Spinocerebellar ataxia 17 (SCA17) and Huntington’s disease-like 4 (HDL4).
Giovanni Stevanin, Alexis Brice

To cite this version:

HAL Id: inserm-00293796
http://www.hal.inserm.fr/inserm-00293796
Submitted on 26 Mar 2009

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
SPINOCEREBELLAR ATAXIA 17 (SCA17) AND HUNTINGTON'S DISEASE-LIKE 4 (HDL4)

GIOVANNI STEVANIN\textsuperscript{1,2,3} & ALEXIS BRICE\textsuperscript{1,2,3}

\textsuperscript{1}INSERM, U679, 75013 Paris, France;  
\textsuperscript{2}Université Pierre et Marie Curie – Paris 6, UMR S679, Institut Fédératif de Recherche en Neurosciences, Groupe Hospitalier Pitié-Salpêtrière, 75013 Paris, France;  
\textsuperscript{3}APHP, Groupe Hospitalier Pitié-Salpêtrière, Département de Génétique et Cytogénétique, 75013 Paris, France

Correspondence: Giovanni Stevanin, PhD, INSERM U679, Groupe Pitié-Salpêtrière, 47 Boulevard de l’Hôpital, 75651 Paris Cedex 13, France.  
E-mail: stevanin@ccr.jussieu.fr

Running title: SCA7 and HDL4
Abstract

Spinocerebellar ataxia 17 (SCA17) or Huntington’s disease-like-4 is a neurodegenerative disease caused by the expansion above 44 units of a CAG/CAA repeat in the coding region of the TATA box binding protein (TBP) gene leading to an abnormal expansion of a polyglutamine stretch in the corresponding protein. Alleles with 43 and 44 repeats have been identified in sporadic cases and their pathogenicity remains uncertain. Furthermore, incomplete penetrance of pathological alleles with up to 49 repeats has been suggested. The imperfect nature of the repeat makes intergenerational instability extremely rare and de novo mutations are most likely the result of partial duplications. This is one of the rarer forms of autosomal dominant cerebellar ataxia but the associated phenotype is often severe, involving various systems (cerebral cortex, striatum, and cerebellum), with extremely variable age at onset (range: 3-75 years) and clinical presentation. This gene is thought to account for a small proportion of patients with a Huntington’s disease-like phenotype and cerebellar signs. Parkinson’s disease-like, Creutzfeldt-Jakob disease-like and Alzheimer disease-like phenotypes have also been described with small SCA17 expansions. The abnormal protein is expressed at the same level as its normal counterpart and forms neuronal intranuclear inclusions containing other proteins involved in protein folding or degradation. The increase in the size of the glutamine stretch enhances transcription in vitro, probably leading to transcription deregulation. Interestingly, the TBP protein mutated in SCA17 is recruited in the inclusions of other polyglutaminopathies, suggesting its involvement in the transcription down-regulation observed in these diseases.

Key words: Spinocerebellar ataxias, spinocerebellar degenerations, Huntington’s disease, SCA17, HDL4
Introduction

Autosomal dominant cerebellar ataxias (ADCA), often referred to as spinocerebellar ataxias (SCA), are a group of neurological disorders that are clinically and genetically highly heterogeneous (1). They are characterized by progressive cerebellar ataxia that results in uncoordinated movements, unsteady gait and dysarthria often associated with other neurological signs such as ophthalmoplegia, pyramidal or extrapyramidal signs, deep sensory loss and dementia. Onset is generally observed during the third or fourth decade but can also occur in childhood or old age. Neuropathologically, prominent atrophy of the cerebellum and brainstem is usually observed, but other structures may also be affected leading to a considerable range of phenotypes.

Fifteen genes and their mutations have been identified. Translated (CAG)n/polyglutamine repeat expansions are responsible for the disease caused by 7 of these genes, SCA 1-3 (2-6), 6 (7), 7 (8-10), 17 (11) and dentatorubral-pallidoluysian atrophy (DRPLA) (12,13), and account for the vast majority of all ADCAs with a known genetic basis, although the precise frequency varies with geographical origin. Other genes with such mutations are unlikely to be identified. Two different studies using the Repeat Expansion Detection technique or the 1C2 antibody that recognizes large polyglutamines found no evidence of other disease-causing genes with large CAG repeats or proteins with polyglutamine expansions encoded by codons CAA or CAG (14,15). Indeed, the majority of newly identified forms, which represent only a small proportion of ADCAs, have non-coding repeat expansions or “classical” mutations in other genes. Non-coding repeat expansions have been reported at the SCA8 (16), SCA10 (17) and SCA12 (18) loci. More recently, mutations in the genes encoding fibroblast growth factor 14 [FGF14/SCA27, (19,20)], protein kinase C gamma [PKCG/SCA14, (21-28)], spectrin beta III [SPTBN2/SCA5, (29)] and potassium channel KCNC3 [SCA13, (30)] were also implicated in ADCA cases. In addition, a point mutation in the promoter region of a gene on chromosome 16 encoding
puratrophin-1, a new Rho GTPase protein, was found in 52 Japanese ADCA type III families (31).

**SCA17/HDL4**

Spinocerebellar ataxia 17 (SCA17) or Huntington’s disease-like 4 (HDL4) is a rare neurodegenerative disorder (MIM#607136) that belongs to the group commonly referred to as “polyglutaminopathies” that also includes Huntington’s disease (HD), spinal and bulbar muscular atrophy and 6 other forms of ADCA (32). In the absence of treatment, they can all lead to dramatic neurological dysfunction and ultimately to death. The number of glutamines observed in the pathological proteins varies from 21 to >400 in the 9 diseases currently identified, but in most cases the phenotype manifests above a repeat number varying between 35 and 40. This class of disorders also shares, with few exceptions, other common clinical, genetic and physiopathological features suggesting common pathological mechanisms: i.e., a negative correlation between the size of the repeat expansion and the age at onset, anticipation with parental sex bias, instability of the repeat on expanded alleles and the formation of intranuclear inclusions in neurons.

SCA17 was first reported in a sporadic case of a complex neurological disorder with cerebellar ataxia, pyramidal signs and severe intellectual impairment. This patient carried 63 trinucleotide repeats in the gene encoding the TATA-box binding protein (TBP) on chromosome 6q27 (11). This new genetic entity was subsequently identified in familial ADCA cases and was shown to differ in several aspects from other polyglutaminopathies (33-35). Pathological expansions were also found in patients with an HD-like phenotype (HDL4) or with clinical features compatible with Alzheimer, Parkinson’s or Creutzfeldt-Jakob disease, highlighting the clinical heterogeneity of this genetic entity (36-38).

**TATA-box binding protein**
TBP is an important and general transcription factor ubiquitously expressed from a single gene on chromosome 6q27 and constitutes an integral component of the transcription initiation complexes of the 3 RNA polymerases (39-41). The TBP protein is the DNA-binding subunit of the RNA polymerase II transcription factor D (TFIID), a protein complex involved in mRNA transcription, and anchors the complex to the TATA box upstream of the first codon. The TBP protein also plays a role in TATA-less promoter genes by correctly positioning the polymerase on the DNA.

**Size and structure of the normal repeat in the TBP gene**

The N-terminus of the protein that modulates the DNA binding activity of the C-terminus (41), contains a long stretch of glutamines, as in other transcription factors or homeobox proteins (42). This repeat is impure and is encoded by 3 CAG stretches, interrupted by 1 to 3 CAA codons (Table 1). The glutamine stretch is polymorphic in the normal population and large population studies (>5000 control chromosomes) have determined that the normal range is between 25 to 42 residues, most alleles containing 32 to 39 repeats (11,33-35,37,40,43-45). The allelic distribution varies slightly, however, according to the ethnic/geographical origins (43,45). In a more recent Japanese study, alleles with up to 45 repeats were detected in the control population (38).

**Behaviour of the pathological expansions: range and incomplete penetrance**

Given its high polymorphism and the mean size of the repeat, which is above the pathological threshold of most polyglutamine diseases, the TBP gene was considered a good candidate gene for neurodegenerative and psychiatric diseases in which anticipation was suspected (40,45). An abnormally expanded CAG repeat (63 repeats) was initially described in a 14-year-old child with severe signs of ataxia and cognitive impairment without family history of neurological disorders (11). A series of studies world-wide subsequently reported familial cases with other repeat...
expansions in this gene and allowed the pathological range to be defined. The threshold for pathological expansions varies according to the study from 43 to 45 repeats (36,38,46-48). Sporadic patients carrying from 43 to 63 repeats have been identified, while affected members of families with dominant transmission of the disease carry between 45 and 66 CAG/CAA repeats (34-38,47-57).

Oda et al. reported a family in which one patient carried 43 repeats while another carried normal alleles, suggesting that this repeat size may not be pathogenic in this family (38). In addition, alleles with a similar number of repeats were reported in patients carrying known ADCA mutations and have been detected in controls, reinforcing the hypothesis that they are not pathogenic (38,48). In the absence of evidence of co-segregation of the allele with 44 repeats (36,38) and because of the overlap between controls’ and patients’ ranges, caution is needed in diagnosis for such small expansions, which so far have only accounted for sporadic cases.

Determination of the pathological threshold is also complicated by the existence of an incomplete penetrance, which has been suggested for patients carrying 45 to 49 repeats since healthy carriers with 46, 48 and 49 CAG/CAA repeats aged 59, 69 and 76 years, respectively, have been reported (36,52,54).

Instability and origin of the expansions in the TBP gene

Elongation of repeated CAG elements, alone or as the result of the loss of CAA interruptions, is the major mechanism leading to abnormally elongated SCA17 repeats (11,15,33-36,38,47,50-52,54-58). In 3 cases, including 2 de novo expansions, the expanded repeat is the result of partial duplication or insertion of repeats into the CAG/CAA stretch (11,57). Koide et al. excluded meiotic unequal crossover and suggested either a displacement of the 5’ end of the Okazaki fragment generating a flap endonuclease FEN1-resistant hairpin or unequal sister chromatid recombination potentially leading to partial intramolecular duplication (11). In SCA2, SCA6, SCA7 and HD, neomutations occur mostly on large normal paternal alleles which undergo the
expansion of pure repeats to the pathological range (59-66). In the two SCA17 de novo cases, expansions also occurred on paternal chromosomes carrying 37 to 39 repeats, although with a different mechanism.

The structure of the expanded repeat therefore varies according to i) the number of repeats in internal CAG stretches, particularly the third one in which most expansions occur, ii) the loss of CAA interruptions, which could influence the stability of the region, as well as iii) the presence of internal duplications or insertions (Table 1).

Compared to other polyglutamine diseases, the SCA17 mutation is unusually stable during parent-child transmissions. The discontinuous distribution of repeat size in different populations reflects this stability of the normal repeat (44). This may well result partially from the presence of CAA interruptions, as already observed in SCA1 or SCA2 normal alleles. This would make it unlikely for the multistep gradual expansion to be observed in SCA17. Indeed, the rare cases of intergenerational instability, with increases of +1 to +13, have only been reported in alleles lacking CAA interruptions, resulting in pure CAG stretches over 40 units (Table 1). In these instances, instability is observed both in paternal and maternal transmission (33,52,56).

**Epidemiology and relative frequency of SCA17/HDL4**

To date, ~55 SCA17 families or cases have been reported world-wide, representing approximately 130 patients. Most families/cases are from Japan (n=17 families) (11,34,38,50,67) and Germany (n=19 families) (33,48,49,52,54,55,68), a distribution reminiscent of SCA6, which is also frequent in both these countries. The remaining families, when the origins have been mentioned, are as follows: 9 from Italy (15,46,53,56,58,69), 3 from Taiwan (37,51), 2 from England (70), 2 from France (36), and one each from Belgium (35), the USA (57) and Portugal (47). The frequency of SCA17 ranges from 0.3 to 3% among studies of ADCA families (11,15,35,38,47,48,67) but represents less than 1% of HD-like patients (36,49). SCA17 was not
found in other series of ADCA or HD-like families (71-73). Its minimal prevalence was estimated to be 0.16/100,000 in the north-east of England (70).

More than ten SCA17 cases had no family history of neurological diseases; two of these cases were proven to result from *de novo* expansions (11,57) while incomplete penetrance was observed in four others (36,38,52,54), which emphasizes the importance of analyzing this gene in isolated cases with a compatible phenotype.

**Clinical heterogeneity of SCA17/HDL4**

A series of studies have attempted to establish the clinical spectrum of this particular and very heterogeneous form of ADCA (11,11,33-38,47-57,68,74). The clinical and neuropathological spectrum associated with this mutation appears to be broader than previously suspected.

The clinical signs in SCA17 patients reported in the literature are summarized in Table 2. The symptoms at onset, which occur at a mean age of 34.6 +/- 13.2 years (range: 3-75), are predominantly gait instability (15,47,56) or other movement disorders, such as focal dystonia (58,68) or chorea (36,49). Psychiatric disturbances such as behavioural changes, psychosis or depression as well as dementia can also represent the presenting symptoms (11,35,36,49).

At the time patients are examined, the most prevalent abnormality after cerebellar ataxia is dementia (77%). This is particularly important in clinical practice since overt and early dementia is rare in ADCA, with the exception of DRPLA. Psychiatric alterations (35,48,49,56,58) and abnormal movements are frequent, especially chorea, choreoathetosis, and dystonia (34,48,56,58,68,74). Parkinsonism occurs in half of the patients and epilepsy is commonly observed (34,58). Spasticity with brisk reflexes may also be found (11,33,38). The cardinal features of SCA17 are therefore the association of cerebellar ataxia with dementia and other movement disorders. These signs are typically observed in a small proportion of families with an HD-like phenotype, and indeed SCA17 accounts for less than 1% of HD-like cases with cerebellar ataxia (range: 43 to 52 repeats) (36,46,49,50,72). In addition, patients with
schizophrenia, multiple system atrophy, Parkinson’s disease with dementia-, Alzheimer disease- or Creutzfeldt-Jakob disease-like phenotypes have been reported to carry expansions in the TBP gene (range: 45 to 55 repeats) (37,51,57,75,76). SCA17 was not, however, found to be a common cause of Parkinson’s disease, primary dystonia, epilepsy, bipolar disorder or schizophrenia in large series (11,45,48,77,78).

After short disease durations (2-3 years), MRI findings vary greatly, from normal to moderate global atrophy or a focal atrophy of the cerebellum (33,68). After longer durations, the atrophy is always pronounced in the cerebellum, mild in the brain with relative sparing of the brainstem. Putaminal rim hyperintensities have been reported in one case (79). Dopamine transporter (putamen) and glucose metabolism (putamen cerebellum and caudate nucleus) have been found to be reduced in SCA17 patients (80).

Diagnosis is established by genetic testing and other laboratory investigations are not necessary. Unfortunately, once the disease has manifested, it is unremittingly progressive, leading to loss of autonomy, with death occurring at a mean age of 39 +/- 20 years, after a mean disease duration of 19 +/- 9 years. Treatment is purely symptomatic.

**Phenotype-genotype correlations**

The clinical picture and age at onset are variable even among patients of the same family carrying the same number of repeats, suggesting that the size of the repeat has a limited influence on the course of the pathology (35). There is a correlation, although not as strong as in other ADCAs (81), between the age at onset and the size of the repeat (Figure 1). Exponential regression shows that only 64% of the variance in the age at onset is explained by the repeat size. The influence of modifier genes could be crucial to explain the remaining variance and could also account for the wide clinical heterogeneity. Since most of the SCA17 expansions are stable, it is unlikely that somatic mosaicism of the size of the expansion accounts for the inter-individual variability, in contrast to other polyglutaminopathies. Alternatively, the very low correlation could be due to
the difficulty in determining the exact age at onset because of the variability in the presenting sign, which is not always cerebellar ataxia. Interestingly, age at death correlated with the size of the triplet repeat in a small cohort of 16 patients of diverse origins (Figure 1) (34,35,48,56,58,74).

Anticipation does not appear to be a feature of this disease, which is in accordance with the very rare instability of the CAG/CAA repeat. Maltecca et al., however, reported a familial case with a marked anticipation associated with a marked instability of the repeat (56).

Homozygosity has been shown to lower the age at onset in DRPLA, SCA3 and SCA6, but not in HD, which, however, shows increased severity (82-85). Three SCA17 patients homozygous for repeat expansions in the TBP gene were not more severely affected than patients carrying one abnormal copy of the gene, supporting a gain of function hypothesis (38,50,54). This might be due to incomplete penetrance of one of the expanded alleles. Neuropathological alterations did however extend to the hippocampus and brainstem in one homozygous patient (50).

Neuropathology of SCA17/HDL4

While the clinical profile of SCA17 is reminiscent of DRPLA, its neuropathological basis differs. Neuropathological lesions are mild in the brainstem compared to other ADCA entities (35) but are similarly marked in the cerebellum and the cerebral cortex.

Six patients’ brains have been investigated neuropathologically and showed similar features (34,35,48,50,58). There was a mild global atrophy of the brain, predominant in the cerebellum because of severe Purkinje cell loss and Bergman’s gliosis. Neuronal loss was mild in the dentate nucleus (except in Rolfs et al., ref. 48) and the granular layer. Atrophy was moderate in the cerebral cortex, predominating in the motor cortex and visual areas with abnormal arborisation of neuronal dendrites and spongiosis (35,50,58). In the brainstem, the pontine nuclei were spared but the locus coeruleus and the substantia nigra were mildly affected, with a few deposits of free melanin pigment in the latter (35,58).
There were, however, differences according to the size of the repeat and/or disease duration. Atrophy of the substantia nigra was only observed in patients with the longest disease duration (48). The inferior olivary nuclei were also atrophied in all but one patient, who carried the smallest repeat size (n=46) and had a disease duration of only 10 years (35,48,58). Similarly, the basal ganglia were spared in this patient (35), whereas atrophy was severe in the other patients, particularly in the caudate nucleus (50,58). Finally, the spinal cord was normal except in a patient with a 54-repeat expansion and a 24-year disease duration, who showed a loss of anterior horn cells (48). There were no significant differences at the pathological level between heterozygous and homozygous patients, except additional atrophy of the hippocampus in one of the latter (50).

**Physiopathological consequences of the expansion**

The SCA17 gene product, TBP, has a well known function and is widely expressed in the central nervous system and other tissues, which contrasts with the selective pattern of degeneration observed in patients.

As in other ADCAs, the pathological hallmarks of this disease are the presence of neuronal intranuclear inclusions (NIIs) containing the pathological proteins, as well as heat shock proteins and ubiquitin (34,35), however with a lower frequency. Staining, using specific antibodies or the 1C2 antibody (14,86), is essentially nuclear, often diffuse and is focal in 0 to 3% of the neurons according to the structure (50,58). NIIs were not detected in visceral organs (50) but have been observed in various structures of the brain. They are found predominantly in the cerebral cortex and the basal ganglia, the mid-brain reticular formation, but also in structures that are spared, such as the pontine nuclei, dentate nucleus, anterior horn and inferior olives (35,50,58). However, they are not detected in Purkinje cells, which severely degenerate (48). In general, except for the cerebral cortex, there is an inverse correlation between the presence of NIIs and the severe lesions in a given structure (35,58): i.e., no NIIs are detected in the Purkinje and granule cell
layers or in the locus coeruleus, all of which degenerate, but they are detected in the putamen, dentate nucleus and pontine nuclei, which are unaffected or only mildly affected (35). Moderate atrophy of the inferior olivary nuclei was, however, reported in one case which had the highest density of NII s (58). More interestingly, Bruni et al observed a link between the density of diffuse nuclear staining and cell loss, suggesting a more toxic effect of the non-aggregated protein (58).

The fact that the lack of TBP in TBP knock-out mice is embryonic lethal, whereas homozygosity for SCA7 trinucleotide expansions in humans is not, indicates that the expansion is not responsible for a major loss of TBP function (87). The absence of major differences between heterozygous and homozygous carriers suggests complete dominance, which is compatible with a gain of function mechanism or with a dominant negative effect of the mutation.

In vitro, SCA17 models demonstrated that the increase in the size of the glutamine stretch inside full-length TBP enhances its insolubility and aggregation as well as the transcription of a CRE-mediated luciferase reporter gene (44). Interestingly, TBP is sequestered in other polyQ diseases, suggesting its direct involvement in the transcription deregulation, although this is an early downregulation of transcription (88-90). The exact mechanisms remain unknown but, given the role of TBP in anchoring the transcription machinery to the DNA, it can be postulated that alteration of the tertiary structure of this protein would lead to an alteration of its binding to the DNA and/or activation or binding function of other TFIID components.

Conclusion

SCA17 is a rare neurodegenerative disorder occurring in Asians and Caucasians. The cardinal features are the association of cerebellar ataxia, dementia, psychiatric features and parkinsonism, with frequent occurrence of abnormal movements such as chorea or dystonia. This clinical profile overlaps with those of other neurodegenerative diseases and patients with Alzheimer disease-like, Creutzfeldt-Jakob disease-like or Parkinson’s disease-like phenotypes or, more
importantly, with a Huntington’s disease-like phenotype (HDL4) have been reported to carry SCA17 mutations.

SCA17 is caused by CAG expansions that can be associated with a loss of CAA interruptions, or partial CAG/CAA repeat duplications in the TBP gene, leading to polyglutamine expansions above 43-44 repeats. Incomplete penetrance concerns repeats between 45 and 49 units and the repeat is stable except in expanded alleles having lost CAA interruptions. The pathogenicity of repeats with 43 and 44 repeats remains unclear. These features have consequences for genetic counselling, particularly the existence of reduced penetrance for presymptomatic testing.

TBP and ubiquitin-positive NIIs are detected in the cerebral cortex, basal ganglia, pons and dentate nucleus but are absent in Purkinje cells, a pattern that does not match perfectly with neuronal loss. Atrophy mainly concerns the cerebellum, with global atrophy of the cortex, dentate nucleus, substantia nigra and locus coeruleus.

TBP, which is also involved in other polyglutamine disorders, probably represents a key element of the pathology in these disorders, all of which are associated with transcription deregulation.

Acknowledgments

The authors’ work is financially supported by grants from the European Community (to the EUROSCA network), the Verum Foundation, the association Connaître les Syndromes Cérébelleux (to the SPATAX network) and the Programme Hospitalier de Recherche Clinique.
References


43. Gostout B, Liu Q, Sommer SS. "Cryptic" repeating triplets of purines and pyrimidines (cRRY(1)) are frequent and polymorphic: analysis of coding cRRY(1) in the proopiomelanocortin (POMC) and TATA-binding protein (TBP) genes. Am J Hum Genet. 1993;52:1182-1190.


45. Rubinsztein DC, Leggo J, Crow TJ, DeLisi LE, Walsh C, Jain S et al. Analysis of polyglutamine-coding repeats in the TATA-binding protein in different human populations


75. Lin IS, Wu RM, Lee-Chen GJ, Shan DE, Gwinn-Hardy K. The SCA17 phenotype can include features of MSA-C, PSP and cognitive impairment. Parkinsonism Relat Disord. 2006;

76. Lee-Chen GJ, Lane HY, Chen CM, Wu YR, Ro LS, Chen FL et al. Expanded trinucleotide repeats in the TBP/SCA17 gene mapped to chromosome 6q27 are associated with schizophrenia. Schizophr Res. 2005;


Homozygosity for CAG mutation in Huntington disease is associated with a more severe clinical course. Brain. 2003;126:946-955.


Figure 1. Correlation (exponential) between age at onset (n=87, $r^2=0.41$) or age at death (n=16, $r^2=0.78$) and the size of the repeat in SCA17 affected patients [(11,15,33-36,38,47-52,54,56-58,68-70,74,79,80) and unpublished data].
**Table 1.** Structure of the CAG/CAA repeat in wild type and expanded alleles (11,15,33-36,38,47,50-52,54-58,70)

<table>
<thead>
<tr>
<th>Repeat number</th>
<th>Structure of the repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>25-42* CAG3 CAA3 CAG7-11 CAACAGCAA CAG9-21 CAACAG</td>
</tr>
<tr>
<td>Koide et al. 1999 (11) spo, de novo</td>
<td>63 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Shatunov et al. 2004 (57) spo, de novo</td>
<td>55 CAG3 CAA3 CAG9 CAACAGCAA CAG9-21 CAACAG</td>
</tr>
<tr>
<td>Nakamura et al. 2001 (34) spo</td>
<td>55 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Fujigasaki et al. 2001 (35) spo</td>
<td>46 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Nakamura et al. 2001 (34) spo</td>
<td>46 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Nakamura et al. 2001 (34) spo</td>
<td>46 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Zuhlke et al. 2001 (33) spo, homoZ</td>
<td>51 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Stevanin et al. 2003 (36) spo, reduced penetrance</td>
<td>46 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Stevanin et al. 2003 (36) spo</td>
<td>46 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Zuhlke et al. 2003 (55) spo, homoZ</td>
<td>47 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Zuhlke et al. 2003 (54) reduced penetrance</td>
<td>48 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Oda et al. 2004 (38) 4 spo, 1 homoZ</td>
<td>44-47 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Brusco et al. 2004 (15) spo, reduced penetrance?</td>
<td>45 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Brusco et al. 2004 (15) spo</td>
<td>45 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Toyoshima et al. 2004 (50) homoZ</td>
<td>46 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Bruni et al. 2004 (58) spo</td>
<td>52 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Wu et al. 2004, 2005 (51) spo</td>
<td>46 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Craig et al. 2005 (70)</td>
<td>52 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Craig et al. 2005 (70)</td>
<td>44 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Maltecca et al. 2003 (56) paternally unstable</td>
<td>53-66 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Zuhlke et al. 2001 (33) maternally unstable</td>
<td>53-55 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
<tr>
<td>Zuhlke et al. 2005 (52) paternally unstable reduced penetrance</td>
<td>49-53 CAG3 CAA3 CAG9 CAACAGCAA CAG15 CAACAGCAA CAG17 CAACAG</td>
</tr>
</tbody>
</table>

spo: sporadic cases; homoZ: homozygous cases; *the structure of the wild-type alleles has not been determined in all cases.
Table 2. Frequency of the most commonly associated neurological signs reported in SCA17 patients (11,33-38,47-57,68-70,74,79)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of families</td>
<td>51</td>
</tr>
<tr>
<td>No. of patients</td>
<td>122</td>
</tr>
<tr>
<td>Mean age at onset (range)</td>
<td>34.6 +/- 13.2 (3-75 years)</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>97% (78/80)</td>
</tr>
<tr>
<td>Dementia</td>
<td>77% (54/70)</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td>67% (36/54)</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>57% (23/40)</td>
</tr>
<tr>
<td>Abnormal movements</td>
<td>56% (42/75)</td>
</tr>
<tr>
<td><em>Dystonia</em></td>
<td>64% (28/44)</td>
</tr>
<tr>
<td><em>Chorea, choreoathetosis</em></td>
<td>36% (16/45)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>50% (24/48)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>35% (15/43)</td>
</tr>
</tbody>
</table>