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Spinocerebellar ataxia type 10

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INTRODUCTION

Spinocerebellar ataxia type 10 (SCA10; OMIM + 603516) is a dominantly inherited cerebellar ataxia syndrome (Grewal et al., 1998; Matsuura et al., 1999a; Zu et al., 1999). SCA10 differs from other autosomal dominant spinocerebellar ataxias in three aspects. First, SCA10 is a disease with a combination of pure cerebellar ataxia and epilepsy (Matsuura et al., 1999a). Second, it has exclusively been found in American continents (Grewal et al., 1998; Matsuura et al., 2002; Teive et al., 2004). Third, SCA10 is the only disease caused by an expansion of a pentanucleotide (ATTCT) repeat (Matsuura et al., 2000). In this chapter, we will review these features of SCA10, and speculate on their relevance to the origin of the mutation and the pathogenic mechanism.

CLINICAL FEATURES OF SCA10

The hallmark of the SCA10 phenotype is a combination of cerebellar ataxia and epilepsy with relative paucity of other clinical abnormalities (Matsuura et al., 1999a; Rasmussen et al., 2001; Grewal et al., 2002). There are other autosomal dominant neurodegenerative disorders that present with cerebellar ataxia and epilepsy. However, patients with most, if not all, of these disorders exhibit other conspicuous neurological abnormalities. For example, ataxia and epilepsy may be found in dentatorubral–pallidoluysian atrophy, Huntington's disease, and various disorders classified as autosomal dominant cerebellar ataxia type I (ADCA-I) by Harding (Harding, 1993), especially in cases with the juvenile onset. However, these disorders have other variable but striking neurological signs, including pyramidal and extrapyramidal tract signs, dementia, psychosis, brainstem signs, spinal cord impairments, and polyneuropathy (Wells and Ashizawa, 2006). Thus, the diagnosis of SCA10 could be suspected based on the clinical phenotype alone in many families.

Cerebellar ataxia

SCA10 was first described as a pure cerebellar ataxia syndrome and thus classified as the category of autosomal dominant cerebellar ataxia type III (ADCA-III) by Harding's criteria (Harding, 1993). Gait imbalance is typically the presenting symptom of SCA10 patients. The age of onset varies from 10 to 49 years old (Matsuura et al., 2000). Families with

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SCA10 show anticipation (Matsuura et al., 1999a; Zu et al., 1999), a genetic phenomenon defined as progressively earlier age of onset in successive generations with increasing severity of the disease phenotype in a given family (Ashizawa and Conneally, 1999). Gait ataxia is soon followed by the onset of slurred speech. Hand incoordination is often noted as poor handwriting and difficulties in manipulating small objects. The disease progression is typically slow, and the full cerebellar syndrome may take 5–10 years to develop. The disease eventually results in total incapacitation due to severe pancerebellar ataxia. Consequently, the physical examination of patients with SCA10 shows variable severity of cerebellar signs. Gait imbalance may be subtle and is only detectable by tandem gait testing at first, but it subsequently becomes a wide-based ataxic gait with turning en bloc, and finally progresses to inability to stand without support. In most severe cases, truncal ataxia is so severe that sitting in a chair without back or side supports may become difficult. In the upper extremities, dysdiadochokinesia is often the earliest sign of cerebellar ataxia. Initially, it is characterized by a slightly slow rate, but as the disease progresses, dysrhythmic motions become increasingly apparent. The finger–nose–finger test initially shows subtle past-pointing or terminal hesitation, which progresses to typical dysmetria with intention tremor. Other cerebellar signs, such as loss of check with the "rebound phenomenon", "spooning" of the hand, hypotonia, and pendular reflexes, may also be found. Speech abnormality is characterized by typical scanning dysarthria, with slow output and enunciated consonants, especially those with "explosive" ones. The voice often shows signs of ataxia with fluctuating pitch and volume and disruptive breathing. Pursuit eye movements show irregularity with intrusion of saccades. Rare patients have shown ocular flutter. Horizontal, vertical, and rotatory nystagmus may be detected, although anticonvulsant therapy may contribute to the development of nystagmus in some patients. Saccadic velocity and initiation remain normal in SCA10 patients.

Epilepsy

Although some patients in the original Hispanic family with SCA10 had epilepsy, it was attributed to neurocysticercosis, which is common among Mexicans (Grewal et al., 1998). However, when the second Mexican-American SCA10 family was discovered, it became apparent that epilepsy is an integral feature of SCA10, because affected members with the combination of cerebellar ataxia and epilepsy showed no signs of cerebral cysticercosis on brain imaging studies (Matsuura et al., 1999a). This was confirmed in a subsequent six SCA10 families from Mexico in which affected members had cerebellar ataxia and epilepsy in the absence of detectable neurocysticercosis (Rasmussen et al., 2001). Retrospectively, epilepsy in the original SCA10 family was also a part of the SCA10 phenotype (Grewal et al., 1998, 2002).

Seizures in SCA10 patients are typically generalized tonic-clonic seizures or complex partial seizures with or without secondary generalization (Matsuura et al., 2000; Rasmussen et al., 2001). Less frequently, simple focal motor seizures have been found. Interictal electroencephalographic (EEG) recordings in affected individuals are normal in some families but often show diffuse cortical dysfunction with slow, fused and disorganized activities in other families with SCA10 from Mexico (Rasmussen et al., 2001; Grewal et al., 2002). Focal cortical irritability or slow activity may also be found. The epilepsy

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was initially thought to be non-progressive and easily controllable with conventional anticonvulsive drugs, such as phenytoin, carbamazepine, or valproate. However, subsequent observations suggest that a subpopulation of SCA10 patients has progressively more severe epilepsy in the later stage of the disease, with a need for increasingly more aggressive treatments, including combination anticonvulsant therapy and vagal nerve stimulation. Epilepsy surgery has been considered in some SCA10 patients with intractable seizures. In patients with severe epilepsy, complex partial seizures occur several times a day with frequent generalized motor seizures that often lead to status epilepticus, and a few patients have died from complications of status epilepticus.

The occurrence of progressive and severe epilepsy in patients with pure cerebellar ataxia is rare, although it is not exclusively seen in SCA10 and has been described in SCA14 (Alonso et al., 2005). Epilepsy is far more commonly seen in patients with ADCA-I, especially those with dentatorubral–pallidoluysian atrophy and SCA17, and ADCA-II (SCA7), in which cerebellar ataxia is accompanied by extracerebellar signs, such as pyramidal and extrapyramidal signs, dementia, peripheral neuropathy, and, in cases of ADCA-II, macular degeneration. In patients with ADCA-I and ADCA-II, epilepsy is attributable to cerebral cortical lesions, which have been documented by histopathological and imaging studies of the brain. In contrast, SCA10 patients show pancerebellar atrophy without detectable evidence of extracerebellar atrophy on brain CT and MRI. For this reason, it has been postulated that epilepsy in SCA10 might be a form of “cerebellar epilepsy” (Grewal et al., 2002). However, SCA10 patients could also have extracerebellar signs, some of which could be attributable to cerebral cortical dysfunctions.

Other nervous system abnormalities

Although cerebellar ataxia and epilepsy are the hallmark of clinical phenotype in SCA10, some patients with SCA10 show extracerebellar manifestations other than epilepsy (Rasmussen et al., 2001). In Mexican families, intelligence quotient (IQ) tended to be low (mean ± standard deviation = 79 ± 11) in a limited number of patients (n = 6) tested. Depressive, aggressive, and/or irritable traits were detectable in some patients. While patients with SCA10 seldom complain of sensory symptoms, neurological examination sometimes shows mild sensory loss in distal part of the legs. Nerve conduction studies may confirm the presence of sensorimotor polyneuropathy. However, whether sensory neuropathy is an integral part of SCA10 phenotype remains to be further investigated. Partial corticospinal tract signs with bilateral hyperreflexia, spastic hypertonus, unsustained clonus or Babinski sign may be detected, often with only one or two of them present. There have been no reports of SCA10 cases with parkinsonism or movement disorders other than cerebellar ataxia.

Possible involvement of organs outside the nervous systems

Liver dysfunction with increased serum levels of ALT and AST, fatal hepatic failure, normocytic normochromic anemia and thrombocytopenia, and possible cardiac anomalies have been reported to co-segregate with SCA10 in one small Mexican family (Rasmussen et al., 2001). However, the number of affected members is too small to determine whether these are a part of the SCA10 phenotype or coincidental association of different disease(s).

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Brazilian phenotype of SCA10

Four years after the discovery of Mexican SCA10 families, we identified families with SCA10 in southern Brazil (Teive et al., 2004). While Mexican patients with SCA10 exhibit either cerebellar ataxia alone, cerebellar ataxia and epilepsy, or cerebellar ataxia, epilepsy and other subtle neurological abnormalities, all Mexican SCA10 families reported to date have had at least one member with cerebellar ataxia and epilepsy (Rasmussen et al., 2001; Grewal et al., 2002). In contrast, Brazilian SCA10 patients invariably show a pure cerebellar ataxia syndrome, which can be classified in Harding's ADCA-III category (Teive et al., 2004) (Table 32.1). Although mild corticospinal tract signs have been noted in some patients, EEGs have shown no epileptiform discharges, and EMG and nerve conduction studies have been normal in Brazilian patients (Teive et al., 2004). Psychological disturbances are also rare among Brazilian SCA10 patients although some patients show symptoms and signs of depression (Teive et al., 2004). Interestingly, the socioeconomic status of Brazilian SCA10 families is conspicuously better than their Mexican counterparts. While most Mexican families live in rudimentary housing in poor neighborhoods, most Brazilian families live in middle class neighborhoods, and many affected family members have college education (Ashizawa, unpublished observations). Whether this socioeconomic disparity is attributable to differences in disease phenotype or those in regional socioeconomic environment remains unclear.

CLINICAL GENETICS OF SCA10

SCA10 shows autosomal dominant inheritance with anticipation in both Mexican and Brazilian families (Grewal et al., 2002; Teive et al., 2004). Anticipation has been found in many diseases caused by expanded trinucleotide repeats that increase in length in successive generations (Ashizawa and Conneally, 1999). The variable expressivity of the mutation is dependent on geographic or ethnic origin of the affected family, as discussed previously. Penetrance is usually complete. However, there have been cases of apparently reduced penetrance (Alonso et al., 2006; Matsuura et al., 2006). Interestingly, one of the families with reduced penetrance had a child with an early onset of the disease. However, the effect of the parental gender on the phenotype of the offspring has not been clearly described. These issues will be discussed further as genotype–phenotype correlation in a later section of this chapter.

GENETIC MUTATION

The genetic mutation of SCA10 is an expansion of the ATTCT pentanucleotide repeat in intron 9 of the ATXN10 gene, which was identified by positional cloning (Matsuura et al., 2000). The expanded ATTCT repeat shows instability of size as it is transmitted from one generation to the next, and in the somatic and germline tissues (Matsuura et al., 2004). Sequences of expanded ATTCT repeats are variably interrupted in some patients while they consist of a relatively pure stretch of tandemly repeated ATTCTs in other patients (Matsuura et al., 2006). ATTCT repeats form unpaired structures (Potaman et al., 2003). Genotype–phenotype correlation is complex although there is a weak inverse correlation between the

expansion size and the age of onset (Matsuura et al., 2000, 2004; Grewal et al., 2002; Teive et al., 2004).

Positional cloning

The search for the mutation was started with a positional cloning strategy. In 1999, we (Matsuura et al., 1999b) and others (Zu et al., 1999) independently mapped the SCA10 locus to chromosome 22q13-qter by linkage analysis of these two large families. Two recombination events in these families narrowed the critical SCA10 region to a 3.8-cM interval between D22S1140 and D22S1160. Using additional polymorphic markers, we further narrowed the SCA10 region to a 2.7-cM segment between D22S1140 and D22S1153 (Matsuura et al., 1999b). In the same year, the Human Genome Project led to acquisition of the "complete" sequence of chromosome 22 (Dunham et al., 1999). However, the "complete" sequence still contained 11 gaps in heterochromatic parts of the chromosome, and D22S1160 and D22S1153 are located in one of these gaps, leaving the exact physical size of the SCA10 candidate region elusive. Nevertheless, two contigs of bacterial artificial chromosomes (BACs), phage P1-derived artificial chromosomes (PACs), and cosmids covered a part of this region. Because available SCA10 families exhibited anticipation (Matsuura et al., 1999a; Zu et al., 1999), which is a hallmark of disorders caused by trinucleotide repeat expansion, we investigated 14 trinucleotide repeats (>4 repeats in length) listed in this region of chromosome 22 in the genome database. However, none of these repeats showed expansions in the affected members of our SCA10 families, and our repeat expansion detection (RED) analyses (Schalling et al., 1993) for CAG or CAA repeats showed no expansions other than those at the ERDA1 (Ikeuchi et al., 1998) and SEF2–1 (Breschel et al., 1997) loci, at which CAG repeats are frequently expanded in normal subjects. Furthermore, the monoclonal antibody 1C2 that recognizes expanded polyglutamine tracts (an antibody against the TATA-box-binding protein) (Trottier et al., 1995) identified no proteins on Western blot of proteins obtained from patients' lymphoblastoid cells. Because of these negative findings, we extended our investigation to microsatellite repeats other than trinucleotide repeats.

Among these repeats, PCR analysis of a pentanucleotide (ATTCT) repeat in intron 9 of the E46L gene (GeneID: 25814) showed a repeat-number polymorphism in normal individuals, ranging from 10 to 22 repeats with 82.1% heterozygosity. In SCA10 families, the PCR analysis demonstrated a uniform lack of heterozygosity of this repeat in all affected individuals and carriers of the disease haplotype, with the amplified allele shared by the unaffected parent in all cases (Matsuura et al., 1999a, 2000). The single allele amplified from the affected parent was never transmitted to any of the affected offspring whereas it was transmitted to all offspring who did not carry the at-risk haplotype. This observation suggested that the affected parent has apparent hemizygosity and that only the allele on the wild-type (non-SCA10) chromosome is amplified. To further investigate these observations, Southern blot analysis of restriction-digested genomic DNA was performed with a non-repetitive probe obtained by PCR amplification of the region immediately upstream of the ATTCT repeat. Affected individuals and carriers of the disease chromosome showed one normal-size allele and an additional variably expanded allele which was 4.0–22.5 kb larger

than the normal allele. These expanded alleles have not been observed in DNA samples from over 1000 normal individuals (Matsuura et al., 2000).

Expanded ATTCT repeat

The expanded ATTCT repeat in SCA10 is the only human mutation involving a pentanucleotide repeat expansion and is one of the largest microsatellite expansions (Ashizawa et al., 1993; Matsuura et al., 2000; Day et al., 2003). This very large repeat is located in an intron. These collectively make the SCA10 repeat unique among other expanded repeats.

Instability of expanded SCA10 ATTCT repeat

Instability during transmission: In virtually all SCA10 families, the expanded ATTCT repeat shows repeat-size instability when it is transmitted from generation to generation (Matsuura et al., 2004). The pattern of the intergenerational instability depends on the sex of the transmitting parent (Matsuura et al., 2004). During paternal transmission, the expanded ATTCT repeats are highly unstable, whereas maternal transmission is mostly accompanied by no changes or changes of a smaller magnitude. Repeat-size instability during transmissions has been observed in almost all diseases with expanded microsatellite repeats. However, the parental sex effect found in the SCA10 family is rather unique. Most autosomal dominant diseases caused by an expanded CAG repeat coding for a polyglutamine tract show greater instability in paternal transmission than in maternal transmission. However, the intergenerational instability is usually biased toward further expansion, giving rise to paternally driven anticipation in these disorders (Ashizawa and Wells, 2006). In SCA10, the intergenerational repeat-size changes can be both expansions and contractions. In myotonic dystrophy type 1 (DM1; OMIM 160900), CTG repeats in the premutation range (37–50 CTGs) show instability with further expansion with paternal transmission, giving rise to “de novo” mutations (Martorell et al., 2001); however, when paternal CTG repeats exceed 1000 copies, they tend to contract with transmission (Ashizawa et al., 1994; Ashizawa and Harper, 2006). Furthermore, large CTG repeats of >1000 copies are predominantly transmitted by affected mothers, resulting in the severe congenital form of DM1 (Ashizawa et al., 1994). In fragile X syndrome (fragile site mental retardation 1; FMR1; OMIM + 309550), it is the maternal transmission that expands the premutation CGG repeat alleles to full-mutation alleles in the offspring (Fu et al., 1991; Nolin et al., 2003), whereas paternal transmission of fully expanded CGG repeat often shows contraction (Malter et al., 1997). The GAA repeat of Friedreich ataxia (FRDA; OMIM #229300) (De Michele et al., 1998) and the CTG repeat of SCA8 (OMIM 603680) (Moseley et al., 2000) also contract during paternal transmission.

It should be noted that expanded repeats of DM1, FMR1, FRDA, and SCA8 are non-coding and substantially larger than those of polyglutamine expansion diseases. Conversely, SCA6 (OMIM #183086) and oculopharyngeal muscular dystrophy (OMIM 164300), in which expansion of coding CAG and GCG repeats are substantially shorter, show only negligible instability (Zhuchenko et al., 1997; Brais et al., 1998). Thus, the expansion size and the location of the repeat in the gene, as well as in the genome, may influence the stability of the repeat. With regards to the very large size of expansion and its intronic location, myotonic

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dystrophy type 2 (DM2; OMIM #602668) resembles SCA10. However, in DM2, affected offspring show markedly shorter expansions than do their affected parents, with a mean size difference of −17 kb (−4250 CCTGs) (Day et al., 2003), raising a possibility that the repeat unit sequence could be an additional modifier of the repeat instability. Thus, the sex of the transmitting parent, the motif of the repeat unit, the length of the repeat, the location of the repeat in the gene, and the surrounding sequences (i.e., cis elements) appear to be important determinants for the pattern of instability in repeat expansion disorders, including SCA10.

Somatic instability: In patients with SCA10, blood leukocytes, lymphoblastoid cells, buccal cells, and sperm have a variable degree of mosaicism in ATTCT expansion, which can be detected as a "smear" of the allele on the Southern and PCR analyses (Matsuura et al., 2000). Further evidence of somatic repeat-size mosaicism comes from the occasional presence of band(s) distinct from the major allele (Matsuura et al., 2004). Despite the mosaicism, changes in the length of the expanded repeat were undetectable in blood leukocytes obtained from individuals over a 5-year period (Matsuura et al., 2004). This relative stability of expanded alleles contrasts with the highly unstable expanded CCTG repeats in blood leukocytes from DM2-affected patients with conspicuous age-dependent repeat-size instability (Day et al., 2003).

To further investigate the somatic instability of expanded ATTCT repeats, we used lymphoblastoid cell lines (LBCLs) derived from patients' blood cells. We found that the size of repeat expansion of LBCLs often differs from that of the original peripheral blood leukocytes (PBLs) with a varying pattern of the smear (Matsuura et al., 2004). Furthermore, the expanded allele frequently changes size in culture. This may be due to selective growth of a subpopulation of cells from progenitor cells, which have heterogeneous repeat sizes (Matsuura et al., 2004). However, ongoing somatic instability of the expanded repeat could also explain this observation. To examine this possibility, we established clonal LBCLs derived from a single cell. Most clonal cell lines showed stable expanded alleles without smears, although one cell line showed a clear repeat-size change after passages in culture, suggesting somatic repeat-size mutations are rare but do occur (Matsuura et al., 2004).

Germline instability: Sperm samples have been obtained from a few patients with SCA10. The frequency and magnitude of instability in sperm were greater than those in somatic tissues, especially blood (Matsuura et al., 2004). The prominent instability in sperm may account for the intergenerational instability observed with paternal transmission. Although female germline tissues are unavailable, the remarkably stable maternal transmission of the expanded ATTCT repeat and the relatively low level of somatic instability suggest that expanded ATTCT repeats are relatively stable during oogenesis.

In summary, expanded ATTCT repeats in somatic tissues of SCA10 patients show repeat-size instability although the magnitude of instability is less than large repeats at other expansion loci. In contrast, germlines of SCA10 patients show striking gender-dependent patterns of instability, suggesting that the expanded SCA10 repeat is more unstable during spermatogenesis than during oogenesis.

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Interrupted and uninterrupted sequence of expanded ATTCT repeats—Initial analysis of sequences of 40 SCA10 alleles ranging from 11 to 16 repeats showed tandem ATTCT repeats without interruptions (Matsuura et al., 2000). However, subsequent sequence analysis of large normal alleles (17 repeats), which constitute about 7% of normal alleles, showed that 71% of these alleles have ATTGT-TTTCT or TTTCT interruptions (Matsuura et al., 2006). This contrasts with the uninterrupted pentanucleotide repeats in all 11–16-repeat alleles examined (Table 32.2). The interruptions in the large normal alleles were located at the second to the last repeat. Interestingly, the sequence of a 280 ATTCT repeat allele, which is the smallest expansion found in a family with suspected reduced penetrance of SCA10, showed a complex pattern of interruptions; multiple repetitive ATGCT repeats interrupted the 5′ end of the expansion whereas ATTCTAT septanucleotide repeats interrupted the 3′ end (Table 32.2). Sequencing fully expanded ATTCT repeat alleles is technically difficult. However, we were able to use the repeat-primed PCR (RP-PCR), in which the forward PCR primer anneals a sequence upstream of the repeat and the reverse primer anneals randomly within the pure ATTCT repeat tract, to differentiate uninterrupted and interrupted ATTCT repeat alleles. The RP-PCR product from pure uninterrupted ATTCT expansions showed a continuous ladder of products on polyacrylamide gel electrophoresis. In contrast, interrupted repeats yielded PCR products showing irregularity of the repeat ladder coinciding with interruptions. Sequences of cloned PCR products of expanded alleles from SCA10 patients showed interruptions by multiple ATTTTCTs and ATATTCTs (Matsuura et al., 2006) (Table 32.2).

The degree of repeat-size instability is generally dependent on the length of the stretch of pure uninterrupted repeats. In most diseases caused by microsatellite repeat expansions, the loss of interruptions coincides with the decreased stability of the repeat, leading to expansion mutations (Ashizawa and Wells, 2006). While the repeat-size variability in expanded SCA10 repeats appear to be located within the uninterrupted ATTCT repeat tract, interruptions are found only in large normal alleles and expanded alleles. Thus, the interrupting sequences may offer an important clue in deciphering the mechanism of SCA10 repeat expansion. Further studies of SCA10 alleles in patients and those in vitro may shed light on the mechanism of repeat instability and expansion in the SCA10 ATTCT repeat.

Non-B DNA structure of ATTCT repeats—Most trinucleotide repeats show non-B DNA structures. CAG/CTG repeats are known to form hairpins with slipped strands, which may play an important role in the mechanism of repeat-size instability (Pearson et al., 1998, 2003). GAA repeats at the FRDA locus have been shown to form the “sticky DNA” structure (Sakamoto et al., 1999). In contrast, in vitro studies provided evidence that ATTCT repeats take unpaired structures, in which two strands are separated (Potaman et al., 2003). Two-dimension (2D) agarose gel electrophoresis of plasmid topoisomers containing (ATTCT) 11–46 repeats suggested that the repeats form uncoiled DNA under superhelical tension. Atomic force microscopy confirmed unpairing of the two strands in these ATTCT repeats. Furthermore, chloroacetylaldehyde bound the repeat region of the supercoiled plasmid, indicating accessibility of this reagent to the uncoiled region (Potaman et al., 2003). Although the unpaired DNA structure may induce chromosome fragility and DNA methylation, our cytogenetic study, in collaboration with Dr. Lisa G. Shaffer of Washington

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State University, showed no evidence of chromosome-22 fragility in leukocytes obtained from SCA10 patients (unpublished data). Our Southern blot analysis of genomic SCA10 DNA digested with methylation-dependent and -independent enzymes showed no evidence of aberrant methylation in the SCA10 region (data not shown).

Short ATTCT repeat sequences undergo repeat-length mutations in plasmids. Unlike other repeats in plasmids, the ATTCT repeat expansion involves complex events, including inversion and transition. The number of the ATTCT repeat unit may increase or decrease. Most expansion mutations accompany an inversion of the repeat containing 5′(TATTC)n(GAATA)n3′ in either orientation. All plasmids were head to tail dimers, containing an A●T to G●C transition at the 3′ end within the AGAAT repeat. These characteristics may have resulted from an inter- or intra-molecular strand switch (Potaman et al., 2006). Whether these plasmid data of relatively short ATTCT repeats (less than 50 ATTCTs) are relevant to expanded ATTCT repeat in humans is not clear. However, inter- and intra-molecular strand switches may be relevant to the complex interruptions of the expanded ATTCT repeat observed in patients with SCA10.

Genotype–phenotype correlation—When the ATTCT repeat expansion was identified as the SCA10 mutation in 2000, it became apparent that there was a weak inverse correlation between the repeat expansion size and the age of disease onset ($r2 = 0.37$) (Matsuura et al., 2000). However, this inverse correlation turned out to be highly variable from family to family; for example, in one large family there was a strong inverse correlation ($r2 = 0.79$) whereas another large family showed no correlation (Grewal et al., 2002). Interestingly, both families appeared to show anticipation. In the latter family, there were unexpected contractions of the expanded allele with paternal transmissions, which were associated with earlier onset of the disease in offspring. The genotype–-phenotype correlation is further complicated by variability of repeat interruptions in expanded alleles. Affected members of the former family had uninterrupted expansion alleles, whereas mutation alleles in the latter family consistently showed interruptions (Matsuura et al., 2006). Additionally, the different penetrance of the epilepsy phenotype between these two families may be correlated with the presence and absence of interruptions. We have documented that Brazilian SCA10 patients display no epilepsy phenotype whereas Mexican SCA10 families variably exhibit the epilepsy phenotype (Rasmussen et al., 2001; Teive et al., 2004). We are planning to investigate the correlation between the epilepsy phenotype and repeat-interruption patterns.

POPULATION GENETICS OF SCA10

The exact prevalence of SCA10 is unknown. However, to date, there have been reports of six families of Mexican origin (Rasmussen et al., 2001; Grewal et al., 2002) and five families from southern Brazil (Teive et al., 2004), in which over 100 affected members have been identified. We have recently identified an additional five Mexican and two Brazilian SCA10 families (unpublished data). Thus, SCA10 seems relatively common in these ethnic populations. Indeed, SCA10 is the second most common autosomal dominant ataxia after SCA2 in Mexico (Rasmussen et al., 2001), and after Machado–Joseph disease (MJD) in southern Brazil (Teive et al., 2004). In contrast, other ethnic populations such as non-Mexican North Americans, Europeans including Spanish and Portuguese, and Asians

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including Japanese, Chinese, and Indians, have no identifiable SCA10 families (Fujigasaki et al., 2002; Matsuura et al., 2002; Sasaki et al., 2003; Brusco et al., 2004; Jiang et al., 2005; Seixas et al., 2005; Silveira, personal communication). Native American populations have been extensively mixed with the Spanish population in Mexico. The physical characteristics, such as facial features and skin color, and genealogical histories suggested an admixture of Native American ancestry with Spanish immigrants in all Mexican SCA10 families. It is worth mentioning that the Native Americans account for only 4% of the southern Brazilian population, yet all seven SCA19 families identified in this region had clear genealogical documentation of Native American admixture in the affected lineage (Teive, personal communication). Our preliminary haplotype analysis of the ATXN10 region using both microsatellite and single nucleotide polymorphisms showed that the Mexican families and Brazilian families share the same haplotype (unpublished data). Thus, the SCA10 mutation may have arisen in one of the Native American populations in the "New World" (Teive et al., 2004). Further haplotype studies of normal populations with various ethnic backgrounds, in comparison to the SCA10 haplotype, may provide additional insights into the ethnic origin of SCA10.

The SCA10 ATTCT repeat alleles in normal individuals showed similar repeat length distributions among Mexicans, white North Americans, and Japanese; we have not found increased frequency of upper normal alleles in the at-risk populations (Matsuura et al., 2000). The ethnic distribution of the interrupted large normal alleles showed no bias for a specific ethnic group. Examinations of various Native American subpopulations would also be important for understanding the evolution of the SCA10 alleles and identifying the origin of the mutation.

ATXN10 GENE

ATXN10, a novel gene of unknown function, consists of 12 exons spanning 172.8 kb, with an open reading frame (ORF) of 1428 bp (Matsuura et al., 2000). The ATXN10 cDNA is 2.1 kb in size. Intron 9 of the ATXN10 gene, where the expanded ATTCT repeat resides, is large (66,420 bp). Our in silico sequence analysis, using the NIX algorithms (http://www.hgmp.mrc.ac.uk/NIX) indicated no additional conventional genes in this intron. The sequence immediately downstream of the ATTCT repeat in intron 9 is rich in various repeat sequences.

The genes of known function closest to the ATTCT repeat are the fibulin 1 gene (FBLN1), whose 3′ end is >200 kb centromeric to the ATTCT repeat, and the peroxisome proliferative activated receptor alpha (PPARA) gene, ~286 kb telomeric to the ATTCT repeat. There are several closer putative genes upstream and downstream of the ATTCT repeat, but their presence has only been predicted by genomic sequence analyses.

ATAXIN-10 PROTEIN

Ataxin-10 is a novel protein whose amino acid sequence shows no homology to known human proteins. Consequently, the physiological function of ataxin-10 remains unknown. However, recent studies have shed light on the structure and function of this protein.

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Structure of the ataxin-10 protein

Analysis of the amino acid sequence of the human ataxin-10 protein suggests that it is a globular protein containing no transmembrane domains, nuclear localization signal, or other known functional motifs (Matsuura et al., 2000). However, the C-terminal domain (287–433) of ataxin-10 contains two armadillo repeat domains that have been found in membrane-associated proteins such as b-catenin. Marz and colleagues (2004) showed that ataxin-10 is a 53-kDa (475-amino-acid) protein, which, in solution, tends to form a tip-to-tip homotrimeric complex with the concave sides of the molecule facing each other. Orthologs of ATXN10 include mouse Atxn10 (GenBank GeneID 54138), rat Atxn10 (GenBank GeneID 170821), and Drosophila CG4975-PA (GenBank GeneID 37016), suggesting conservation among species. The mouse ataxin-10 shows 82% identity and 91% similarity to the human ataxin-10.

Expression of ataxin-10

ATXN10 is also known as “mouse brain protein E46 like (E46L)” human protein. E46 has been known to be highly expressed in mouse brain. The level of the mRNA expression of ATXN10 in the brain appears to correlate with the neuronal density, but is highest in the cerebellum and hippocampus (Wakamiya et al., 2006). We have shown that human ataxin-10 mRNA is expressed in many tissues but at highest levels in the brain, followed by skeletal muscle, the heart, the liver, and the kidney (Matsuura et al., 2000). Marz et al. (2004) recently showed that the ataxin-10 protein is expressed predominantly in perinuclear cytoplasm of neurons restricted to olivocerebellar regions.

Function of ataxin-10

Marz and colleagues (2004) found that ataxin-10 deficiency, induced by small interfering RNA (siRNA), caused apoptosis of cerebellar neurons in primary cell culture. Ataxin-10 has been shown to interact with O-linked GlcNAc transferase, which catalyzes modifications of several nuclear and cytoplasmic proteins in metazoans (Andrali et al., 2005). However, the exact biological function of ataxin-10 remains unknown. We have recently explored biological functions of ataxin-10 by overexpressing the protein in PC12 cells in culture and “knocking out” the gene in a genetic mouse models (Waragai et al., 2006).

The effect of ataxin-10 overexpression in PC12 cells—Using a yeast two-hybrid system, we screened a human brain cDNA library and identified the heteromeric G-protein beta 2 subunit (Gβ2) as an ataxin-10 partner (Waragai et al., 2006). We confirmed the interaction between ataxin-10 and Gβ2 by a “pull down” assay in vitro, co-immunoprecipitation in mammalian cells, and documenting cytoplasmic co-localization by confocal microscopy. The functional importance of this interaction was studied in PC12 cells transfected to express these two proteins. PC12 cells overexpressing ataxin-10 show morphological changes characterized by flattening, clumping of cells, and long neurite outgrowth. Coexpression of ataxin-10 and Gβ2 further potentiates the ataxin-10-induced differentiation by activating the Ras-MAP kinase-Elk-1 cascade in PC12 cells. However, an inhibition of TrkA receptor by K252a had no effects on the changes induced by the ataxin-10/Gβ2 coexpression. These observations suggest that the ataxin-10 may have an

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important role in neuronal differentiation through interacting with Gβ2 (Waragai et al., 2006).

Ataxin-10-deficient mice—To further investigate the biological function of ataxin-10, we generated genetic mouse models deficient of mouse ATXN10 homolog, Atxn10, using mouse embryonic stem cell (ES cell) clones, in which Atxn10 was inactivated by insertion of a gene-trap vector (Wakamiya et al., 2006). We obtained two such clones, OmniBank OST237477 and OST184877 (Lexicon Genetics Inc., Woodlands, TX). In clone OST237477, the gene-trap vector inserted in the 5′ UTR of Atxn10 exon 1 prohibits any part of the Atxn10 protein from being produced. In OST184877, the vector was inserted in intron 1, producing a chimeric protein comprised of only the first 39 amino acids encoded by Sca10 fused to the neomycin-resistance gene product. Using these clones, chimeric males and, subsequently, F1 heterozygous mice were generated. Intercrossing heterozygous mutants generated more than 100 live-born offspring for each mutant line. Only wild-type and heterozygous animals were found at the ratio of 1: 2. We found that homozygous mutants died at early post-implantation stage (unpublished data), and heterozygous mutants were overtly normal. These data suggest that ataxin-10 plays an important role in early embryogenesis (Wakamiya et al., 2006). We are further investigating functional contributions of Atxn10 expression to mouse embryogenesis.

PATHOGENIC MECHANISMS OF SCA10

Considering the functional importance of ataxin-10 in the early embryonic development of the mouse, neuritogenic differentiation of PC12 cells, and survival of primary cerebellar neurons in culture, pathogenic models of SCA10 should include a simple loss of function of ataxin-10. However, several lines of available data appear to contradict this model. Expanded ATTCT repeats could also alter the expression of neighboring genes although, again, we do not have evidence to support such a hypothesis. While simple gain of function by the mutant protein is unlikely in SCA10 where the expansion mutation resides in the middle of a large intron, the effect of this very large repeat on processing of the ataxin-10 RNA transcript is an attractive alternative model for the pathogenesis of SCA10.

Loss-of-function model

Whether haploinsufficiency of ataxin-10 can cause neuronal dysfunction or cell death in human brain remains unknown, primarily due to the lack of brain tissue from patients with SCA10. Nonetheless, genetic mouse lines homozygous for ataxin-10 deficiency (Atxn10–/–) showed early embryonic lethality (Wakamiya et al., 2006). The clinical phenotype and the gene dosage effect on the phenotype in mice often differ from those in humans. Importantly, the ataxin-10 mRNA is strongly expressed in the brain and the ataxin-10 protein is preferentially detected in cerebellar neurons. Deficiency of ataxin-10, induced by SiRNA, caused cell death in a primary culture of cerebellar neurons (Marz et al., 2004). Overexpression of human ataxin-10 induces neuritogenic differentiation in PC12 cells, and an interaction between ataxin-10 and the beta 2 subunit of heteromeric G-protein enhances this neuronal differentiation (Waragai et al., 2006). Therefore, the simple loss of function of ATXN10 may be considered a viable model for the pathogenic mechanism of SCA10.

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A large intronic expansion may cause a transcriptional hindrance. In FRDA, an expansion of GAA trinucleotide repeat to several hundred GAAs readily causes almost complete transcriptional silencing (Bidichandani et al., 1998), which has been attributed to the “sticky DNA” structure formed by the expanded GAA repeat causing RNA polymerase stole (Sakamoto et al., 2001). However, a large CCTG tetranucleotide repeat expansion in intron 1 of the ZNF9 gene causes no adverse effects on the transcription of the gene (Margolis et al., 2006). The effect of the ATTCT pentanucleotide repeat expansion on the transcription of ATXN10 was unknown. While ATTCT repeats could form a weak triplex structure, experimental data strongly suggested unpaired structures which are unlikely to hinder transcription. Ataxin-10 mRNA levels in peripheral tissues, such as skin fibroblasts, circulating leukocytes, and transformed lymphoblastoid cell lines, obtained from patients with SCA10 did not differ from controls (Wakamiya et al., 2006). Likewise, the ataxin-10 mRNA level was unaltered in somatic cell hybrid (SCH) lines compared with the control SCH containing the normal chromosome 22 from the same patient (Wakamiya et al., 2006). Furthermore, genetic mice heterozygous for ataxin-10 deficiency (Atxn10−/−) showed no phenotype, suggesting that haploinsufficiency of ataxin-10 does not cause adverse effects in mice (Wakamiya et al., 2006). These mice performed normally on rotarod testing and foot print analysis, and their cerebellum and hippocampus did not show any histopathological abnormalities (Wakamiya et al., 2006). These data suggest that the simple haploinsufficiency model is unlikely for the pathogenic mechanism of SCA10, although the final conclusion cannot be drawn until ataxin-10 mRNA and protein levels are determined in affected tissues (i.e., cerebellar neurons) of SCA10 patients.

Effects on splicing of the ATXN10 transcript

The (AUUCU)n expansion in the transcript of ATXN10 could alter the splicing pattern, leading to aberrant isoforms with toxic or dominant negative effects. However, we expected that aberrant isoforms would be an unlikely result of the ATTCT repeat expansion since the repeat is located 12 kb and 55 kb of the upstream and downstream intron–exon junctions, respectively. Northern blotting and RT-PCR analyses confirmed that there are no major isoforms of alternatively spliced ATXN10 transcript (Wakamiya et al., 2006). However, subtle alterations in the sequence may escape detection by Northern blot and RT-PCR analyses. Therefore, we cloned the exons 1–7 and exons 5–12 RT-PCR products derived from the SHC samples. Sequence analysis of multiple clones showed the full-length ATXN10 cDNA sequence. We did, however, find a small number of clones with novel forms of ATXN10 transcript. The wild-type SCH lines contained ATXN10 transcript lacking exons 2–5 (481 bp) sequence (exons 2–5) whereas the mutant SCH lines contained isoforms lacking exon 6 (81 bp) sequence (exon 6) and exons 2–6 (562 bp) sequence (exons 2–6) in addition to exons 2–5 (Wakamiya et al., 2006). The protein encoded by the exon 6 transcript should lack 27 amino acids encoded by exon 6. The exclusion of exons 2–5 or exons 2–6 sequence results in a frameshift with amino acid sequences divergent from the full-length ataxin-10 protein after the first 39 amino acids. The armadillo repeat domain is excluded from these isoforms. Biological functions of these minor mRNA species remain to be determined. Although two of the isoforms were found only in the SCHs containing an ATXN10 mutant allele, these isoforms represent only a minor fraction of the entire ATXN10

mRNA. Thus, unless these isoforms display gain of a potent toxic function, they are unlikely to play major roles in the pathogenic mechanism of SCA10.

Effects on neighboring genes

Genes flanking the ATXN10 locus are fibulin 1 (FBLN1) and the peroxisome proliferative activated receptor alpha (PPARA). The 3′ end of FBLN1 is >200-kb centromeric, and PPARA is ~286-kb telomeric, to the ATTCT repeat. The real-time RT-PCR analysis of transcripts of these genes in SCA10 and control cell lines, including lymphoblast, fibroblast, myoblast, and SCH lines, showed that the levels of FBLN1 transcript and PPARA transcript were not substantially altered in SCA10 cells.

RNA gain of function

The preceding subsections of this chapter described evidence suggesting that a simple gain or loss of function of ATXN10 and the "neighboring gene effect" are unlikely pathogenic mechanisms of SCA10. Although we found minor species of splicing isoforms, they are unlikely to play pathogenic roles. Among remaining pathogenic mechanisms, a trans-dominant gain of toxic function by a large expansion of the AUUCU repeat may be considered as a favorable pathogenic mechanism of SCA10. In this hypothesis, expanded AUUCU repeats bind to proteins, causing the dysfunction of these proteins. The RT-PCR data suggest that expanded repeats in ATXN10 are transcribed into the pre-mRNA in SCA10 cells, providing the foundation for this RNA-based hypothesis (Wakamiya et al., 2006). We have identified some polypyrimidine tract-binding proteins (PTBs) as proteins that bind to expanded AUUCU repeats (unpublished data). PTBs are known to bind pyrimidine-rich sequences, often containing optimal UCUU motifs, and regulate RNA splicing. It would be interesting to see if impaired PBT function plays any roles in SCA10.

It should be noted that the pathogenic mechanism of other diseases, whose mutations are expanded non-coding repeats, may also involve gain-of-function mechanisms, mediated by repeat-containing RNA. In SCA8, for example, the transcript may function as an antisense RNA to a transcript encoding a novel actin-binding protein, KLHL1 (Koob et al., 1999). The expanded CTG repeat in the 3′ UTR of the mutant SCA8 gene could alter this antisense function. Expanded CUG repeats transcribed from the mutant SCA8 gene may also interact with CUG-binding proteins, initiating the pathogenic cascade. In SCA12, the expanded CAG repeat in the 5′ UTR of a protein phosphatase subunit gene, PPP2RB, may increase the expression of this gene (Holmes et al., 2003). A large CTG repeat expansion in the 3′ UTR of the DMPK gene causes DM1 (Fu et al., 1992). Similarly, a CCTG repeat expansion in the first intron of the zinc finger 9 gene causes DM2 (Liquori et al., 2001). The transcripts containing expanded CUG or CCUG repeats sequester muscleblind proteins, forming RNA–protein complexes in intranuclear foci, which play an important role in DM pathogenesis (Day and Ranum, 2005). Thus, these diseases and SCA10 constitute a group of disorders that are caused by mutant RNA containing expanded microsatellite repeats outside the coding regions.

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DIAGNOSIS

The diagnosis of SCA10 should be strongly suspected when the patient is suffering from an autosomal dominant cerebellar ataxia associated with epilepsy in the above-mentioned areas of the world. DNA testing confirms the diagnosis in these cases. However, when the patient exhibits cerebellar ataxia in the absence of epilepsy or a family history of ataxic disorders, DNA testing may be the only way to make the diagnosis of SCA10.

Clinical diagnosis

SCA10 should be suspected when the patient presents with slowly progressive, late-onset cerebellar ataxia with epilepsy which consists of either generalized motor seizures, complex partial seizures, or both. Autosomal dominant inheritance suggested by the family history further increases the probability of SCA10 as the diagnosis. If such a patient is of Mexican or Brazilian descent, the clinical diagnosis of SCA10 may be made with a considerable accuracy after excluding non-degenerative pathology by brain imaging studies. However, DNA testing is necessary to confirm the diagnosis in all suspected cases.

DNA diagnosis

Genomic DNA obtained from peripheral blood leukocytes or buccal cells is subjected to PCR analysis using a set of primers that anneal to sequences flanking the ATTCT repeat within intron 9 of the ATXN10 gene. Amplification of two distinct normal alleles indicates that the subject does not have an ATTCT repeat expansion (Matsuura et al., 2000). Samples that yield a single normal allele are either homozygous for the normal allele or heterozygous with the normal allele and a non-amplifiable large expansion allele. To differentiate these two possibilities, these samples are then subjected to repeat-primed PCR (Matsuura and Ashizawa, 2002; Cagnoli et al., 2004). If the amplification products show a ladder extending only up to the size of the normal allele, the sample is homozygous for the normal allele; however, if the ladder extends beyond the normal size, the sample should contain the mutant allele, and should be subjected to Southern blot analysis for determining the expansion size (Matsuura et al., 2000).

When the test subject is already symptomatic for SCA10, the SCA10 DNA testing can be obtained as “diagnostic DNA testing”. However, when an asymptomatic at-risk subject wishes to be tested, the SCA10 DNA testing should be considered as “predictive DNA testing”. Prenatal testing, which is technically feasible with either amniocentesis or chorionic villi sampling, has not been reported. “Guidelines for the molecular genetics predictive test in Huntington’s disease” (International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington’s Chorea, 1994) may be helpful as a reference for physicians and genetic counselors who provide “predictive DNA testing” for SCA10.

TREATMENT

There have been no effective treatments for SCA10 except anticonvulsive drugs for prevention of seizures. Although anticonvulsive drugs commonly used for generalized tonic-clonic seizures and complex partial seizures are generally effective, breakthrough seizures

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are not uncommon, and poor compliance may lead to status epilepticus, occasionally associated with mortality (Rasmussen et al., 2001; Grewal et al., 2002). Pseudoseizures may complicate the management of epilepsy in some cases.

There has been no effective treatment of cerebellar ataxia. Buspirone and other minor tranquilizers (Svetel et al., 1999) may improve ataxia by preventing patients from rushing in attempts to complete tasks. A double-blind randomized control study of taltirelin hydrate in Japan has shown efficacy of this medication in treatment of spinocerebellar ataxia (Kanazawa et al., 1997). However, the drug has not been studied in other countries, and consequently, is commercially unavailable outside Japan.

CONCLUSIONS

SCA10 is an autosomal dominant neurodegenerative disorder with cerebellar ataxia. The mutation of this disease is a large expansion of the ATTCT repeat in intron 9 of the ATXN10 gene, whose biological functions are not fully understood. SCA10 has been reported only in Mexicans and Brazilians who had admixed with indigenous Indian populations. The clinical phenotype is variable from individual to individual, and potentially differs between Mexicans and Brazilians. Anticipation has also been variably observed. A stretch of ATTCT repeats forms an unpaired DNA structure in vitro. Large normal alleles and expanded alleles of the ATTCT repeat are interrupted by cryptic repeats. Expanded ATTCT repeats exhibit repeat-length mosaicism in male germline and, to a lesser degree, in somatic cells. The pathogenic mechanism of SCA10 remains unknown; however, we consider that simple gain or loss of function of ATXN10 is an unlikely model based on unaltered levels of the ATXN10 mRNA in several SCA10 cell lines and the absence of disease phenotype in heterozygous Atxn10-deficient (Atxn10+/−) genetic mice. We are investigating the trans-dominant RNA gain-of-function model as an alternative hypothesis.

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Table 32.1

Differences between Mexican and Brazilian SCA10

	Common clinical phenotype	Frequently associated features	Brain MRI	Age of onset (years)	Electrophysiologic diagnosis	Anticipation	(ATTCT)n expansion	Onset-expansion correlation
SCA10 Mexicans	Cerebellar ataxia	Epilepsy (GM, CPS)	Cerebellar atrophy	10–49	EEG: diffusely slow (100%), irritability (38%)	+	n = 800–4500	Inverse correlation (r2 = 0.264)
		Sensory neuropathy						
		Low IQ			NCS: sensory neuropathy (66%)			
		Pyramidal signs						
SCA10 Brazilians	Cerebellar ataxia	Soft pyramidal signs	Cerebellar atrophy	23–46	EEG: normal NCS: normal	+ (?)	n = 1350–2400	Inverse correlation (r2 = 0.532)

GM, “grand mal” seizures; CPS, complex partial seizures; EEG, electroencephalography; NCS, nerve conduction studies. Data based on Rasmussen et al., 2001 and Teive et al., 2004.

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Table 32.2

Sequences of SCA10 ATTCT-repeat alleles

1. Sequences of normal alleles.
11–16 repeats:
(ATTCT)n
17–29 repeats:
(ATTCT)n – 29%.
(ATTCT)n(ATTGT)(TTTCT)(ATTCT) or (ATTCT)n (TTTCT)(ATTCT) – 71%.
2. The sequence of an intermediate (280-ATTCT repeat) allele:
(ATTCT)10 (ATGCT)19 (ATTCT)14 (ATGCT) (ATTCT) 2 (ATGCT)5 (ATTCT)2 (ATGCT) (ATTCT)8 (ATGCT) (ATTCT)3 (ATGCT) (ATTCT)10 (ATGCT)2 (ATTCT)5 (ATGCT) (ATTCT)6 (ATGCT) (ATTCT)2 (ATGCT) (ATTCT)5 (ATGCT) (ATTCT)4 (ATGCT) (ATTCT) (ATGCT) (ATTCT)2 (ATGCT)3 (ATTCT) (ATGCT) (ATTCT)2 (ATGCT)3 (ATTCT) (ATGCT) (ATTCT)4 (ATGCT)2 … (ATTCT)79 (ATTCTAT) (ATTCT) 2 (ATTCTAT) (ATTCT)3 (ATTCTAT) (ATTCT)3 (ATTCTAT) (ATTCT)12.
3. The 5′ sequence of expanded alleles from one Mexican family.
(ATTCT)41 (ATTTTCT) (ATTCT) (ATATTCT) (ATTCT) (ATATTCT) (ATTCT) (ATTTTCT) (ATTCT)11 (ATATTCT) (ATTCT)5 (ATATTCT) (ATTCT)10….
Entire lengths of expanded alleles could not be obtained because of technical limitations in PCR and cloning

From Matsuura et al., 2006.