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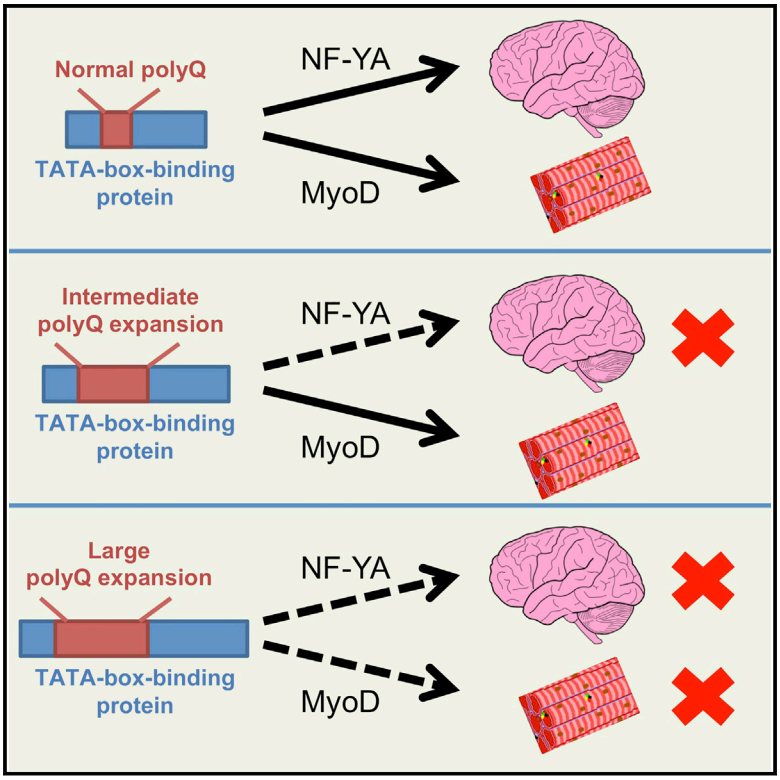
Large Polyglutamine Repeats Cause Muscle Degeneration in SCA17 Mice

Graphical Abstract



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In Brief

Huang et al. find that a large polyglutamine repeat in TATA-box-binding protein causes preferential muscle degeneration in a knockin mouse model of spinocerebellar ataxia 17. Muscle degeneration is caused by reduced expression of muscle-specific genes, which resulted from an impaired association of TBP with MyoD, a muscle-specific transcription factor.

Highlights

- A large polyQ repeat in TBP causes primary muscle degeneration
- The severity of muscle degeneration is polyQ-number dependent
- Different polyQ numbers differentially affect TBP's interaction with NF-YA and MyoD
- Impaired transcriptional activity of MyoD underlies muscle degeneration in SCA17

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Large Polyglutamine Repeats Cause Muscle Degeneration in SCA17 Mice

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SUMMARY

In polyglutamine (polyQ) diseases, large polyQ repeats cause juvenile cases with different symptoms than those of adult-onset patients, who carry smaller expanded polyQ repeats. The mechanisms behind the differential pathology mediated by different polyQ repeat lengths remain unknown. By studying knockin mouse models of spinal cerebellar ataxia-17 (SCA17), we found that a large polyQ (105 glutamines) in the TATA-box-binding protein (TBP) preferentially causes muscle degeneration and reduces the expression of muscle-specific genes. Direct expression of TBP with different polyQ repeats in mouse muscle revealed that muscle degeneration is mediated only by the large polyQ repeats. Different polyQ repeats differentially alter TBP's interaction with neuronal and muscle-specific transcription factors. As a result, the large polyQ repeat decreases the association of MyoD with TBP and DNA promoters. Our findings suggest that specific alterations in protein interactions by large polyQ repeats may account for the unique pathology in juvenile polyQ diseases.

INTRODUCTION

Polyglutamine (polyQ) expansion causes at least nine inherited neurodegenerative disorders, including Huntington's disease (HD), spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, and 17, dentatorubral-pallidoluysian atrophy (DRPLA), and spinal bulbar muscular atrophy (SBMA) (Orr and Zoghbi, 2007). Studies of various polyQ disease proteins have shown that expanded polyQ tracts affect the function of the disease proteins, leading to a gain or loss of function (Lim et al., 2008). It is also clear that the function of polyQ proteins can impact disease severity and progression. For example, SCA17, which is caused by polyQ expansion in the TATA-box-binding protein TBP, a transcription factor essential for the transcription of a wide range of genes (Vannini and Cramer, 2012), is associated with more severe neurological phenotypes than in other polyQ diseases, despite the fact that the repeat in mutant TBP is often shorter than 64Q (van Roon-Mom et al., 2005). In addition, different polyQ diseases display distinct pathology. For example, SBMA is characterized by muscle atrophy (Cortes et al., 2014; Lieberman et al., 2014), which is reported to be moderate or absent in other polyQ diseases.

The selectivity of polyQ toxicity apparently comes from protein context, because it determines protein-protein interactions, half-life and stability, subcellular localization, etc. However, the length of the polyQ repeat also seems to modulate the selectivity of polyQ protein toxicity. There is strong evidence that in HD, polyQ repeats larger than 60 glutamines cause juvenile cases that display different symptoms and more widespread degeneration in the brain. For example, juvenile HD patients do not display chorea, but they have severe cognitive dysfunction and seizure that is absent in adult HD patients (Vargas et al., 2003; Squitieri et al., 2006). Juvenile HD patient brains also have more nuclear aggregates, whereas adult HD brains have more neuripil aggregates, also suggesting that polyQ lengths mediate different pathogenic pathways (DiFiglia et al., 1997; Gutekunst et al., 1998). Despite the well-known phenomenon of differential pathology and symptoms in early- and adult-onset polyQ diseases, the mechanism underlying this phenomenon has not been investigated rigorously, and understanding it is critical if we are to develop effective therapies for polyQ diseases.

SCA17 is a good candidate for investigating the mechanism behind the cell-type-specific pathology in polyQ disease. The CAG repeat in the normal human *TBP* gene ranges from 30 to 42 units. Expansion of the polyQ tract (>42 glutamines) in *TBP* induces striking clinical features in SCA17 patients, including ataxia, dystonia, parkinsonism, dementia, and seizures (Bruni et al., 2004; Koide et al., 1999; Nakamura et al., 2001; Rolfs et al., 2003). Marked cerebellar atrophy and Purkinje cell loss are typical in SCA17 patients, with less pronounced neurodegeneration occurring in other brain regions (Bruni et al., 2004; Koide et al., 1999; Nakamura et al., 2001; Rolfs et al., 2003; Toyoshima et al., 2004; Bauer et al., 2004). However, when polyQ repeats exceed 63Q, mutant TBP induces juvenile symptoms, with retarded growth and muscle weakness characterized by impaired laryngeal and sphincter muscle function that results in difficulties in swallowing, talking, and walking, as well as a