



OPEN ACCESS

EDITED BY

John Douglas Cleary,
State University of New York at Albany,
United States

REVIEWED BY

Jose Laffita Mesa,
Karolinska Institutet (KI), Sweden
Marija Cvetanovic,
University of Minnesota Twin Cities,
United States
Hannah Shorrock,
University at Albany, United States

*CORRESPONDENCE

Tatsuaki Kurosaki,
tatsuaki_kurosaki@urmc.rochester.edu
Tetsuo Ashizawa,
tashizawa@houstonmethodist.org

SPECIALTY SECTION

This article was submitted to
Neurogenomics,
a section of the journal
Frontiers in Genetics

RECEIVED 05 May 2022

ACCEPTED 25 August 2022

PUBLISHED 15 September 2022

CITATION

Kurosaki T and Ashizawa T (2022), The
genetic and molecular features of the
intronic pentanucleotide repeat
expansion in spinocerebellar ataxia
type 10.
Front. Genet. 13:936869.
doi: 10.3389/fgene.2022.936869

COPYRIGHT

© 2022 Kurosaki and Ashizawa. This is
an open-access article distributed
under the terms of the [Creative
Commons Attribution License \(CC BY\)](#).
The use, distribution or reproduction in
other forums is permitted, provided the
original author(s) and the copyright
owner(s) are credited and that the
original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution
or reproduction is permitted which does
not comply with these terms.

The genetic and molecular features of the intronic pentanucleotide repeat expansion in spinocerebellar ataxia type 10

Tatsuaki Kurosaki^{1,2*} and Tetsuo Ashizawa^{3*}

¹Department of Biochemistry and Biophysics, School of Medicine and Dentistry, University of Rochester, Rochester, NY, United States, ²Center for RNA Biology, University of Rochester, Rochester, NY, United States, ³Stanley H. Appel Department of Neurology, Houston Methodist Research Institute and Weil Cornell Medical College at Houston Methodist Houston, TX, United States

Spinocerebellar ataxia type 10 (SCA10) is characterized by progressive cerebellar neurodegeneration and, in many patients, epilepsy. This disease mainly occurs in individuals with Indigenous American or East Asian ancestry, with strong evidence supporting a founder effect. The mutation causing SCA10 is a large expansion in an ATTCT pentanucleotide repeat in intron 9 of the *ATXN10* gene. The ATTCT repeat is highly unstable, expanding to 280–4,500 repeats in affected patients compared with the 9–32 repeats in normal individuals, one of the largest repeat expansions causing neurological disorders identified to date. However, the underlying molecular basis of how this huge repeat expansion evolves and contributes to the SCA10 phenotype remains largely unknown. Recent progress in next-generation DNA sequencing technologies has established that the SCA10 repeat sequence has a highly heterogeneous structure. Here we summarize what is known about the structure and origin of SCA10 repeats, discuss the potential contribution of variant repeats to the SCA10 disease phenotype, and explore how this information can be exploited for therapeutic benefit.

KEYWORDS

spinocerebellar ataxia type 10, intronic repeat expansion, pentanucleotide repeat, repeat interruption, RNA-gain-of-function mechanism

Introduction

Non-coding microsatellite repeat expansions are responsible for a wide range of dominantly and recessively inherited autosomal or X-linked human disorders (summarized in [Table 1](#)). Compared with microsatellite repeats in coding regions, non-coding microsatellite repeats tend to be more unstable, resulting in massive repeat expansions of hundreds to thousands of repeats ([Table 1](#)). However, the disease mechanisms related to these repeats in non-coding regions remain largely uncharacterized.

TABLE 1 Noncoding microsatellite repeat expansion diseases.

| Disease | Gene | Chr | Location | Inheritance | Repeat motif | Alternative motif/interruption | Normal | Pathogenic | Adjacent retrotransposon | References |
|--|----------------|----------|-----------------|-------------|--------------|--------------------------------|-----------------|-------------|--------------------------|---|
| Amyotrophic lateral sclerosis/ frontotemporal dementia (ALS/FTD) | <i>C9ORF72</i> | 9p21.2 | 5'UTR/ intron | AD | GGGGCC | | 2–24 | 45–2,100 | N | Renton et al. (2011) DeJesus-Hernandez et al. (2011) Gijssels et al. (2016) |
| Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) | <i>RFC1</i> | 4p14 | intron | AR | AAGGG | AAAAG, AAAGG, AAGAG, AGAGG | 11 (AAAAG) | 400–2000 | Y (AluSx) | Cortese et al. (2019) |
| Desbuquois dysplasia 2 (DBQD2) | <i>XYLT1</i> | 16p12.3 | promoter | AR | GGC | AGC, GGA | 9–20 | 100–800 | N | Lacroix et al. (2019) |
| Myotonic dystrophy type 1 (DM1) | <i>DMPK</i> | 19q13.32 | 3'UTR | AD | CTG | CCG | 5–37 | 50–4,000 | N | Mahadevan et al. (1992) Turner and Hilton-jones (2010) |
| Myotonic dystrophy type 2 (DM2) | <i>CNBP</i> | 3q21.3 | intron | AD | CCTG | | 11–30 | 75–11,000 | Y (AluSx) | Liquori et al. (2001) Turner and Hilton-jones (2010) Kurosaki et al. (2012) |
| Progressive myoclonic epilepsy type 1 (EPM1) | <i>CSTB</i> | 21q22.3 | promoter/ 5'UTR | AR | CCCCGCCCGCG | | 2–3 | 30–75 | N | Lalioti et al. (1997), Lalioti et al. (1998) |
| Familial adult myoclonic epilepsy type 1 (FAME1) | <i>SAMD12</i> | 8q24 | intron | AD | TTTCA | TTTTA | 11–800 (TTTTA) | 440–3,680 | Y (AluSq) | Cen et al. (2018), Ishiura et al. (2018) |
| Familial adult myoclonic epilepsy type 2 (FAME2) | <i>STARD7</i> | 2q11.2 | intron | AD | TTTCA | TTTTA | 9–30 (TTTTA) | 661–928 | N | Corbett et al. (2019) |
| Familial adult myoclonic epilepsy type 3 (FAME3) | <i>MARCH6</i> | 5p15.2 | intron | AD | TTTCA | TTTTA | 9–20 (TTTTA) | 791–1,035 | Y (AluSx) | Florian et al. (2019) |
| Familial adult myoclonic epilepsy type 4 (FAME4) | <i>YEATS2</i> | 3q27.1 | intron | AD | TTTCA | TTTTA | 4–1,219 (TTTTA) | 1,000–1,600 | Y (AluSx) | Cen et al. (2018), Yeetong et al. (2019) |
| Familial adult myoclonic epilepsy type 6 (FAME6) | <i>TNRC6A</i> | 16p12.1 | intron | AD | TTTCA | TTTTA | 28 (TTTTA) | ND | Y (AluSx) | Cen et al. (2018), Ishiura et al. (2018) |
| Familial adult myoclonic epilepsy type 7 (FAME7) | <i>RAPGEF2</i> | 4q32.1 | intron | AD | TTTCA | TTTTA, TATTA | 18 | ND | N | Ishiura et al. (2018) |
| Fuchs endothelial corneal dystrophy type 3 (FECD3) | <i>TCF4</i> | 18q21.2 | intron | AD | CCCTCT | | 12–40 | 50–3,000 | N | Mootha et al. (2014), Wieben et al. (2021) |
| Friedreich ataxia (FRDA) | <i>FXN</i> | 9q21.11 | intron | AR | GAA | | 6–27 | 44–1,700 | Y (AluSx) | Campuzano et al. (1996), Montermini et al. (1997), Al-mahdawi et al. (2018) |

(Continued on following page)

TABLE 1 (Continued) Noncoding microsatellite repeat expansion diseases.

| Disease | Gene | Chr | Location | Inheritance | Repeat motif | Alternative motif/interruption | Normal | Pathogenic | Adjacent retrotransposon | References |
|--|--|----------|------------------|-------------|--------------|---|---------------|------------|--------------------------|---|
| Fragile X syndrome (FXS) | <i>FMR1</i> | Xq27.3 | 5'UTR | XLD | CGG | AGG | 6–54 | >200 | N | Fu et al. (1991), Willemssen et al. (2013), Hagerman et al. (2017) |
| Fragile X-associated tremor/ataxia syndrome (FXTAS) | <i>FMR1</i> | Xq27.3 | 5'UTR | XLD | CGG | | 6–54 | 55–200 | N | Fu et al. (1991), Willemssen et al. (2013), Hagerman et al. (2017) |
| Global developmental delay, progressive ataxia, and elevated glutamine (GDPAG) | <i>GLS</i> | 2q32.2 | 5'UTR | AR | GCA | | 5–38 | 400–1,500 | N | van Kuilenburg et al. (2019) |
| Intellectual developmental disorder, X-linked 109 (MRX109) | <i>AFF2</i> | Xq28 | 5'UTR | XLR | CCG | | 6–25 | >200 | N | Knight et al. (1993), Knight et al. (1994) |
| Neuronal intranuclear inclusion disease (NIID) | <i>NOTCH2NLC</i> | 1q21.2 | 5'UTR | AD | CGG | AGG | 9–43 | 90–180 | N | Ishiura et al. (2019) |
| Oculopharyngodistal myopathy-1 (OPDM1) | <i>LRP12</i> | 8q22.3 | 5'UTR | AD | CGG | CGT | 13–45 | 90–130 | N | Ishiura et al. (2019) |
| Oculopharyngodistal myopathy-2 (OPDM2) | <i>GIPC1</i> | 19p13.12 | 5'UTR | AD | GGC | | 12–32 | 70–138 | N | Deng et al. (2020), Xi et al. (2021) |
| Oculopharyngeal myopathy with leukoencephalopathy (OPML1) | <i>NUTM2B-AS1</i> | 10q22.3 | noncoding | AD | CGG | CCG | 3–16 | 700 | N | Ishiura et al. (2019) |
| Spinocerebellar ataxia 8 (SCA8) | <i>ATXN8OS</i> (noncoding)/ <i>ATXN8</i> (coding) | 13q21 | noncoding/coding | AD | CTG/CAG | CTA, CTC, CCA, CTT, CCG | 16–37 | 107–127 | N | Koob et al. (1999), Moseley et al. (2000), Moseley et al. (2006) |
| Spinocerebellar ataxia 10 (SCA10) | <i>ATXN10</i> | 22q13.31 | intron | AD | ATTCT | ATTGT, ATCCC, ATCCT, ATTCC, TTCT, ATATTCT, ATTTTCT, ATTCTCT, ATTCTTCT | 9–32 | 280–4,500 | Y (AluSx) | Matsuura et al. (2000), Kurosaki et al. (2009), McFarland et al. (2013) |
| Spinocerebellar ataxia 12 (SCA12) | <i>PPP2R2B</i> | 5q32 | 5'UTR | AD | CAG | | 4–31 | 51–78 | N | Holmes et al. (1999), Srivastava et al. (2017) |
| Spinocerebellar ataxia 31 (SCA31) | <i>BEAN1/TK2</i> | 16q21 | intron | AD | TGGAA | TAAAA, TAGAA, TAAAAATAGAA | 8–140 (TAAAA) | >500 | Y (AluSx) | Sato et al. (2009) |
| Spinocerebellar ataxia 36 (SCA36) | <i>NOP56</i> | 20p13 | intron | AD | GGCCTG | | 3–14 | 650–2,500 | N | Kobayashi et al. (2011), Garcia-Murias et al. (2012) |
| Spinocerebellar ataxia 37 (SCA37) | <i>DAB1</i> | 1p32 | intron | AD | TTTCA | TTTTA | 7–400 (TTTTA) | 150–250 | Y (AluJb) | Seixas et al. (2017) |
| X-linked dystonia-parkinsonism (XDP) | <i>TAF1</i> | Xq13.1 | intron | XLR | CCCTCT | | None | 35–52 | Y (SINE-VNTR-Alu) | Bragg et al. (2017) |

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant neurodegenerative disorder that presents clinically with progressive cerebellar ataxia variably associated with epilepsy (Matsuura et al., 1999; Matsuura et al., 2000; Lin and Ashizawa, 2003; Lin and Ashizawa, 2005). SCA10 was the first human genetic disorder discovered to be caused by an expanded intronic pentanucleotide (ATTCT) repeat in intron 9 of the *ATXN10* gene on chromosome 22q13.3 (Figure 1) (Matsuura et al., 1999; Matsuura et al., 2000). Normal individuals usually have 9–32 ATTCT repeats, but SCA10 patients can have up to 4,500 (~22.5 kb) repeats (Matsuura et al., 2000; McFarland et al., 2013). Since the first discovery of the SCA10 mutation, many diseases have subsequently been reported to be caused by expanded intronic pentanucleotide repeats, including SCA31, SCA37, familial adult myoclonic epilepsy (FAME), and cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS). Nevertheless, the SCA10 repeat is one of the largest expansions reported to date in microsatellite repeat expansion disorders (Table 1).

The length of the expanded ATTCT repeat is highly unstable, especially during paternal transmission, and shows a variable degree of somatic and germline instability (Matsuura et al., 2004). Disease onset is usually in early adulthood, although initial symptoms can occur in teenagers and the elderly (Grewal et al., 2002; Bushara et al., 2013). While some families show conspicuous anticipation, others do not, suggesting that the genetic mechanisms underlying SCA10 are complex (Matsuura et al., 2000; Rasmussen et al., 2001; Grewal et al., 2002; Teive et al., 2004).

SCA10 can be diagnosed by southern blotting, repeat-primed PCR, or long-range PCR, which detect the repeat expansion (Matsuura et al., 2000; Matsuura et al., 2004; Matsuura et al., 2006; Kurosaki et al., 2008). However, due to technical limitations inherent in Sanger sequencing for reading long repetitive sequences (>~1 kb), the sequence structure of SCA10 repeats was uncertain for a long time. However, recent progress in repeat-primed PCR coupled with pulse-field capillary electrophoresis or long-read sequencing technology, e.g., single-molecule real-time (SMRT) sequencing, has enabled the definition of the entire SCA10 repeat expansion sequence structure, providing new insights into the repetitive sequence and associated disease phenotypes (Mcfarland et al., 2015; Schüle et al., 2017; Hashem et al., 2020). In this review, we discuss recent progress in SCA10 research, focusing on its molecular genetics, sequence structure, and related disease mechanisms. In doing so, we explore the potential contribution of variant repeats to the SCA10 disease phenotype and explore how this information can be exploited for therapeutic benefit.

The clinical features of SCA10

Patients with SCA10 are characterized by the core clinical phenotype of progressive cerebellar ataxia, and although epilepsy is frequently observed, its occurrence is more variable within and between families than ataxia (Matsuura et al., 1999; Zu et al., 1999; Matsuura et al., 2000; Grewal et al., 2002; Seixas et al., 2005; Raskin et al., 2007; Teive et al., 2010; de Castilhos et al., 2014; Schüle et al., 2017; Domingues et al., 2019; Domingues et al., 2019; Nascimento et al., 2019; Ramirez-Garcia et al., 2022) (Table 2). SCA10 has been reported in Mexican, Brazilian, Colombian, Argentinian, Peruvian, Bolivian, or Venezuelan families with Indigenous American ancestry (Matsuura et al., 2000; Rasmussen et al., 2001; Alonso et al., 2007; Gatto et al., 2007; Gatto et al., 2007; Raskin et al., 2007; Roxburgh et al., 2013; Leonardi et al., 2014; Baizabal-Carvalho et al., 2015; Paradisi et al., 2015; Domingues et al., 2019; Ramirez-Garcia et al., 2022) and in Chinese and Japanese families (Wang et al., 2015; Naito et al., 2017; Mao et al., 2022). A majority (~68%) of SCA10 patients exhibit pure cerebellar ataxia but, highlighting the clinical heterogeneity, only ~5%–7% have epilepsy in Brazilian populations from the Parana and Santa Catarina states (Domingues et al., 2019; Domingues et al., 2019) but ~65% of patients from other regions of Brazil develop seizures (de Castilhos et al., 2014). Similarly, epilepsy frequency in Mexican families ranges anywhere from 20% to 80% (Matsuura et al., 1999; Zu et al., 1999; Rasmussen et al., 2001; Grewal et al., 2002; Teive et al., 2004; Teive et al., 2010; Schüle et al., 2017). While SCA10 is usually diagnosed in patients aged 14–48 years (Table 2), one patient from Minnesota developed SCA10 ataxia at 83 years of age (Bushara et al., 2013). Of note, SCA10 patients with epilepsy tend to be younger (24 ± 16 years) than patients without epilepsy (35 ± 9 years) (Domingues et al., 2019). In addition to cerebellar ataxia and epilepsy, patients in some families also exhibit cognitive impairment and peripheral neuropathy (Table 2). Indeed, a recent magnetic resonance imaging (MRI) study of Mexican SCA10 patients has revealed neurodegeneration not only in the cerebellum but also in other brain regions, including the brainstem, thalamus, and putamen (Hernandez-Castillo et al., 2019).

The most common signs and symptoms of cerebellar dysfunction in SCA10 patients are gait ataxia, dysarthria, and nystagmus (Table 2). The Scale for Assessment and Rating of Ataxia (SARA), a semi-quantitative instrument to assess impairment from ataxia, has been validated and is correlated with quality of life in SCA patients (Schmitz-Hübsch et al., 2006). The SARA score correlates positively with disease duration in SCA10 patients ($r = 0.89$, $p < 0.0001$) (Zonta et al., 2022). The disease progression rate, calculated as the SARA score divided by total disease duration in years, is slower in SCA10 than in other SCAs (e.g., SCA10 = 0.84; SCA2 = 1.16; SCA3 = 1.53) (Tensini et al., 2017; Zonta et al., 2022).

Geographic distribution and origin of the SCA10 repeat expansion

SCA10 is mainly reported in individuals from Latin American countries such as Mexico (Matsuura et al., 2000; Matsuura et al., 2002; Rasmussen et al., 2001; Alonso et al., 2007), Brazil (Raskin et al., 2007; Teive et al., 2010; Domingues et al., 2019; Nascimento et al., 2019), Peru (Leonardi et al., 2014), Bolivia (Baizabal-Carvalho et al., 2015), Venezuela (Teive et al., 2010; Paradisi et al., 2015), Colombia (Roxburgh et al., 2013), or Argentina (Gatto et al., 2007; Teive et al., 2010) but not in European, African, South Asian, or Oceanic countries. The geographic distribution strongly supports a founder effect in the SCA10 allele. The subsequent identification of one SCA10 patient with Sioux Indigenous American ancestry and no Hispanic or Latino heritage solidified the hypothesis that SCA10 originates from the Indigenous American population (Bushara et al., 2013). Haplotype analyses of SCA10 patients in Latin America showed a common haplotype of six polymorphic loci, i.e., four SNPs (rs5764850-C/A, rs72556348-G/A, rs72556349-G/A, rs72556350-C/T) and two dinucleotide repeats (D22S1140 and D22S1153). Strikingly, SCA10 families typically share the common or closely related haplotype, further strengthening the evidence that the SCA10 repeat originally emerged in Indigenous Americans migrating throughout North and South America around 7,000–15,000 years ago (Almeida et al., 2009; Bushara et al., 2013; Rodríguez-labrada et al., 2020). More recently, SCA10 families have also been reported in China (Wang et al., 2015; Mao et al., 2022) and Japan (Naito et al., 2017). Haplotype analyses of these individuals have revealed that the haplotypes (rs5764850-C, rs72556348-G, rs72556349-G, rs72556350-C) common in North and South American populations are shared by Chinese and Japanese SCA10 patients (Naito et al., 2017; Mao et al., 2022), suggesting that the SCA10 mutation initially emerged at an earlier time point in Indigenous Americans before migration from East Asia to North America.

Evolutionary origin of the *ATXN10* ATTCT repeat

In normal individuals, *ATXN10* intron 9 repeats are typically uninterrupted repetitive ATTCT units. By contrast, repeat interruptions are a common feature in the orthologous region in other higher primates (Figure 1B) (Kurosaki et al., 2009). Comparative analysis of primate genomes has shown that the pentanucleotide repeat locates at the 3'-end of the *Alu* element in humans, apes, and Old World monkeys but is entirely absent in prosimians, New World monkeys, and other primate species (Figure 1B). The pentanucleotide repeats originally arose from the poly(A) stretch of the *Alu* element in conjunction with the RNA polymerase III TTTT terminator sequence in the opposite

direction of the *ATXN10* gene around ~50 million years ago (Kurosaki et al., 2009).

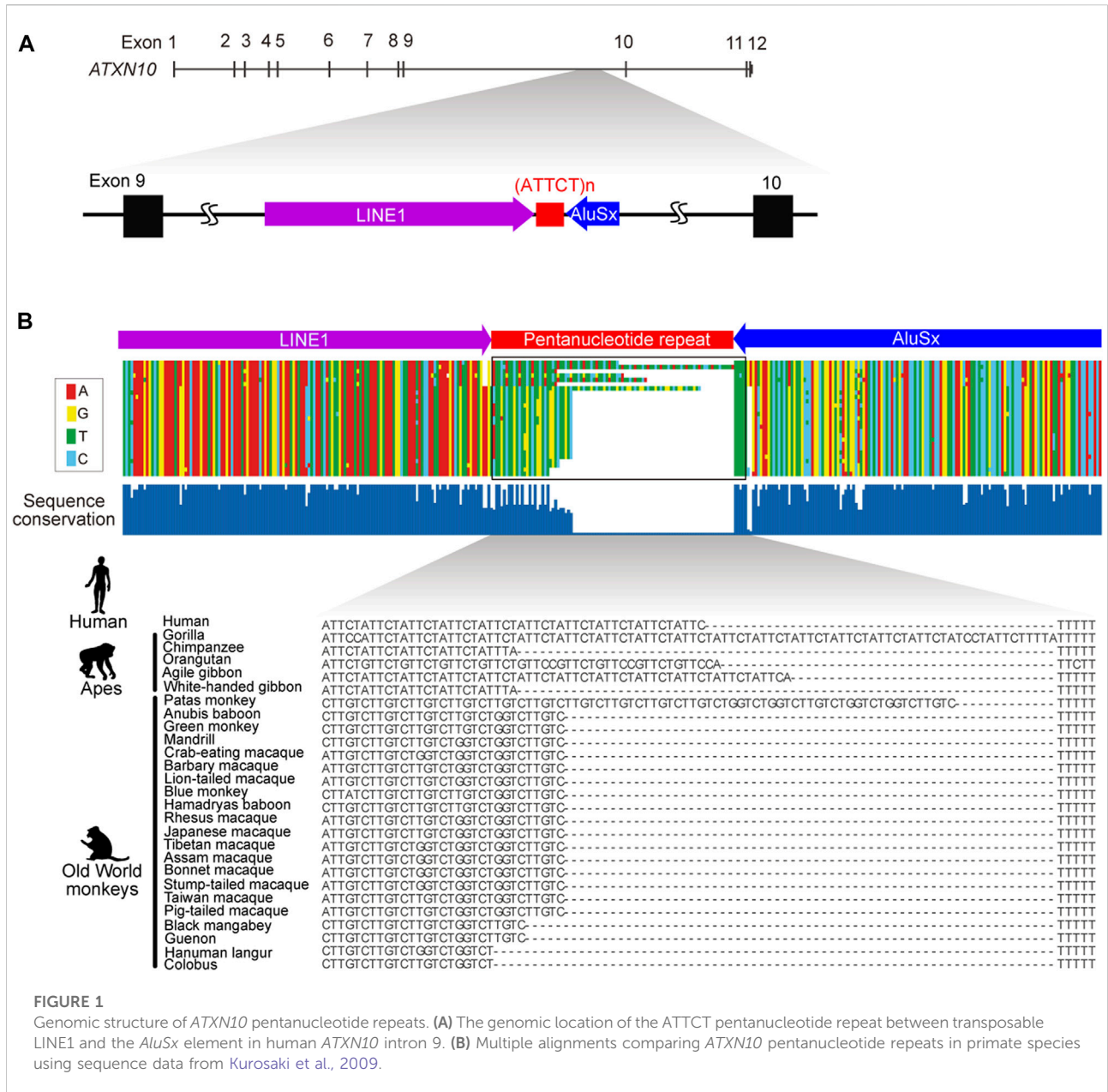
The *Alu* element is a primate-specific non-coding transposable element (TE). There are approximately one million copies of the *Alu* element in the human genome, representing ~11% of the entire genome (Lander et al., 2001). Active *Alu* elements transcribed by RNA polymerase III are sometimes retrotransposed into the human genome to cause several human diseases by disrupting coding sequences or splicing signals (Deininger, 2011). Thus, *Alu* elements generally suffer from purifying selection to inactivate the transposing activity by rapidly shortening and accumulating mutations in the poly(A) stretch (Roy-Engel et al., 2002; Comeaux et al., 2009). This heterogeneous poly(A) stretch then becomes a source of microsatellite repeats (Roy-Engel et al., 2002; Comeaux et al., 2009).

It is conspicuous that disease-causing microsatellite repeats are frequently observed in the vicinity of *Alu* elements, e.g., the GAA motif in Friedreich ataxia (Justice et al., 2001), the CCTG motif in myotonic dystrophy type 2 (DM2) (Kurosaki et al., 2012), the TGGAA/TAAAA motif in SCA31 (Sato et al., 2009), the TTTCA/TTTTA motif in SCA37 (Seixas et al., 2017), the CCCTCT motif in X-linked dystonia-parkinsonism (XDP) (Bragg et al., 2017), the ATTTC/ATTTT repeat motif in FAME1, FAME3, FAME4, and FAME6 (Ishiura et al., 2018; Florian et al., 2019; Yeetong et al., 2019), and AAGGG/AAAAG/AAAGG/AAGAG/AGAGG motifs in CANVAS (Cortese et al., 2019) (Table 1). Abundant *Alu* elements are supposed to lead to large genomic rearrangements during DNA replication through segmental duplication or *Alu-Alu*-mediated recombination (Bailey et al., 2003; Hedges and Deininger, 2007). Although TE-mediated genomic instability is potentially involved in the microsatellite repeat instability in these neurological disorders, further mechanistic studies are warranted to establish the exact pathobiology.

Heterogeneity of SCA10 pentanucleotide repeats and associations with disease phenotype

The origin of the mutant SCA10 repeat is unknown, and there are only limited data on the molecular basis of the instability of this repeat. SCA10 repeat expansions are beyond the limits of analysis by conventional Sanger sequencing. However, recent characterization of the complex pattern of ATTCT repeat sequences in normal individuals and some SCA10 families has provided new avenues for understanding the genetic basis and molecular mechanisms underlying SCA10 (Matsuura et al., 2006; Mcfarland et al., 2014; Mcfarland et al., 2015).

In normal individuals, the repeat shows length polymorphism of 9–32 tandem ATTCT units, although some



large normal alleles (≥ 17 repeats) have TTTCT or TTTCT-ATTGT insertions in the 3' end of the repeat (Matsuura et al., 2006). Initial studies suggested that highly interrupted intermediate alleles of 280 and 850 repeats have reduced penetrance, whereas alleles larger than this range were thought to be fully penetrant (Matsuura et al., 2006; Raskin et al., 2007). However, recent evidence indicates that SCA10 repeat expansions containing ATCCT interruptions lead to contractions during paternal transmission, with no correlation between repeat size and age of onset (McFarland et al., 2013; McFarland et al., 2014), contradicting the classical rule of genetic anticipation in repeat expansion diseases.

Furthermore, data indicate that ATCCT interruptions appear to be a significant risk factor for an epileptic phenotype in SCA10 (McFarland et al., 2013; McFarland et al., 2014). By contrast, pure ATTCT expansion is sometimes associated with parkinsonism (Schüle et al., 2017). These observations suggest that the mechanisms of disease associated with the repeat structure in SCA10 are complex.

Recent progress in next-generation DNA sequencing technology, especially single-molecule real-time (SMRT) sequencing permitting exceptionally long read lengths, has made it possible to determine the entire SCA10 expansion sequence. SCA10 expansions are frequently interrupted by

TABLE 2 The clinical features of SCA10.

| Clinical features (%) | Domingues et al. (2019) | Nascimento et al. (2019) | de Castilhos et al. (2014) | Teive et al. (2010) | Schüle et al. (2017) | Teive et al. (2010) | Rasmussen et al. (2001) | Zu et al. (1999) | Paradisi et al. (2015) | Teive et al. (2010) | Teive et al. (2010) |
|--|-------------------------|--------------------------|----------------------------|---------------------|----------------------|---------------------|-------------------------|------------------|------------------------|---------------------|---------------------|
| Gait ataxia | 99 | 95 | 100 | 100 | 80 | 100 | 94 | 100 | 100 | 100 | 100 |
| Dysarthria | 96 | 94 | 95 | 100 | 80 | NA | 88 | 100 | 100 | NA | NA |
| Nystagmus | 85 | 87 | 85 | NA | 80 | NA | 29 | 100 | 33 | NA | NA |
| Dysphagia | 12 | 8 | 95 | 100 | NA | NA | NA | NA | NA | NA | NA |
| Dysmetria | NA | NA | NA | NA | NA | NA | 88 | NA | 33 | NA | NA |
| Dysdiadochokinesia | NA | NA | NA | NA | 80 | NA | 82 | NA | 33 | NA | NA |
| Slow saccades/ocular apraxia | 7 | 6 | 70 | NA | 60 | NA | 71 | NA | 17 | NA | NA |
| Ophthalmoplegia | 11 | 10 | NA | NA | NA | NA | NA | 0 | NA | NA | NA |
| Tremor/peripheral neuropathy | 7 | 6 | 31 | 0 | 60 | 66 | 35 | NA | 0 | NA | NA |
| Pyramidal signs/hyperreflexia/spasticity | 1 | NA | 80 | 11 | 20 | 42 | 29 | 0 | 0 | NA | 40 |
| Babinski sign | NA | 1 | NA | NA | 0 | NA | 29 | NA | NA | NA | NA |
| Hypotonia | NA | NA | NA | NA | 0 | NA | 24 | NA | NA | NA | NA |
| Hyporeflexia | NA | 2 | 10 | NA | NA | NA | 24 | NA | 17 | NA | NA |
| Cognitive impairment/depression | 2 | 4 | 10 | NA | 100 | NA | 53 | NA | 17 | NA | NA |
| Epilepsy/deizure | 7 | 5 | 65 | 4 | 60 | 72 | 72 | 20 | 33 | 80 | 100 |
| Affected individuals (n) | 91 | 84 | 23 | 80 | 5 | 19 | 17 | 10 | 6 | 5 | 5 |
| Ethnic group | Brazilian | Brazilian | Brazilian | Brazilian | Mexican | Mexican | Mexican | Mexican | Venezuelan | Venezuelan | Argentinean |
| Gender (male %) | 48 | 46 | NA | 50 | 40 | NA | 24 | NA | NA | NA | NA |
| Age of onset (years) | 34 ± 9 | 35 ± 10 | 34 ± 10 | ~36 | 37–48 | ~27 | 14–44 | NA | 33–46 | ~14 | ~35 |
| Disease duration (years) | 10 ± 9 | 10 ± 9 | 13 ± 8 | ~15 | 16–36 | NA | 1–34 | NA | NA | NA | NA |
| Expansion (ATTCT)n | 1842 ± 341 | 1874 ± 422 | NA | ~1820 | 1,000–1,400 | ~2,838 | 1,300–4,140 | NA | NA | ~4,400 | ~1,100 |

ATCCT ATCCC, ATTCC, ATTTCT, ATATTCT, ATTCTTCT, or ATTCTTCT (Table 1) (Mcfarland et al., 2015; Landrian et al., 2017). Given that certain types of repeat expansion, which typically consist of the TTTCA motif but not the TTTTA motif, accompany the disease phenotype in SCA37, FAME1, FAME2, FAME3, FAME4, FAME6, and FAME7 (Table 1), variant repeats in SCA10 may differentially contribute to the disease phenotype.

At the molecular level, short tandem repeats tend to change the repeat length by forming stable hairpin structures to induce misalignment of DNA strands during DNA replication, which is sometimes prone to expansion (Pearson et al., 2005). Repeat interruptions are generally thought to function as a repeat stabilizing factor by disrupting the long hairpin structure to reduce replication slippage and protect the repeats from expansion (Richards, 2001; Chintalaphani et al., 2021). Additionally, repeat interruptions modulate disease penetrance and severity, which are widely reported in several repeat expansion disorders such as DM1, SCA2, SCA8, and Huntington's disease (Moseley et al., 2000; Sobczak and Krzyzosiak, 2005; Moseley et al., 2006; Braida et al., 2010; Wright et al., 2019). However, how these repeat interruptions drive the disease phenotype remains poorly understood.

SCA10 repeat interruptions such as ATTTTCT and ATATTCT appear to strengthen assembly with hyperacetylated histones (Hagerman et al., 2009). Since histone acetylation is critical for chromatin disassembly and transcriptional activation (Verdin and Ott, 2015), SCA10 repeat interruptions may upregulate gene expression and induce the accumulation of expanded repeats relative to pure repeats, influencing the SCA10 disease phenotype (Figure 2A). Additionally, histone acetylation may also play a significant role in chromatin decompaction to promote DNA replication (Ruan et al., 2015). The long ATTCT repeat has been shown to function as a DNA unwinding element to induce aberrant DNA replication (Liu et al., 2007). Thus, repeat interruptions may also be involved in the DNA replication process (Figure 2A). However, further studies on the relationship between the interrupted structure of SCA10 repeats and the underlying molecular mechanisms are still needed.

Molecular mechanisms of SCA10: Toxic RNA-mediated gain-of-function

ATXN10 mRNAs are abundantly expressed in the juvenile (10-day-old) and adult (4-month-old) mouse (Matsuura et al., 2000) and human brain as well as the heart, skeletal muscle, and kidney (Wakamiya et al., 2006). Ataxin 10 appears to play an essential role in neurite genesis (Waragai et al., 2006) and cerebellar neuron survival (März et al., 2004). However, there is no aberrant expression of *ATXN10* (including splicing

abnormalities) or of its flanking genes *FBLN1* and *PPARA* in SCA10 lymphoblasts, fibroblasts, and myoblasts (Wakamiya et al., 2006). Moreover, while *Atxn10* knockout mice show embryonic lethality, heterozygous (*Atxn10*^{+/-}) mice have no motor phenotype (Wakamiya et al., 2006). In addition, individuals harboring a translocation of chromosome 2p25.3 into intron 2 of *ATXN10* (22q13.31) show no SCA10-like symptoms, indicating that *ATXN10* haploinsufficiency does not cause the disease (Keren et al., 2010). Thus, a gain or loss of *ATXN10* function is unlikely to be the main pathogenic mechanism in SCA10.

Similar to other non-coding repeat expansion disorders, SCA10 is proposed to be caused by a toxic RNA-mediated gain-of-function mechanism (White et al., 2010; White et al., 2012). The AUUCU expansions form RNA accumulations, detected as RNA foci in the nucleus and cytoplasm of SCA10 fibroblasts and lymphoblasts (White et al., 2010). The RNA foci trap heterogeneous nuclear ribonucleoprotein K (hnRNP K) and compromise its function. This dysfunction in hnRNP K induces translocation of protein kinase C (PKC) δ to mitochondria, which subsequently induces an apoptotic pathway by releasing cytochrome c and activating caspase 3 in SCA10 cells (Figure 2B) (White et al., 2010; White et al., 2012). A transgenic mouse model of SCA10 expressing 500 ATTCT repeats within the 3'UTR of the *LacZ* gene, driven by the prion (*Prnp*) promoter (White et al., 2012), shares many phenotypic similarities with SCA10 patients, including irregular gait, increased seizure susceptibility, and neuronal loss in the cerebral cortex and hippocampus. However, this mouse does not recapitulate the cerebellar degeneration typically seen in SCA10 in humans (White et al., 2012). Thus, efforts are underway to further model the SCA10 disease phenotype, for instance, by introducing ATTCT repeats with or without repeat interruptions into the intronic region of a gene using either a pan-neuronal neuronal enolase (*Eno2*) promoter or a Purkinje cell-specific Purkinje cell protein-2 (*Pcp2*) promoter to express more expanded repeats in the cerebellum and brainstem (McFarland and Ashizawa, 2012). Furthermore, it remains unclear whether other RNA-binding proteins play a role in SCA10 pathogenesis to cause the variable SCA10 phenotype.

An alternative pathogenetic mechanism for SCA10 is bidirectional transcription producing toxic antisense transcripts or repeat-associated non-ATG (RAN) translation, as observed in DM1, DM2, fragile X-associated tremor/ataxia syndrome (FXTAS), C9orf72 amyotrophic lateral sclerosis and frontotemporal dementia ALS/FTD, and SCA8 (Zu et al., 2011; Ash et al., 2013; Todd et al., 2013; Zu et al., 2013; Zu et al., 2017). Translation of SCA10 AUUCU repeats would produce Ile-Leu-Phe-Tyr-Ser (ILFYS) pentapeptide repeats. However, there has yet to be a study of these pentapeptides in SCA10 cells and SCA10 mice, and a thorough molecular analysis is still required.

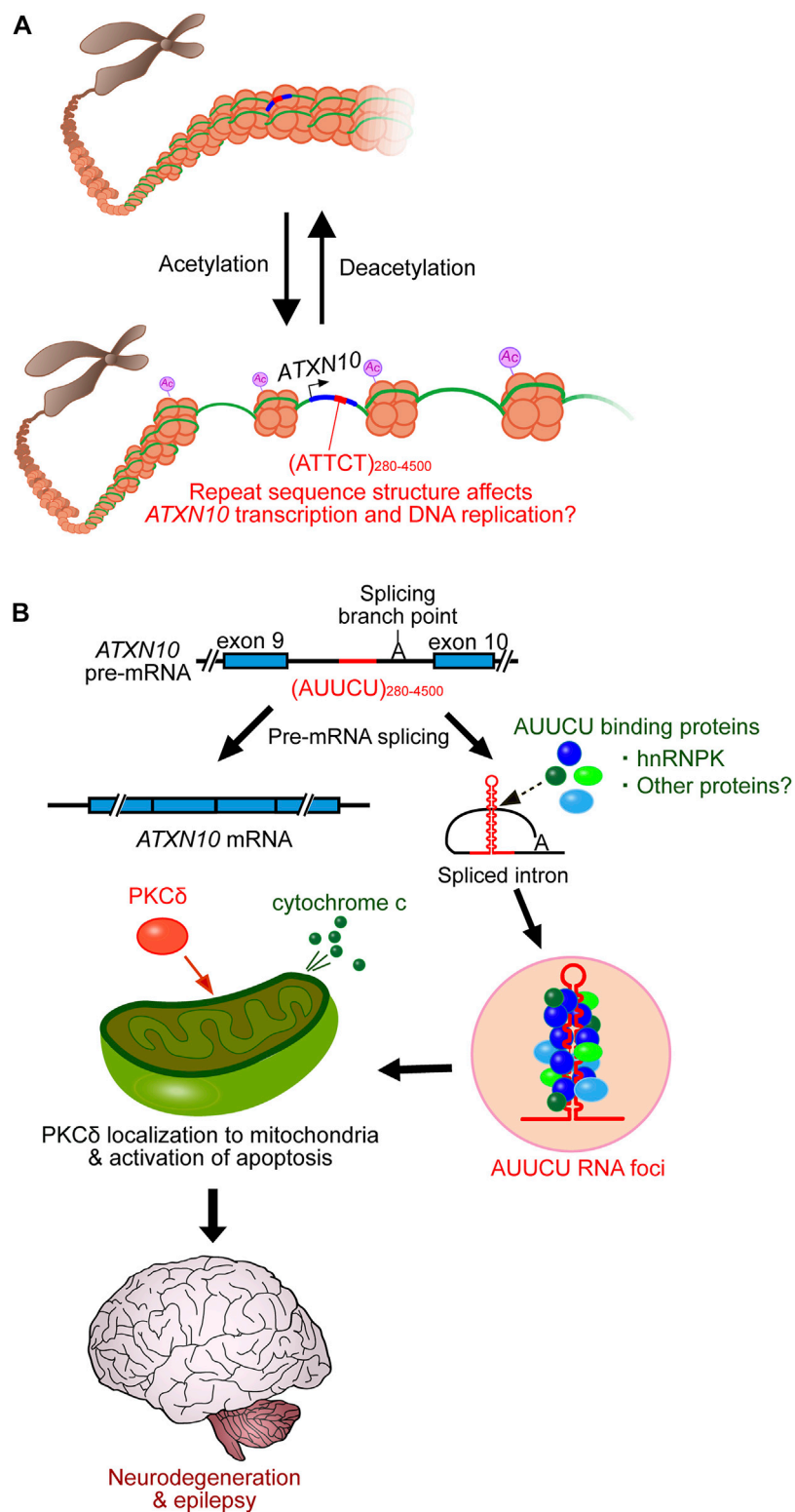


FIGURE 2

SCA10 disease model. (A) SCA10 ATTCT repeat expansion promotes histone acetylation, which subsequently enhances transcription and DNA replication, which may be affected by repeat interruptions. (B) Expanded AUUCU repeats trap hnRNP in RNA accumulations (RNA foci). Dysfunction of hnRNP induces PKCδ localization to mitochondria, which subsequently triggers cytochrome c release from mitochondria, activating apoptosis and eventually triggering neurodegeneration.

Moving towards effective SCA10 therapeutics

The molecular basis of the unstable repeat expansion and the underlying disease mechanism in SCA10 patients are still poorly characterized, hampering efforts to develop effective therapeutics for affected individuals. The AUUCU repeat forms an unusual hairpin structure *in vitro* via the hydrogen bonds formed between A-U and U-U base pairs (Handa et al., 2005). The small molecule dimeric compound 2AU-2 selectively binds to A-U base pairs to disrupt RNA folding and AUUCU accumulations in SCA10 fibroblasts (Yang et al., 2016). Furthermore, 2AU-2 treatment effectively reduced PKC δ localization to mitochondria and reduced apoptosis (Yang et al., 2016). Remarkably, 2AU-2 treatment neither reduced the abundance of normal *ATXN10* transcripts nor triggered apoptosis in healthy fibroblasts (Yang et al., 2016). Thus, the bioactivity of 2AU-2, which is applicable not only to SCA10 patients but also to other AU-rich repeat expansion disorders, needs further evaluation in relevant neuronal models.

In addition to small molecules, other RNA silencing therapies could be applicable to SCA10. RNA silencing therapies include antisense oligonucleotides (ASOs) (Mceachin et al., 2020; Schwartz et al., 2021), artificial microRNAs (miRNAs) (Martier et al., 2019), CRISPR-Cas9 system approaches (Batra et al., 2017; Zhang et al., 2020), and DNazymes (Zhang et al., 2021). SCA10 is suited to these therapeutic strategies because 1) the repeat is in the intron of both normal and expanded alleles and is not translated, so the repeat can be silenced whilst minimizing adverse consequences; 2) the silencing of this expanded pentanucleotide repeat would suppress all downstream pathogenic pathways; 3) no opposite strand transcripts containing the repeat have been detected at the SCA10 locus; and 4) preferential targeting of the mutant RNA may be feasible with therapeutics that directly engage the repeat units because of the unique and large size of mutant repeat alleles. Further mechanistic studies are likely to facilitate the development of effective therapeutics for SCA10.

Conclusion

SCA10 was the first human genetic disorder discovered to be caused by an expanded intronic pentanucleotide repeat. Since the first discovery of the *SCA10* mutation, many diseases have subsequently been reported to be caused by expanded intronic pentanucleotide repeats, including SCA31, SCA37, FAME, and CANVAS. Therefore, elucidating the molecular basis of SCA10 will provide more generalizable insights into the disease mechanisms underpinning similar intronic repeat

expansion disorders. Furthermore, in the absence of reliable biomarkers and the variable disease onset, this molecular knowledge should provide new avenues for the development of biomarkers so that affected individuals can receive early interventions and support.

While there is currently no therapy for SCA10, advances in sequencing technology, disease models, our understanding of the genetic, transcriptomic, and proteomic features of the consequences of expanded SCA10 repeats, and developments in nucleic acid-based therapies are likely to contribute to the development of a clinically translatable strategy to detect and treat patients with SCA10 and other similar neuronal disorders.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

This work was supported by grants from the NIH (R01NS115002, R01NS083564, R01NS041547) to TA. and a URM Schmitt Program on Integrative Neuroscience (SPIN) research grant to TK.

Acknowledgments

We thank Charles Thornton for critical comments on this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Al-mahdawi, S., Ging, H., Bayot, A., Cavalcanti, F., Cognata, V., Giunti, P., et al. (2018). Large interruptions of GAA repeat expansion mutations in Friedreich ataxia are very rare. *Front. Cell. Neurosci.* 12, 443. doi:10.3389/fncel.2018.00443
- Almeida, T., Alonso, L., Martins, S., Ramos, E. M., Azevedo, L., Ohno, K., et al. (2009). Ancestral origin of the ATTCT repeat expansion in spinocerebellar ataxia type 10 (SCA10). *PLoS One* 4, e4553. doi:10.1371/journal.pone.0004553
- Alonso, E., Marti, L., Ochoa, A., Yescas, P., Gutie, R., White, M., et al. (2007). Distinct distribution of autosomal dominant spinocerebellar ataxia in the Mexican population. *Mov. Disord.* 22, 1050–1053. doi:10.1002/mds.21470
- Ash, P. E. A., Bieniek, K. F., Gendron, T. F., Caulfield, T., Lin, W. L., DeJesus-Hernandez, M., et al. (2013). Unconventional translation of C9ORF72 GGGGCC expansion generates insoluble polypeptides specific to C9FTD/ALS. *Neuron* 77, 639–646. doi:10.1016/j.neuron.2013.02.004
- Bailey, J. A., Liu, G., and Eichler, E. E. (2003). An Alu transposition model for the origin and expansion of human segmental duplications. *Am. J. Hum. Genet.* 73, 823–834. doi:10.1086/378594
- Baizabal-Carvalho, J. F., Xia, G., Botros, P., Laguna, J., Ashizawa, T., and Jankovic, J. (2015). Bolivian kindred with combined spinocerebellar ataxia types 2 and 10. *Acta Neurol. Scand.* 132, 139–142. doi:10.1111/ane.12371
- Batra, R., Nelles, D. A., Pirie, E., Corbett, K. D., Swanson, M. S., Yeo, G. W., et al. (2017). Elimination of toxic microsatellite repeat expansion RNA by RNA-targeting Cas9. *Cell* 170, 899–912. doi:10.1016/j.cell.2017.07.010
- Bragg, D. C., Mangkalaphiban, K., Vaine, C. A., Kulkarni, N. J., Shin, D., Yadav, R., et al. (2017). Disease onset in X-linked dystonia-parkinsonism correlates with expansion of a hexameric repeat within an SVA retrotransposon in TAF1. *Proc. Natl. Acad. Sci. U. S. A.* 114, E11020–E11028. doi:10.1073/pnas.1712526114
- Braida, C., Stefanatos, R. K. A., Adam, B., Mahajan, N., Smeets, H. J. M., Niel, F., et al. (2010). Variant CCG and GGC repeats within the CTG expansion dramatically modify mutational dynamics and likely contribute toward unusual symptoms in some myotonic dystrophy type 1 patients. *Hum. Mol. Genet.* 19, 1399–1412. doi:10.1093/hmg/ddq015
- Bushara, K., Bower, M., Liu, J., McFarland, K. N., Landrian, I., Hutter, D., et al. (2013). Expansion of the spinocerebellar ataxia type 10 (SCA10) repeat in a patient with Sioux native American ancestry. *PLoS One* 8, e81342–11. doi:10.1371/journal.pone.0081342
- Campuzano, V., Montermini, L., Moltò, M. D., Pianese, L., Cossée, M., Cavalcanti, F., et al. (1996). Friedreich's ataxia: Autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* 271, 1423–1427. doi:10.1126/science.271.5254.1423
- Cen, Z., Jiang, Z., Chen, Y., Zheng, X., Xie, F., Yang, X., et al. (2018). Intronic pentanucleotide TTTCA repeat insertion in the SAMD12 gene causes familial cortical myoclonic tremor with epilepsy type 1. *Brain* 141, 2280–2288. doi:10.1093/brain/awy160
- Corbett, M. A., Kroes, T., Veneziano, L., Bennett, M. F., Florian, R., Schneider, A. L., et al. (2019). Intronic ATTTC repeat expansions in STARD7 in familial adult myoclonic epilepsy linked to chromosome 2. *Nat. Commun.* 10, 4920. doi:10.1038/s41467-019-12671-y
- Chintalaphani, S. R., Pineda, S. S., Deveson, I. W., and Kumar, K. R. (2021). An update on the neurological short tandem repeat expansion disorders and the emergence of long-read sequencing diagnostics. *Acta Neuropathol. Commun.* 9, 98. doi:10.1186/s40478-021-01201-x
- Comeaux, M. S., Roy-Engel, A. M., Hedges, D. J., and Deininger, P. L. (2009). Diverse cis factors controlling Alu retrotransposition: What causes Alu elements to die? *Genome Res.* 19, 545–555. doi:10.1101/gr.089789.108
- Cortese, A., Simone, R., Sullivan, R., Vandrovicova, J., Tariq, H., Yau, W. Y., et al. (2019). Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. *Nat. Genet.* 51, 649–658. doi:10.1038/s41588-019-0372-4
- de Castilhos, R. M., Furtado, G. V., Gheno, T. C., Schaeffer, P., Russo, A., Barsottini, O., et al. (2014). Spinocerebellar ataxias in Brazil — Frequencies and modulating effects of related genes. *Cerebellum* 13, 17–28. doi:10.1007/s12311-013-0510-y
- Deininger, P. (2011). Alu elements: Know the SINEs. *Genome Biol.* 12, 236–312. doi:10.1186/gb-2011-12-12-236
- DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., Boxer, A. L., Baker, M., Rutherford, N. J., et al. (2011). Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron* 72, 245–256. doi:10.1016/j.neuron.2011.09.011
- Deng, J., Yu, J., Li, P., Luan, X., Cao, L., Zhao, J., et al. (2020). Expansion of GGC repeat in GIPC1 is associated with oculopharyngodistal myopathy. *Am. J. Hum. Genet.* 106, 793–804. doi:10.1016/j.ajhg.2020.04.011
- Domingues, B. M. D., Nascimento, F. A., Meira, A. T., Moro, A., Raskin, S., Ashizawa, T., et al. (2019). Clinical and genetic evaluation of spinocerebellar ataxia type 10 in 16 Brazilian families. *Cerebellum* 18, 849–854. doi:10.1007/s12311-019-01064-y
- Florian, R. T., Kraft, F., Leitao, E., Kaya, S., Klebe, S., Magnin, E., et al. (2019). Unstable TTTTA/TTTCA expansions in MARCH6 are associated with familial adult myoclonic epilepsy type 3. *Nat. Commun.* 10, 4919. doi:10.1038/s41467-019-12763-9
- Fu, Y. H., Kuhl, D. P. A., Pizzuti, A., Pieretti, M., Sutcliffe, J. S., Richards, S., et al. (1991). Variation of the CGG repeat at the fragile X site results in genetic instability: Resolution of the Sherman paradox. *Cell* 67, 1047–1058. doi:10.1016/0092-8674(91)90283-5
- García-Murias, M., Quintáns, B., Arias, M., Seixas, A. I., Cacheiro, P., Tarrío, R., et al. (2012). Costa da Morte[®] ataxia is spinocerebellar ataxia 36: Clinical and genetic characterization. *Brain* 135, 1423–1435. doi:10.1093/brain/aww069
- Gatto, E. M., Gao, R., White, M. C., Uribe Roca, M. C., Etcheverry, J. L., Persi, G., et al. (2007). Ethnic origin and extrapyramidal signs in an Argentinean spinocerebellar ataxia type 10 family. *Neurology* 69, 216–218. doi:10.1212/01.wnl.0000265596.72492.89
- Gijssels, I., Van Mossevelde, S., Van Der Zee, J., Sieben, A., Engelborghs, S., De Bleecker, J., et al. (2016). The C9orf72 repeat size correlates with onset age of disease, DNA methylation and transcriptional downregulation of the promoter. *Mol. Psychiatry* 21, 1112–1124. doi:10.1038/mp.2015.159
- Grewal, R. P., Achari, M., Matsuura, T., Durazo, A., Tayag, E., Zu, L., et al. (2002). Clinical features and ATTCT repeat expansion in spinocerebellar ataxia type 10. *Arch. Neurol.* 59, 1285–1290. doi:10.1001/archneur.59.8.1285
- Hagerman, K., Ruan, H., Edamura, K. N., Matsuura, T., Pearson, C. E., and Wang, Y.-H. (2009). The ATTCT repeats of spinocerebellar ataxia type 10 display strong nucleosome assembly which is enhanced by repeat interruptions. *Gene* 434, 29–34. doi:10.1016/j.gene.2008.12.011
- Hagerman, R. J., Berry-Kravis, E., Hazlett, H. C., Bailey, D. B., Moine, H., Kooy, R. F., et al. (2017). Fragile X syndrome. *Nat. Rev. Dis. Prim.* 3, 17065. doi:10.1038/nrdp.2017.65
- Handa, V., Yeh, H. J. C., McPhie, P., and Usdin, K. (2005). The AUUCU repeats responsible for spinocerebellar ataxia type 10 form unusual RNA hairpins. *J. Biol. Chem.* 280, 29340–29345. doi:10.1074/jbc.M503495200
- Hashem, V., Tiwari, A., Bewick, B., Teive, H. A. G., Moscovich, M., Schüele, B., et al. (2020). Pulse-Field capillary electrophoresis of repeat-primed PCR amplicons for analysis of large repeats in Spinocerebellar Ataxia Type 10. *PLoS One* 15, e0228789. doi:10.1371/journal.pone.0228789
- Hedges, D. J., and Deininger, P. L. (2007). Inviting instability: Transposable elements, double-strand breaks, and the maintenance of genome integrity. *Mutat. Res.* 616, 46–59. doi:10.1016/j.mrfmmm.2006.11.021
- Hernandez-Castillo, C. R., Diaz, R., Vaca-Palomares, I., Torres, D. L., Chirino, A., Campos-Romo, A., et al. (2019). Extensive cerebellar and thalamic degeneration in spinocerebellar ataxia type 10. *Park. Relat. Disord.* 66, 182–188. doi:10.1016/j.parkrel.2019.08.011
- Holmes, S. E., O'Hearn, E. E., McInnis, M. G., Gorelick-Feldman, D. A., Kleiderlein, J. J., Callahan, C., et al. (1999). Expansion of a novel CAG trinucleotide repeat in the 5' region of PPP2R2B is associated with SCA12. *Nat. Genet.* 23, 391–392. doi:10.1038/70493
- Ishiura, H., Koichiro, D., Jun, M., Jun, Y., Kawabe Matsukawa, M., Fujiyama, A., et al. (2018). Expansions of intronic TTTC and TTTTA repeats in benign adult familial myoclonic epilepsy. *Nat. Genet.* 12, 581–590. doi:10.1038/s41588-018-0067-2
- Ishiura, H., Shibata, S., Yoshimura, J., Suzuki, Y., Qu, W., Doi, K., et al. (2019). Noncoding CGG repeat expansions in neuronal intranuclear inclusion disease, oculopharyngodistal myopathy and an overlapping disease. *Nat. Genet.* 51, 1222–1232. doi:10.1038/s41588-019-0458-z
- Justice, C. M., Den, Z., Nguyen, S. V., Stoneking, M., Deininger, P. L., Batzer, M. A., et al. (2001). Phylogenetic analysis of the Friedreich ataxia GAA trinucleotide repeat. *J. Mol. Evol.* 52, 232–238. doi:10.1007/s002390010151
- Keren, B., Jacquette, A., Depienne, C., Leite, P., Durr, A., Carpentier, W., et al. (2010). Evidence against haploinsufficiency of human ataxin 10 as a cause of spinocerebellar ataxia type 10. *Neurogenetics* 11, 273–274. doi:10.1007/s10048-009-0227-8
- Knight, S. J. L., Flannery, A. V., Hirst, M. C., Campbell, L., Christodoulou, Z., Phelps, S. R., et al. (1993). Trinucleotide repeat amplification and hypermethylation of a CpG island in FRAXE mental retardation. *Cell* 74, 127–134. doi:10.1016/0092-8674(93)90300-f

- Knight, S. J. L., Voelckel, M. A., Hirst, M. C., Flannery, A. V., Moncla, A., and Davies, K. E. (1994). Triplet repeat expansion at the FRAXE locus and X-linked mild mental handicap. *Am. J. Hum. Genet.* 55, 81–86.
- Kobayashi, H., Abe, K., Matsuura, T., Ikeda, Y., Hitomi, T., Akechi, Y., et al. (2011). Expansion of intronic GGCTG hexanucleotide repeat in NOP56 causes SCA36, a type of spinocerebellar ataxia accompanied by motor neuron involvement. *Am. J. Hum. Genet.* 89, 121–130. doi:10.1016/j.ajhg.2011.05.015
- Koob, M. D., Moseley, M. L., Schut, L. J., Benzow, K. A., Bird, T. D., Day, J. W., et al. (1999). An untranslated CTG expansion causes a novel form of spinocerebellar ataxia (SCA8). *Nat. Genet.* 21, 379–384. doi:10.1038/7710
- Kurosaki, T., Matsuura, T., Ohno, K., and Ueda, S. (2009). Alu-mediated acquisition of unstable ATTCT pentanucleotide repeats in the human ATXN10 gene. *Mol. Biol. Evol.* 26, 2573–2579. doi:10.1093/molbev/msp172
- Kurosaki, T., Matsuura, T., Ohno, K., and Ueda, S. (2008). Long-range PCR for the diagnosis of spinocerebellar ataxia type 10. *Neurogenetics* 9, 151–152. doi:10.1007/s10048-007-0117-x
- Kurosaki, T., Ueda, S., Ishida, T., Abe, K., Ohno, K., and Matsuura, T. (2012). The unstable CCTG repeat responsible for myotonic dystrophy type 2 originates from an AluX element insertion into an early primate genome. *PLoS One* 7, e38379. doi:10.1371/journal.pone.0038379
- Lacroix, A. J., Stabley, D., Sahraoui, R., Adam, M. P., Mehaffey, M., Kernan, K., et al. (2019). GGC repeat expansion and exon 1 methylation of XYLT1 is a common pathogenic variant in Baratale-Scott syndrome. *Am. J. Hum. Genet.* 104, 35–44. doi:10.1016/j.ajhg.2018.11.005
- Lalioi, M. D., Scott, H. S., Buresit, C., Rossier, C., Bottani, A., Morris, M. A., et al. (1997). Dodecamer repeat expansion in cystatin B gene in progressive myoclonus epilepsy. *Nature* 386, 847–851. doi:10.1038/386847a0
- Lalioi, M. D., Scott, H. S., Genton, P., Grid, D., Rabet, A. M., Ibrahim, S., et al. (1998). A PCR amplification method reveals instability of the dodecamer repeat in progressive myoclonus epilepsy (EPM1) and no correlation between the size of the repeat and age at onset. *Am. J. Hum. Genet.* 62, 842–847. doi:10.1086/301798
- Lander, E. S., Linton, L. M., Birren, B., Nusbaum, C., Zody, M. C., Baldwin, J., et al. (2001). Initial sequencing and analysis of the human genome. *Nature* 409, 860–921. doi:10.1038/35057062
- Landrian, I., McFarland, K. N., Liu, J., Mulligan, C. J., Rasmussen, A., and Ashizawa, T. (2017). Inheritance patterns of ATCCT repeat interruptions in spinocerebellar ataxia type 10 (SCA10) expansions. *PLoS One* 12, e0175958. doi:10.1371/journal.pone.0175958
- Leonardi, L., Marcotulli, C., McFarland, K. N., Tessa, A., Difabio, R., Santorelli, F. M., et al. (2014). Spinocerebellar ataxia type 10 in Peru: The missing link in the amerindian origin of the disease. *J. Neurol.* 57, 1691–1694. doi:10.1007/s00415-014-7394-8
- Lin, X., and Ashizawa, T. (2005). Recent progress in spinocerebellar ataxia type 10 (SCA10). *Cerebellum* 4, 37–42. doi:10.1080/14734220510007897
- Lin, X., and Ashizawa, T. (2003). SCA10 and ATTCT repeat expansion: Clinical features and molecular aspects. *Cytogenet. Genome Res.* 188, 184–188. doi:10.1159/000072853
- Liquori, C. L., Ricker, K., Moseley, M. L., Jacobsen, J. F., Kress, W., Naylor, S. L., et al. (2001). Myotonic dystrophy type 2 caused by a CCTG expansion in intron 1 of ZNF9. *Science* 293, 864–867. doi:10.1126/science.1062125
- Liu, G., Bissler, J. J., Sinden, R. R., and Leffak, M. (2007). Unstable spinocerebellar ataxia type 10 (ATTCT)(AGAAT) repeats are associated with aberrant replication at the ATXN10 locus and replication origin-dependent expansion at an ectopic site in human cells. *Mol. Cell. Biol.* 27, 7828–7838. doi:10.1128/MCB.01276-07
- Mahadevan, M., Tsilfidis, C., Sabourin, L., Shutler, G., Amemiya, C., Jansen, G., et al. (1992). Myotonic dystrophy mutation: An unstable CTG repeat in the 3' untranslated region of the gene. *Science* 255, 1253–1255. doi:10.1126/science.1546325
- Mao, C., Li, X., Su, Y., Luo, H., Fan, L., Zheng, H., et al. (2022). Spinocerebellar ataxia type 10 with atypical clinical manifestation in Han Chinese. *Cerebellum*. doi:10.1007/s12311-022-01405-4
- Martier, R., Liefhebber, J. M., Miniarikova, J., Zon, T. V., Snapper, J., Kolder, I., et al. (2019). Artificial microRNAs targeting C9orf72 can reduce accumulation of intra-nuclear transcripts in ALS and FTD patients. *Mol. Ther. Nucleic Acids* 14, 593–608. doi:10.1016/j.omtn.2019.01.010
- März, P., Probst, A., Lang, S., Schwager, M., Rose-John, S., Otten, U., et al. (2004). Ataxin-10, the spinocerebellar ataxia type 10 neurodegenerative disorder protein, is essential for survival of cerebellar neurons. *J. Biol. Chem.* 279, 35542–35550. doi:10.1074/jbc.M405865200
- Matsuura, T., Achari, M., Khajavi, M., Bachinski, L. L., Zoghbi, H. Y., and Ashizawa, R. (1999). Mapping of the gene for a novel spinocerebellar ataxia with pure cerebellar signs and epilepsy. *Ann. Neurol.* 45, 407–411. doi:10.1002/1531-8249(199903)45:3<407::aid-ana21>3.0.co;2-d
- Matsuura, T., Fang, P., Lin, X., Khajavi, M., Tsuji, K., Rasmussen, A., et al. (2004). Somatic and germline instability of the ATTCT repeat in spinocerebellar ataxia type 10. *Am. J. Hum. Genet.* 74, 1216–1224. doi:10.1086/421526
- Matsuura, T., Fang, P., Pearson, C. E., Jayakar, P., Ashizawa, T., Roa, B. B., et al. (2006). Interruptions in the expanded ATTCT repeat of spinocerebellar ataxia type 10: Repeat purity as a disease modifier? *Am. J. Hum. Genet.* 78, 125–129. doi:10.1086/498654
- Matsuura, T., Ranum, L. P. W., Volpini, V., Pandolfo, M., Sasaki, H., Tashiro, K., et al. (2002). Spinocerebellar ataxia type 10 is rare in populations other than Mexicans. *Neurology* 58, 983–984. doi:10.1212/WNL.58.6.983
- Matsuura, T., Yamagata, T., Burgess, D. L., Rasmussen, A., Grewal, R. P., Watase, K., et al. (2000). Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. *Nat. Genet.* 26, 191–194. doi:10.1038/79911
- Mceachin, Z. T., Parameswaran, J., Raj, N., Bassell, G. J., and Jiang, J. (2020). RNA-mediated toxicity in C9orf72 ALS and FTD. *Neurobiol. Dis.* 145, 105055. doi:10.1016/j.nbd.2020.105055
- McFarland, K. N., and Ashizawa, T. (2012). Transgenic models of spinocerebellar ataxia type 10: Modeling a repeat expansion disorder. *Genes (Basel)* 3, 481–491. doi:10.3390/genes3030481
- McFarland, K. N., Liu, J., Landrian, I., Gao, R., Sarkar, P. S., Raskin, S., et al. (2013). Paradoxical effects of repeat interruptions on spinocerebellar ataxia type 10 expansions and repeat instability. *Eur. J. Hum. Genet.* 21, 1272–1276. doi:10.1038/ejhg.2013.32
- McFarland, K. N., Liu, J., Landrian, I., Godiska, R., Shanker, S., Yu, F., et al. (2015). SMRT sequencing of long tandem nucleotide repeats in SCA10 reveals unique insight of repeat expansion structure. *PLoS One* 10, e0135906. doi:10.1371/journal.pone.0135906
- McFarland, K. N., Liu, J., Landrian, I., Zeng, D., Raskin, S., Moscovich, M., et al. (2014). Repeat interruptions in spinocerebellar ataxia type 10 expansions are strongly associated with epileptic seizures. *Neurogenetics* 15, 59–64. doi:10.1007/s10048-013-0385-6
- Montermini, L., Andermann, E., Labuda, M., Richter, A., Pandolfo, M., Cavalcanti, F., et al. (1997). The Friedreich ataxia GAA triplet repeat: Premutation and normal alleles. *Hum. Mol. Genet.* 6, 1261–1266. doi:10.1093/hmg/6.8.1261
- Mootha, V. V., Gong, X., Ku, H., and Xing, C. (2014). Association and familial segregation of CTG18.1 trinucleotide repeat expansion of TCF4 gene in Fuchs' endothelial corneal dystrophy. *Invest. Ophthalmol. Vis. Sci.* 55, 33–42. doi:10.1167/iovs.13-12611
- Moseley, M. L., Schut, L. J., Bird, T. D., Koob, M. D., Day, J. W., and Ranum, L. P. W. (2000). SCA8 CTG repeat: En masse contractions in sperm and intergenerational sequence changes may play a role in reduced penetrance. *Hum. Mol. Genet.* 9, 2125–2130. doi:10.1093/hmg/9.14.2125
- Moseley, M. L., Zu, T., Ikeda, Y., Gao, W., Mosemiller, A. K., Daughters, R. S., et al. (2006). Bidirectional expression of CUG and CAG expansion transcripts and intranuclear polyglutamine inclusions in spinocerebellar ataxia type 8. *Nat. Genet.* 38, 758–769. doi:10.1038/ng1827
- Naito, H., Takahashi, T., Kamada, M., Morino, H., Yoshino, H., Hattori, N., et al. (2017). First report of a Japanese family with spinocerebellar ataxia type 10: The second report from Asia after a report from China. *PLoS One* 12, e0177955. doi:10.1371/journal.pone.0177955
- Nascimento, F. A., Rodrigues, V. O. R., Pelloso, F. C., Henrique, C., Camargo, F., Moro, A., et al. (2019). Spinocerebellar ataxias in Southern Brazil: Genotypic and phenotypic evaluation of 213 families. *Clin. Neurol. Neurosurg.* 184, 105427. doi:10.1016/j.clineuro.2019.105427
- Paradisi, I., Ikonomu, V., and Arias, S. (2015). Spinocerebellar ataxias in Venezuela: Genetic epidemiology and their most likely ethnic descent. *J. Hum. Genet.* 61, 215–222. doi:10.1038/jhg.2015.131
- Pearson, C. E., Edamura, K. N., and Cleary, J. D. (2005). Repeat instability: Mechanisms of dynamic mutations. *Nat. Rev. Genet.* 6, 729–742. doi:10.1038/nrg1689
- Ramirez-Garcia, S. A., Sánchez-Corona, J., Volpini-Bertran, V., Moran-Moguel, M. C., Gutiérrez-Rubio, S. A., Castañeda-Cisneros, G., et al. (2022). A Female case of spinocerebellar ataxia type 10 with suicidal behavior and endocrinopathies associated with a massive expansion (ATTCT) of the gene ATXN10. *Actas Esp. Psiquiatr.* 50, 58–62.
- Raskin, S., Ashizawa, T., Teive, H. A. G., Arruda, W. O., Fang, P., Gao, R., et al. (2007). Reduced penetrance in a Brazilian family with spinocerebellar ataxia type 10. *Arch. Neurol.* 64, 591–594. doi:10.1001/archneur.64.4.591

- Rasmussen, A., Matsuura, T., Ruano, L., Yescas, P., Ochoa, A., Ashizawa, T., et al. (2001). Clinical and genetic analysis of four Mexican families with spinocerebellar ataxia type 10. *Ann. Neurol.* 50, 234–239. doi:10.1002/ana.1081
- Renton, A. E., Majounie, E., Waite, A., Simón-Sánchez, J., Rollinson, S., Gibbs, J. R., et al. (2011). A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 72, 257–268. doi:10.1016/j.neuron.2011.09.010
- Richards, R. I. (2001). Dynamic mutations : A decade of unstable expanded repeats in human genetic disease. *Hum. Mol. Genet.* 10, 2187–2194. doi:10.1093/hmg/10.20.2187
- Rodríguez-Labrada, R., Martins, A. C., Magaña, J. J., Vazquez-mojena, Y., Medrano-montero, J., Fernandez-ruiz, J., et al. (2020). Founder effects of spinocerebellar ataxias in the American continents and the Caribbean. *Cerebellum* 19, 446–458. doi:10.1007/s12311-020-01109-7
- Roxburgh, R. H., Smith, C. O., Lim, J. G., Bachman, D. F., Byrd, E., and Bird, T. D. (2013). The unique co-occurrence of spinocerebellar ataxia type 10 (SCA10) and Huntington disease. *J. Neurol. Sci.* 324, 176–178. doi:10.1016/j.jns.2012.09.030
- Roy-Engel, A. M., Salem, A. H., Oyeniran, O. O., Deininger, L., Hedges, D. J., Kilroy, G. E., et al. (2002). Active Alu element “A-tails”: Size does matter. *Genome Res.* 12, 1333–1344. doi:10.1101/gr.384802
- Ruan, K., Yamamoto, T. G., Asakawa, H., Chikashige, Y., Kimura, H., Masukata, H., et al. (2015). Histone H4 acetylation required for chromatin decompaction during DNA replication. *Sci. Rep.* 5, 12720. doi:10.1038/srep12720
- Sato, N., Amino, T., Kobayashi, K., Asakawa, S., Ishiguro, T., Tsunemi, T., et al. (2009). Spinocerebellar ataxia type 31 is associated with “Inserted” pentanucleotide repeats containing (TGGAA)_n. *Am. J. Hum. Genet.* 85, 544–557. doi:10.1016/j.ajhg.2009.09.019
- Schmitz-Hübsch, T., Du Montcel, S. T., Baliko, L., Berciano, J., Boesch, S., Depondt, C., et al. (2006). Scale for the assessment and rating of ataxia: Development of a new clinical scale. *Neurology* 66, 1717–1720. doi:10.1212/01.wnl.0000219042.60538.92
- Schüle, B., McFarland, K. N., Lee, K., Tsai, Y.-C., Nguyen, K.-D., Sun, C., et al. (2017). Parkinson’s disease associated with pure ATXN10 repeat expansion. *NPJ Park. Dis.* 3, 27. doi:10.1038/s41531-017-0029-x
- Schwartz, J. L., Jones, K. L., Yeo, G. W., Schwartz, J. L., Jones, K. L., and Yeo, G. W. (2021). Repeat RNA expansion disorders of the nervous system: Post-transcriptional mechanisms and therapeutic strategies. *Crit. Rev. Biochem. Mol. Biol.* 56, 31–53. doi:10.1080/10409238.2020.1841726
- Seixas, A. I., Loureiro, J. R., Costa, C., Ordóñez-Ugalde, A., Marcelino, H., Oliveira, C. L., et al. (2017). A pentanucleotide ATTTC repeat insertion in the non-coding region of DAB1, mapping to SCA37, causes spinocerebellar ataxia. *Am. J. Hum. Genet.* 101, 87–103. doi:10.1016/j.ajhg.2017.06.007
- Seixas, A. I., Maurer, M. H., Lin, M., Callahan, C., Ahuja, A., Matsuura, T., et al. (2005). FXTAS, SCA10, and SCA17 in American patients with movement disorders. *Am. J. Med. Genet. A* 136, 87–89. doi:10.1002/ajmg.a.30761
- Sobczak, K., and Krzyzosiak, W. J. (2005). CAG repeats containing CAA interruptions form branched hairpin structures in spinocerebellar ataxia type 2 transcripts. *J. Biol. Chem.* 280, 3898–3910. doi:10.1074/jbc.M409984200
- Srivastava, A. K., Takkar, A., Garg, A., and Faruq, M. (2017). Clinical behaviour of spinocerebellar ataxia type 12 and intermediate length abnormal CAG repeats in PPP2R2B. *Brain* 140, 27–36. doi:10.1093/brain/aww269
- Teive, H. A. G., Munhoz, R. P., Raskin, S., Arruda, W. O., Paola, L., Werneck, L. C., et al. (2010). Spinocerebellar Ataxia Type 10: Frequency of epilepsy in a large sample of Brazilian patients. *Mov. Disord.* 25, 2875–2878. doi:10.1002/mds.23324
- Teive, H. A. G., Roa, B. B., Raskin, S., Fang, P., Arruda, W. O., Neto, Y. C., et al. (2004). Clinical phenotype of Brazilian families with spinocerebellar ataxia 10. *Neurology* 63, 150963–151512. doi:10.1212/01.wnl.0000142109.62056.57
- Tensini, F. S., Sato, M. T., Shiokawa, N., Ashizawa, T., and Teive, H. A. G. (2017). A comparative optical coherence tomography study of spinocerebellar ataxia types 3 and 10. *Cerebellum* 16, 797–801. doi:10.1007/s12311-017-0856-7
- Todd, P. K., Oh, S. Y., Krans, A., He, F., Sellier, C., Frazer, M., et al. (2013). CGG repeat-associated translation mediates neurodegeneration in fragile X tremor ataxia syndrome. *Neuron* 78, 440–455. doi:10.1016/j.neuron.2013.03.026
- Turner, C., and Hilton-jones, D. (2010). The myotonic dystrophies: Diagnosis and management. *J. Neurol. Neurosurg. Psychiatry* 81, 358–367. doi:10.1136/jnnp.2008.158261
- van Kuilenburg, A. B. P., Tarailo-Graovac, M., Richmond, P. A., Drögemöller, B. I., Pouladi, M. A., Leen, R., et al. (2019). Glutaminase deficiency caused by short tandem repeat expansion in GLS. *N. Engl. J. Med.* 380, 1433–1441. doi:10.1056/NEJMoa1806627
- Verdin, E., and Ott, M. (2015). 50 years of protein acetylation: From gene regulation to epigenetics, metabolism and beyond. *Nat. Rev. Mol. Cell Biol.* 16, 258–264. doi:10.1038/nrm3931
- Wakamiya, M., Matsuura, T., Liu, Y., Schuster, G. C., Gao, R., Xu, W., et al. (2006). The role of ataxin 10 in the pathogenesis of spinocerebellar ataxia type 10. *Neurology* 67, 607–613. doi:10.1212/01.wnl.0000231140.26253.eb
- Wang, K., McFarland, K., Liu, J., Ms, M. D., Zeng, D., Landrian, I., et al. (2015). Spinocerebellar ataxia type 10 in Chinese Han. *Neurol. Genet.* 1, e26. doi:10.1212/NXG.0000000000000026
- Waragai, M., Nagamitsu, S., Xu, W., Li, Y. J., Lin, X., and Ashizawa, T. (2006). Ataxin 10 induces neurogenesis via interaction with G-protein beta2 subunit. *J. Neurosci. Res.* 83, 1170–1178. doi:10.1002/jnr.20807
- White, M. C., Gao, R., Xu, W., Mandal, S. M., Lim, J. G., Hazra, T. K., et al. (2010). Inactivation of hnRNP K by expanded intronic AUUCU repeat induces apoptosis via translocation of PKCdelta to mitochondria in spinocerebellar ataxia 10. *PLoS Genet.* 6, e1000984. doi:10.1371/journal.pgen.1000984
- White, M., Xia, G., Gao, R., Wakamiya, M., Sarkar, P. S., McFarland, K., et al. (2012). Transgenic mice with SCA10 pentanucleotide repeats show motor phenotype and susceptibility to seizure: A toxic RNA gain-of-function model. *J. Neurosci. Res.* 90, 706–714. doi:10.1002/jnr.22786
- Wieben, E. D., Aleff, R. A., Rinkoski, T. A., Baratz, K. H., Basu, S., Id, S. V. P., et al. (2021). Comparison of TCF4 repeat expansion length in corneal endothelium and leukocytes of patients with Fuchs endothelial corneal dystrophy. *PLoS One* 4, e0260837. doi:10.1371/journal.pone.0260837
- Willemsen, R., Levens, J., and Oostra, B. A. (2013). CGG repeat in the FMR1 gene: Size matters. *Clin. Genet.* 80, 214–225. doi:10.1111/j.1399-0004.2011.01723.x
- Wright, G. E. B., Collins, J. A., Kay, C., McDonald, C., Dolzhenko, E., Xia, Q., et al. (2019). Length of uninterrupted CAG, independent of polyglutamine size, results in increased somatic instability, hastening onset of Huntington disease. *Am. J. Hum. Genet.* 104, 1116–1126. doi:10.1016/j.ajhg.2019.04.007
- Xi, J., Wang, X., Yue, D., Dou, T., Wu, Q., Lu, J., et al. (2021). 5’ UTR CGG repeat expansion in GIPCI is associated with oculopharyngodistal myopathy. *Brain* 144, 601–614. doi:10.1093/brain/awaa426
- Yang, W.-Y., Gao, R., Southern, M., Sarkar, P. S., and Disney, M. D. (2016). Design of a bioactive small molecule that targets r(AUUCU) repeats in spinocerebellar ataxia 10. *Nat. Commun.* 7, 11647. doi:10.1038/ncomms11647
- Yeetong, P., Pongpanich, M., Srichomthong, C., Assawapitaksakul, A., Shotelersuk, V., Tantirukdham, N., et al. (2019). TTTC repeat insertions in an intron of YEATS2 in benign adult familial myoclonic epilepsy type 4. *Brain* 142, 3360–3366. doi:10.1093/brain/awz267
- Zhang, N., Bewick, B., Schultz, J., Tiwari, A., Krencik, R., Zhang, A., et al. (2021). DNase cleavage of CAG repeat RNA in polyglutamine diseases. *Neurotherapeutics* 18, 1710–1728. doi:10.1007/s13311-021-01075-w
- Zhang, N., Bewick, B., Xia, G., Furling, D., and Ashizawa, T. (2020). A CRISPR-Cas13a based strategy that tracks and degrades toxic RNA in myotonic dystrophy type 1. *Front. Genet.* 11, 594576–594613. doi:10.3389/fgene.2020.594576
- Zonta, M. B., Teive, H. A. G., Camargo, C. H. F., Meira, A. T., Neto, F. D. N. L., Tensini, F. S., et al. (2022). Comparing loss of balance and functional capacity among patients with SCA2, SCA3 and SCA10. *Clin. Neurol. Neurosurg.* 214, 107150. doi:10.1016/j.clineuro.2022.107150
- Zu, L., Figueroa, K. P., Grewal, R., and Pulst, S. M. (1999). Mapping of a new autosomal dominant spinocerebellar ataxia to chromosome 22. *Am. J. Hum. Genet.* 64, 594–599. doi:10.1086/302247
- Zu, T., Cleary, J. D., Liu, Y., Bañez-Coronel, M., Bubenik, J. L., Ayhan, F., et al. (2017). RAN translation regulated by muscleblind proteins in myotonic dystrophy type 2. *Neuron* 95, 1292–1305. e5. doi:10.1016/j.neuron.2017.08.039
- Zu, T., Gibbens, B., Doty, N. S., Gomes-Pereira, M., Huguet, A., Stone, M. D., et al. (2011). Non-ATG-initiated translation directed by microsatellite expansions. *Proc. Natl. Acad. Sci. U. S. A.* 108, 260–265. doi:10.1073/pnas.1013343108
- Zu, T., Liu, Y., Bañez-Coronel, M., Reid, T., Pletnikova, O., Lewis, J., et al. (2013). RAN proteins and RNA foci from antisense transcripts in C9ORF72 ALS and frontotemporal dementia. *Proc. Natl. Acad. Sci. U. S. A.* 110, E4968–E4977. doi:10.1073/pnas.1315438110