, and the stellate and basket cells of the cerebellar cortex. The nuclei of the remaining Purkinje cells were not reac-

tive. The reaction product was almost always pan-nuclear with a reticulated pattern and often a dense central clump. On occasion, the distribution of reaction product was diffuse and filled the entire nucleus (see Fig 3H). For comparison, the result of immunocytochemistry with 1C2 in SCA2 and SCA3 is shown in Figures 3M (SCA2) and N (SCA3). In these cases, pontine neurons contained nucleoliform inclusions that

often were distinct from the nucleolus (see Fig 3N, *arrow* and *arrowhead*).

Based on the postmortem examination of the described three patients, the following regions of the brain contained nuclear reaction product with anti-TBP and 1C2: basis pontis; nucleus raphe; dorsomedian nucleus of the thalamus; midbrain tegmentum; tegmentum of the medulla oblongata; nucleus basalis of Meynert; stellate and basket neurons of the molecular layer; and the pyramidal neurons (including Betz cells) of the frontal cortex. Immunoreactivity was absent from Purkinje cells, the neurons of the dentate nucleus, putamen, globus pallidus, thalamic nuclei other than the dorsomedian nucleus, the preserved medial accessory olivary nuclei, and the spinal cord. Comparable sections from several patients without neurological disease showed no immunoreactivity with anti-TBP or anti-polyglutamine (1C2).

Discussion

Investigating 1,318 ataxia patients and 684 control subjects, we have genotyped the CAG/CAA tract in *TBP* gene in the largest number of subjects, so far to our knowledge. We detected 43 CAG/CAA repeats in four control persons. Our smallest disease relevant allele consisted of 45 repeats. This is somewhat in contrast with Silveira and colleagues who reported in 2,525 chromosomes a reference range for the repeat from 25 to 42 repeat units.¹⁶ They showed an expanded allele with 43 units in a 64-year-old patient with ataxia and progressive mental deterioration and dementia. On the other hand, Zühlke and colleagues¹⁷ reported incomplete penetrance of 48 CAG/CAA repeats in a German family. Therefore, 43 to 48 CAG/CAA repeats might be considered as intermediate alleles with reduced penetrance. In HD, another CAG repeat disorder, the phenomenon of reduced penetrance has also been observed.¹⁸

We never observed meiotic instability in 10 transmissions of an expanded SCA17 allele. This observation is in accordance with previous studies, because the CAG/CAA tract in *TBP* is known to be stably transmitted.^{9,10} Only Zühlke and colleagues⁸ reported a family with meiotic instability and attributed this phenomenon to the coincidental loss of CAA interruptions with the CAG/CAA stretch.

Although rare among white families with autosomal dominant spinocerebellar ataxia (3%), SCA17 is of special interest because it represents one of the very few known monogenic causes of psychiatric diseases. Some of the identified patients manifested first exclusively with psychiatric symptoms while having no signs of ataxia or movement disorders. Accordingly, CAG/CAA repeat expansion in the *TBP* gene may be considered in psychiatric patients with dementia, apraxia, disorientation, bipolar psychosis, or paranoia. Similar symp-

toms and signs also were observed in a Belgian SCA17 family.¹⁰ Most importantly, dementia occurred in all SCA17 families. In Japanese and Belgian families^{9,10} epilepsy was a frequent diagnosis, but none of our patients presented with seizures.

Extrapyramidal movement disorders are common in SCA17.^{8,9} Especially, chorea and diverse forms of dystonia (blepharospasm, torticollis, writer's cramp, foot dystonia) are frequent in SCA17 but are rare in other types of SCA.¹⁹ Early-onset SCA3 may also present with movement disorders.^{3,20} Spasticity, which is frequent in several types of SCA (eg, SCA1, SCA3, SCA7, SCA8, SCA12) was not observed in SCA17 patients of this series. However, muscle stretch reflexes were increased in several patients. None of our or previously published patients presented with visual impairment. There is a high incidence of dysphagia in SCA17 patients. It remains to be determined whether dysphagia is caused by cricopharyngeal achalasia or whether it is associated with pharyngeal dystonia in these patients. Certainly, this would consequence in distinct therapeutic strategies: myotomia versus neuromuscular blockade via botulinum toxin, for instance.

In most subjects of Family 2 (2-III.3, 2-III.2, 2-III.1, and 3-II.2), F-wave amplitudes evoked by electrical peripheral nerve stimulation, motor threshold, cortical silent period after transcranial magnetic stimulation, intracortical inhibition and facilitation, and central motor conduction time were determined. We did not find a significant reduction of intracortical facilitation in any of the patients. Motor threshold and central motor conduction time were also normal in all patients. Silent period and intracortical inhibition did not differ between patients and controls. Therefore, SCA17 is another example of such hereditary ataxias, which demonstrates no changes of intracortical facilitation induced by transcranial magnetic stimulation and other excitability parameters of the motor system.²¹

Routine cell stains and silver impregnation of the brain of deceased SCA17 patients showed abnormalities that may be interpreted as "pure cerebellar" or "cerebello-olivary atrophy." Though the brainstem was thinner than normal, there was no neuronal loss in the basis pontis that would allow the anatomical diagnosis of olivopontocerebellar atrophy. The findings resemble the neuropathology of SCA6 and some cases of SCA1 but are quite different from those in SCA2, SCA3/Machado-Joseph disease, or SCA7.

The reduction in brain weight, especially in Subject 4-II.6 (930gm) did not correlate with an obvious histopathology. In previous autopsy cases of SCA17,^{9,10} the investigators also observed a relatively diffuse distribution of neuronal inclusions when anti-TBP and 1C2 were used to visualize them. We could not confirm that all 1C2- and TBP-positive nuclei contained ubiquitinated inclusions. The multiple-label confocal

immunofluorescence images of Nakamura and colleagues⁹ suggested such a colocalization. The published positive-contrast images of nuclear reaction product showed much larger inclusions than in SCA2 and SCA3, a finding that was readily confirmed in this study (see Fig 3M, N). In SCA17, pannuclear and coarsely granular reaction products were much more common than small nucleoliform ubiquitin-reactive inclusions. Their abundance in the dorsomedian thalamic nucleus in the cases presented here may explain the prominent cognitive and behavioral decline in the patients.

In conclusion, SCA17 is a rare cause of dominant spinocerebellar ataxia in our population. Nevertheless, it is the only genetically characterized disease that not only presents with cerebellar signs but also must be considered when pure psychiatric or cerebellar signs are inherited in a dominant manner. The CAG/CAA stretch in SCA17 is probably not as dynamic as described in other CAG repeat expansions. Nevertheless, there is a broad variation of phenotypes even within the same family. Although these dominant mutations in SCA17 are subsumed under CAG-repeat disorders, functional and neuropathological findings might indicate a unique and distinctive pathogenesis in SCA17.

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