Chapter 10
Spinocerebellar Ataxia Type 17 (SCA17)

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Abstract In 1999, a polyglutamine expansion was identified in the transcription factor TATA-binding protein (TBP) in a patient with ataxia with negative family history. Subsequently, CAG/CAA repeat expansions in the TBP gene were identified in families with spinocerebellar ataxia (SCA), establishing this repeat expansion as the underlying mutation in SCA type 17 (SCA17). There are several characteristic differences between SCA17 and other polyglutamine diseases. First, SCA17 shows a complex and variable clinical phenotype, in some cases overlapping that of Huntington's disease. Second, compared to the other SCA subtypes caused by expanded trinucleotide repeats, anticipation in SCA17 kindreds is rare because of the characteristic structure of the TBP gene. And thirdly, SCA17 patients often have diagnostic problems that may arise from non-penetrance. Because the gap between normal and abnormal repeat numbers is very narrow, it is difficult to determine a cutoff value for pathologic CAG repeat number in SCA17. Herein, we review the clinical, genetic and pathologic features of SCA17.

Keywords Spinocerebellar ataxia · Huntington's disease-like · Chorea
Dystonia · Dementia

10.1 Clinical Features

SCA17 is an autosomal dominant cerebellar ataxia caused by abnormal expansion of a CAG/CAA repeat encoding a polyglutamine (polyQ) tract in the TATA-box binding protein (TBP) gene on chromosome 6q [1–4]. Though the genetic abnormalities are mostly observed as a hereditary trait, de novo mutations have also been reported [2, 5, 6].

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The clinical symptoms of SCA17 are mainly ataxia and/or dementia, as is the case for other forms of autosomal dominant SCA [7]. However, SCA17 is a more complex disease with extensive phenotypic variability, and the age at onset spans several decades. Clinical heterogeneity can be observed even within the same family [8]. In the present literature review of SCA17 patients (Table 10.1), the age at onset ranged from 3 to 60 years, and about half of the patients developed ataxia as the initial symptom. The age at onset appeared to correlate weakly with the number of repeats (Fig. 10.1). During the disease course, most of the patients (>90%) developed ataxia, which was manifested as gait instability, and slurred speech. Cognitive dysfunction and memory disturbance have also been recognized as an initial symptom [9]; dementia is the second most common symptom (73%) during the disease course. In childhood, mental deterioration may occur instead of dementia. Psychiatric symptoms, such as aggression [10], paranoia [1], euphoria [11] and depression [12, 13] are observed frequently. Behavior or personality changes as initial symptoms may indicate the presence of psychiatric disorders.

Involuntary movement is one of the characteristic features of SCA17 [14, 15]. As chorea is a well-known symptom of SCA 17, the clinical phenotype sometimes overlaps that of Huntington's disease (HD), being characterized by the triad of movement disorder, psychiatric manifestations and cognitive impairment [16]. In many cases of clinically suspected HD, patients lack the CAG repeat expansion that causes HD. Such individuals are said to have HD phenocopy syndromes or HD-like disorders [17–23]. SCA17 has therefore also been termed Huntington's disease-like 4 (HDL4; OMIM #607136) [24]. Wild et al. [21] identified gene abnormalities in 285 HD phenocopy patients in the United Kingdom. Among the patients, five (1.8%) were found to have expansions in *TBP* causing SCA 17. One patient (0.4%) had a 6-octapeptide insertion in the prion protein gene (*PRNP*) [25], and one had HDL2 caused by a pathogenic expansion in the janctofillin gene (*JPH3*) [26]. In addition, one patient was diagnosed later as having Friedreich's ataxia with homozygous expansion in the flataxin gene (*FXN*) [27]. Moss et al. [28] recently reported that ten (1.95%) of 514 HD phenocopy patients had an expanded hexanucleotide repeat in the C9orf72 gene. If patients with HD-like disease have no mutations in huntingtin, the TBP and C9orf72 genes should be examined.

We have previously examined the relationship between repeat number and clinical symptoms (Toyoshima et al. 1993), and found that more than 75% of patients with a CAG/CAA repeat size of 43–50 had intellectual deterioration; in some individuals, intellectual problems and involuntary movements were the only signs. Psychiatric problems or dementia, parkinsonism and chorea, a clinical constellation resembling Huntington disease, are observed more frequently in individuals with CAG/CAA repeats in this range than in those with larger repeats. All individuals showing a CAG/CAA repeat size of 50–60 have ataxia and 75% have reduced intellectual function. Pyramidal signs (e.g., increased deep tendon reflexes) and dystonia are more common in these individuals than in those with smaller repeats. These features were also confirmed in the present literature review (Table 10.1). Two children with over 60 repeats have been reported. One, a familial example, with a CAG/CAA expansion of 66 repeats developed gait disturbance at

Table 10.1 Summary of the clinical features in the SCA17 patients

sex	age at onset	initial symptom	ataxia	dementia	involuntary movement	pyramidal signs	extra pyramidal signs	psychiatric symptoms	CAG/CAA expansion	references
F	60	chorea	–	nc	chorea	–	nc	depression	41	Park et al. [44]
F	35	hand discoordination	nc	nc	chorea, trunk titubation	+	+	depression	41	Herrera et al. [12]
M	59	slurred speech	+	nc	poly-mini-myoclonus	–	–	–	41	Doherty et al. [32]
M	50	ataxia	+	+	nc	+	nc	nc	41	Nanda et al. [42]
M	42	reduced speed working	+	++	–	+	+	nc	43	Nielsen et al. [9]
F	29	gait instability,behavioral change	++	+	chorea	+	–	nc	44	Stevanin et al. [14]
M	48	gait instability	+	+++	dyskinesia	nc	nc	nc	44	Mariotti et al. [13]
F	40	gait instability	+	nc	nc	nc	nc	introvert	44	
F	36	gait instability	+	+	nc	nc	nc	nc	44	
M	41	behavioral change	+	+	dyskinesia	+	nc	nc	45	
F	38	depression	nc	+++	nc	+++	nc	depression	45	
F	40	gait instability	+	+	dyskinesia	nc	nc	nc	45	
M	34	gait instability	+	–	dyskinesia, tremor	+	nc	nc	45	
M	55	chorea	+	nc	chorea, dyskinesia	nc	nc	nc	45	
F	52	gait instability	+	+	dyskinesia	nc	nc	nc	45	
M	55	gait instability	+	+	nc	nc	nc	nc	45	
M	nc	ataxia, urinary dist.	+++	+	–	+	++	euphoria	45	Lin et al. [11]
F	30	speech dist., depression	+	nc	nc	nc	++	depression	45	Rolfs et al. [31]
M	43	gait ataxia	+	nc	nc	nc	nc	depression	45	
F	30	depression	+	+	dystonia, chorea	+	nc	depression, aggression, paranoia	45	
M	23	speech dist, gait ataxia	+	nc	nc	+	nc	–	45	
M	19	behavioral change	+	+	dyskinesia	nc	nc	nc	46	Mariotti et al. [13]
F	44	gait instability, fall, IVM	+	++	chorea, myoclonus	–	+	depression, aggression	46	Schneider et al. [20]
M	37	gait instability, fall, IVM	+	++	chorea, myoclonus	nc	nc	depression, aggression	46	
F	45	gait instability, fall, IVM	+	++	chorea, myoclonus	nc	nc	depression, aggression	46	
F	23	behavioral change, chorea	+	+	chorea	+	+	nc	46	Stevanin et al. [14]
M	37	paranoia psychosis	+	+	choreoathetosis	+	–	paranoia, psychosis	46	Fujigasaki et al. [1]
F	55	ataxia, dementia	+	+	–	+	+	nc	46	
nc	40	nc	+	+	chorea	+	+	nc	47	Nakamura et al. [3]
nc	28	nc	–	+	–	+	+	nc	47	
nc	39	nc	+	+	dystonia	+	+	nc	48	
nc	48	nc	+	+	chorea	+	+	nc	48	
F	38	depression	–	nc	nc	nc	nc	hallcination, suicide attempts	49	Rolfs et al. [31]
F	16	cognitive decline, gait ataxia	+	+++	nc	nc	nc	nc	49	
F	48	chorea	+	nc	chorea	nc	+	paranoia	50	Mariotti et al. [13]
M	55	behavioral change	+	+	dystonia, dyskinesia	nc	nc	nc	50	
M	13	mental deterioration	+	+	–	+	+	nc	51	Zühlke et al. [4]
M	35	ataxia	+	+	nc	nc	nc	nc	52	Belluzzo et al. [30]
F	35	depression	+	+	dyskinesia	nc	nc	depression	52	Mariotti et al. [13]
F	25	paranoia	nc	+++	nc	+++	nc	paranoia	53	
F	35	ataxia	+	+++	dystonia	nc	+	++	53	Maltecca et al. [29]
M	34	ataxia	+	++	dystonia	nc	nc	++	53	
M	23	ataxia	+	++	dystonia	+	+	++	53	
F	34	ataxia, dystonic posture, personality change	+	+	dystonia	++	++	mood change	53	Zühlke et al. [4]
F	34	personality change	+	+	nc	+	+	euphoria	53	Fujigasaki et al. [1]
F	25	gait ataxia	+	++	dystonia, chorea	+	+	nc	54	Koutsis et al. [8]
F	22	gait ataxia	+	+	nc	–	+	depression	54	
F	25	speech dist., memory dist.	+++	+	dystonia	++	++	nc	54*	Bech et al. [5]
M	36	ataxia, psychiatric sign	+	+++	dystonia, chorea	+	nc	aggression, paranoia	54	Rolfs et al. [31]
M	18	ataxia, dementia	+++	++	nc	+	nc	nc	54	
F	23	hallucination	++	+	dystonia, chorea	+	nc	mania	54	
F	18	speech dist.	+	nc	nc	nc	nc	–	54	
M	18	ataxia	+	nc	dystonia	nc	nc	–	54	
nc	20	cognitive dysfunction	+	++	nc	nc	nc	nc	55*	Wu et al. [74]
F	20	dystonic mov. of fingers	+	–	dystonia torcicollis	–	–	nc	55	Zühlke et al. [4]
nc	19	nc	+	+	dystonia	+	+	nc	55	Nakamura et al. [3]
nc	25	nc	+	+	dystonia	+	+	nc	55	
F	6	mental deterioration, gait dist.	+	++	–	+	–	nc	63*	Koide et al. [2]
F	3	ataxia	+	+++	dystonia	+	+	++	66	Maltecca et al. [29]

-, unaffected. +, mild. ++, moderate. +++, severe. nc = not commented, IVM = involuntary movement

Shadowed columns; gray = over 50 CAG/CAA repeats, patients having chorea (red), dystonia (green), and the both (blue). *de novo mutation. References column filled with the first author's name

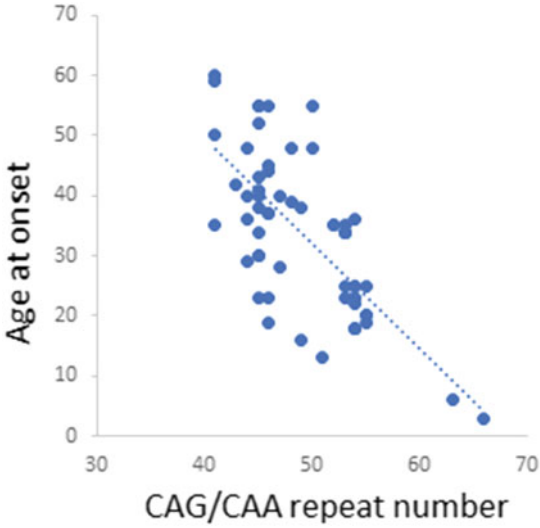

Fig. 10.1 Correlation between age at onset (years) and CAA/CAG repeat number on the expanded allele

the age of 3 years followed by spasticity, dementia and psychiatric symptoms [29]. The other, with a de novo CAG/CAA expansion of 63 repeats, developed ataxia and intellectual deterioration at the age of 6 years, followed later by spasticity [2].

Less common symptoms reported are epilepsy [1–3, 13, 29–31] (20%), autonomic symptoms [4, 11, 31, 32] (9%), apraxia [31] (7%) and peripheral nerve symptoms [12, 13, 29] (3%). Lin et al. [11] reported a patient who developed ophthalmoplegia with parkinsonism, and Rolfs et al. [31] reported a patient showing hypogonadism.

Neuroradiological examination has been reported to demonstrate several characteristic features. In early reports, some degree of cerebellar and cerebral atrophy was shown on MRI [1, 3]. Later, putaminal rim hyperintensity on T2-weighted images was also reported [33]. Striatal hyperintensity on MRI has been reported in a range of disease conditions, including SCA2 [34], dentatorubral-pallidoluysian atrophy (DRPLA) [35], neuroacanthocytosis [36], mitochondrial cytopathy [37] and multiple system atrophy (MSA) [38, 39]. Functional imaging using radioisotopes is helpful for understanding the pathophysiological conditions in the basal ganglia. Günther et al. [40] measured striatal pre-synaptic dopamine transporter (DAT) availability and striatal dopamine D2 receptor (D2R) expression using [^{123}I]FP-CIT and [^{123}I]IBZM, respectively, applying a brain-dedicated single-photon emission computed tomography (SPECT) system; [^{18}F] Fluordeoxyglucose positron emission tomography scanning (PET) was also used for measurement of glucose metabolism. They found that the striatum had a reduction in the availability of presynaptic dopamine transporters, although postsynaptic dopamine D2 receptor binding capacity was reduced only slightly, whereas marked reduction of glucose metabolism was evident in the basal ganglia. Lin et al. [11] reported a patient with parkinsonism partially responsive to L-dopa administration, in whom presynaptic degeneration of the nigrostriatal dopaminergic system was manifested by a marked decrease of dopa uptake in the striatum, as demonstrated by [^{18}F]-6-fluorodopa PET.

10.2 Genetic Cause and Penetrance of SCA17

SCA17 is caused by abnormal expansion of the TBP gene on chromosome 6q. TBP is a transcription factor with a polyglutamine tract encoded by the CAG/CAA sequence [1–3]. The normal repeat range reported is from 25 up to 42–45 units, varying among studies. The highest number of repeats reported to date is 66 [29]. Expansions of between 41 and 49 repeats may constitute an intermediate range with incomplete penetrance. In our previous review [41], the pathologic number of repeats was 43 or more. However, there have been reports of patients with 41 repeats, presenting with progressive cerebellar ataxia and/or involuntary movements [12, 32, 42], late-onset chorea and psychiatric symptoms [43] and parkinsonism with chorea [44]. On the other hand, healthy individuals with 45 [45] and 49 repeats [46] have also been recognized. Because the gap between normal and abnormal numbers of repeats is very narrow, it is difficult to determine the cutoff value for the pathologic number of CAG repeats in SCA17. Shin et al. [47] reported very interesting results from large genetic study conducted in Korea. They examined 2099 patients (classified by dominant clinical phenotype: parkinsonism, n = 1706; ataxia, n = 345; chorea, n = 37; and dystonia, n = 11) and 522 normal controls, and reported that 64 patients had 42 repeats or less (3%) in the TBP gene. Forty-five repeats were the greatest number in normal populations. They recommended that 41 through 45 repeats should be considered as the intermediate range, requiring cautious interpretation.

Compared to the other SCA subtypes caused by expanded trinucleotide repeats, anticipation [48] is rare in SCA17 kindreds because interruption of CAA within the CAG repeat configuration of the TBP gene stabilizes the microsatellite [49, 50]. The allele basic structure is (CAG)3 (CAA)3 (CAG)n CAA CAG CAA (CAG)n CAA CAG. However, when the basic structure is broken, anticipation may be observed [50]. Maltecca et al. [29] reported a family showing marked anticipation. PCR analysis of the CAG repeat region within the TBP gene in the third generation showed a 300-base-pair (bp) band (53 CAG/CAA repeats), whereas the patient in the fourth generation showed a band of ~330 bp (66 repeats). The allele structure of the father was (CAG)3 (CAA)4 (CAG)44 CAA CAG, and that of the daughter was (CAG)3 (CAA)4 (CAG)57 CAA CAG. The basic allele structure was not conserved in patients whose alleles had a simplified pattern with loss of CAA interruptions, possibly leading to a reduction of repeat stability.

We previously reported a patient having 48 CAA/CAG repeats as a homozygous state [15]. The clinical features of that patient essentially did not differ from those of heterozygotes, although homozygosity might have exerted some influence on the severity and progression of dementia. Zühlke et al. [51] also reported a patient who had 47 homozygous glutamine residues caused by apparent partial isodisomy 6. Compared with the heterozygote, the patient had no apparent differences in clinical features.

Almost all SCA17 patients have a family history and the disease is inherited as an autosomal dominant trait. However, a few cases develop de novo mutations in

the TBP gene. One example is the child with 63 repeats mentioned above [2]. In addition, [5] reported a 33-year-old woman presenting with a HD-like phenotype with a de novo 54 CAG/CAA repeat expansion, and Wu et al. (2004) described a de novo 55 CAG repeat expansion in a patient with a Pakinson's disease phenotype. The presence of such cases indicates that even in the absence of a positive family history, genetic testing for SCA17 should be considered in patients with a HD-like, or PD-like, phenocopy.

10.3 Pathological Findings

Several reports have described the pathological findings in SCA17 patients [1, 52]. We previously reported a homozygous patient focusing on the histopathological findings; the patient did not show earlier onset of the disease than heterozygotes reported with similar CAA/CAG-repeat sizes, and the pathological features appeared to be very similar, if not identical, to those described for heterozygotes [15].

The patient died at the age of 49 years, about 6 years after disease onset. The main symptoms were dementia and choreic movement. At autopsy, the brain showed mild atrophy in the caudate nucleus and putamen (Fig. 10.2). Histologically, mild neuronal loss and gliosis were observed in the cerebral cortex, especially the deep layers. Neuronal loss was moderate in the neostriatum, affecting both small and large neurons, and in the Purkinje cell layer with Bergmann gliosis (Fig. 10.3). Mild neuronal loss was also evident in the cornu ammonis region 1 (CA1) of Ammon's horn, subiculum, parahippocampal gyrus, substantia nigra, brainstem reticular formation, and inferior olivary nucleus. It is known that the formation of neuronal intranuclear inclusions (NIIs) is a common hallmark of the CAG repeat diseases [53]. In the above SCA17 patient, immunohistochemistry showed that expanded polyQ stretches had accumulated in the neuronal nuclei in a diffuse pattern [54, 55] (Fig. 10.4a), and no labeling was detected in their cytoplasm or in the neuropil. NII formation was rare (<1%) in affected neurons and was restricted to brain regions

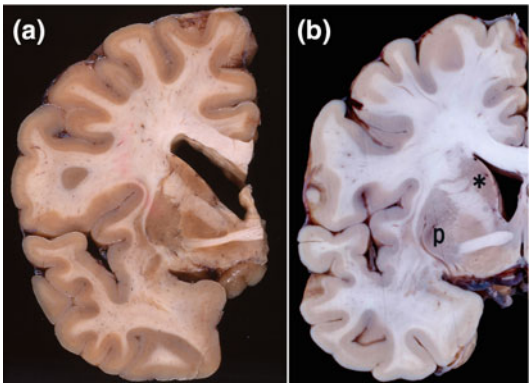

Fig. 10.2 Coronal section of the patient (**a**) showing mild atrophy of the caudate nucleus (*) and putamen (p). (**b**) Age matched control

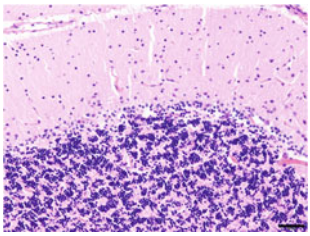

Fig. 10.3 There is moderate loss of Purkinje cells with Bergmann gliosis in the cerebellum. The granule cells are well preserved. Hematoxylin and eosin. Scale bar = 50 μm

such as the cerebral cortex (Fig. 10.4b), putamen, and midbrain reticular formation. The intranuclear diffuse accumulation of polyQ involved many neurons in a wide range of CNS regions far beyond the lesion distribution assessed by neuronal loss. Regions in which more than 40% of neurons were 1C2- immunoreactive included the sixth layer of the cerebral cortex (Fig. 10.5a), neostriatum, hippocampal formation (CA1 and subiculum) (Fig. 10.5b) and Purkinje cell layer. Of note was the high frequency (>60%) of nuclear 1C2 immunoreactivity in the large neurons of the neostriatum. Brain regions showing a frequency of 20–40% included the cerebral cortical layers III and VI, subthalamic nucleus, and inferior olive. In the white matter, a few glial nuclei also were immunolabeled for 1C2. No positive staining was observed in the visceral organs.

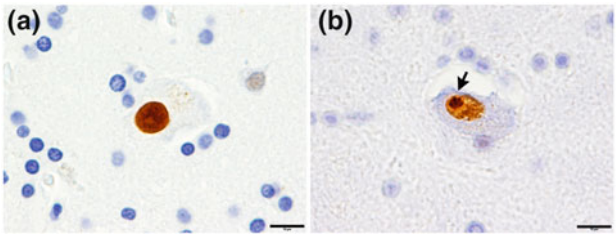

Fig. 10.4 The neuronal nuclei are often stained diffusely by 1C2 (**a**). There are a few neurons showing intra nuclear inclusion (**b**, arrow). **a** putamen. **b** brainstem reticular formation. Immunohistochemistry with a monoclonal antibody (1C2). Scale bar = 10 μm

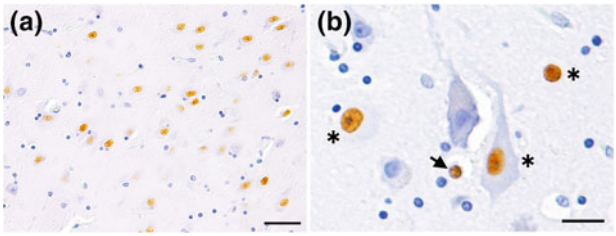

Fig. 10.5 There are many 1C2-positive nuclei in the subiculum of the hippocampal formation (**a**). 1C2-positive neuronal nuclei in the neurons (*) and an oligodendrocyte (arrow) (**b**, frontal cortex). Immunohistochemistry with 1C2. Scale bar = **a** 50 μm, **b** 20 μm

Intranuclear accumulation of mutant proteins has been recognized in many polyQ-disease brains of humans [56, 57] and transgenic mice [54]. The wide neuronal intranuclear distribution of the mutant proteins in the CNS far beyond the lesions assessed by neuronal loss must be important when considering the clinical and pathological correlations in polyQ diseases, including SCA17 [54, 56, 57].

10.4 Pathophysiological Reviews

The molecular mechanisms responsible for the pathogenesis of the polyQ diseases have not yet been completely explained [58, 59]. PolyQ expansion renders the protein more prone to aggregation and formation of inclusion bodies that are a pathological hallmark of polyglutamine diseases [60, 61]. Early discussions focused on whether the tendency of mutant polyQ proteins to aggregate was responsible for the disease-associated neurodegeneration (gain of function). Yet, several studies have indicated that disease severity can be disassociated from the presence of inclusions [62–64]. Moreover, there are data indicating that inclusions may be protective, perhaps as a result of sequestration of the mutant protein [62, 65, 66].

Several disease models, including cells [67, 68], *Drosophila* [59, 69, 70] and rodents [71–74], have been generated to clarify the pathomechanisms of SCA17. Overexpression of full-length-mutant TBP and truncated-mutant TBP lacking the DNA-binding domains (DBDs) was found to cause formation of inclusions, suggesting that insoluble aggregates are causative factors and that the neurotoxicity of mutant TBP is independent of DNA binding [69]. Thus, the pathogenesis of SCA17 seems similar to that of other polyQ diseases [75]. On the other hand, whether or not expanded polyQ tracts affect the function of TBP has yet to be comprehensively addressed. TBP is a general transcription factor [76, 77] essential for formation of the transcription preinitiation complex and transcription of RNA polymerases I, II and III (Pol I, II and III). Aberrant TBP activity is expected to profoundly affect normal cellular function. Inactivation of TBP in mice causes downregulation of Pol I and Pol III transcription, growth arrest and cell death [78]. Friedmann et al. [79] have reported that polyQ expansion reduces in vitro binding of TBP to DNA. Furthermore, they observed that polyQ-expanded TBP fragments, which were incapable of binding DNA, formed nuclear inclusions and caused a severe neurological phenotype in transgenic mice. Huang et al. [80] reported muscle dysfunction in a knock-in mouse model that had long polyQ repeats. They considered that decreased interaction between mutant TBP and MyoD, a muscle-specific transcription factor [81, 82], might affect the association between MyoD and the DNA promoter, thus reducing its transcriptional activity. Hsu et al. [69] recently reported that deactivation of TBP may contribute to SCA17 pathogenesis. They generated novel *Drosophila* models for SCA17 that overexpressed polyQ-expanded TBP, and demonstrated neurotoxic aggregates, the mutant TBP sequestering wild-type TBP in the neuroblasts of the flies. Moreover, they generated *Drosophila* mutants with loss of TDP (dTbp) to examine whether the neurodegeneration was the same as that

of the SCA-17 model flies. They confirmed that loss of TDP function caused age-associated neurodegeneration in *Drosophila*. Interestingly, they reported that dTbp expression exacerbated retinal degeneration induced in polyQ-expanded SCA3 and Huntington's disease fly models. These findings suggest that dysfunction of TBP may play a universal role in polyQ-induced neurodegeneration. Therefore, it is very significant to study the pathophysiology of SCA17 to clarify the causes of other polyglutamine diseases.

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