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Spinocerebellar Ataxia Type 10: From Amerindians to Latin Americans

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Introduction

Autosomal dominant cerebellar ataxias, currently denominated spinocerebellar ataxias (SCAs), constitute a large, complex group of heterogeneous autosomal dominant degenerative diseases characterized by progressive degeneration of the cerebellum and its afferent and efferent connections [1, 2]. Other nervous system structures are usually affected, including the basal ganglia, brainstem nuclei, pyramidal tracts, and posterior column and anterior horn of the spinal cord, as well as the peripheral nerves. SCAs are clinically characterized by the presence of cerebellar gait, limb ataxia (with dysmetria, dysidiadochokinesia, intention tremor), scanning dysarthria, dysphagia, nystagmus, and ocular motility abnormalities, which may be accompanied by extracerebellar signs such as ophthalmoplegia, pyramidal signs, movement disorders (including parkinsonism, dystonia, myoclonus, and chorea), dementia, epilepsy, visual disorders (including pigmentary retinopathy), lower motor neuron disease, and peripheral neuropathy [1–4]. Magnetic resonance imaging has been useful to demonstrate cerebellar atrophy with or without brainstem and occasionally whole brain atrophy depending on the form of the SCA. The prevalence of SCAs differs widely, mainly according to the ethnic distribution in most areas of the world where it has been studied [1–4]. One epidemiological study from the Netherlands [5] suggested that the prevalence of SCAs is 3/100,000 and another from Norway suggested it is 4.2/100,000 [6]. Approximately 36 distinct loci of SCAs have been recognized. Among them, SCA type 3 (or Machado–Joseph disease) is the commonest subtype of SCA in the world. SCA type 10 (SCA10) is a rare form of SCA, but it is the commonest SCA after SCA type 2 in Mexico and SCA type 3 in Brazil [1, 2].

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Hélio A.G. Teive declares that he has no conflict of interest.

Tetsuo Ashizawa has received support for travel to meetings for the study or otherwise from the University of Rochester (to attend an investigator meeting for a study funded by the Muscular Dystrophy Association) and the Muscular Dystrophy Association (to attend the Medical Advisory Committee). He also receives royalties from Baylor College of Medicine for an invention relating to genetic testing.

SCA10—Genetic and Clinical Aspects

SCA10 is an autosomal dominant disorder caused by the expansion of a noncoding, pentanucleotide repeat (ATTCT) in intron 9 of the ataxin 10 gene (*ATXN10*), on chromosome band 22q13.1. The number of ATTCT repeats ranges from ten to 32 in the normal population, and in SCA10 patients the pathological expanded allele contains 800–4,500 ATTCT repeats [1, 2, 7–9]. The pathogenic mechanism of SCA10 has been shown to involve toxic gain of function by the RNA transcript containing the expanded AUUCU repeat. SCA10 was originally described in Mexican patients, with a clinical picture characterized by cerebellar ataxia, including gait and limb ataxia, dysarthria, and ocular abnormalities, associated with extracerebellar involvement, particularly with seizures [1–4, 7–9]. Epileptic seizures were demonstrated in 72.2 % of Mexican patients (ranging from 25 to 80 %), and present as generalized motor seizures and/or complex partial seizures. Peripheral neuropathy was detected in 66 % of patients, and less frequently soft pyramidal signs, ocular dyskinesia, cognitive impairment, and behavioral disturbances were detected. The mean age of onset was 26.7 years and the expanded alleles contained 920–4,140 ATTCT repeats [1–4, 9].

SCA10—the Brazilian Cases

In contrast to Mexican patients with SCA10, the Brazilian series of SCA10 patients predominantly show a “pure” cerebellar ataxia, which in some cases is associated with mild pyramidal signs. In 2004, Teive et al. [3] presented five new unrelated Brazilian families with SCA10 and characterized their clinical phenotype, and identified 74 affected members, of whom 28 were examined. All 74 patients had an admixture of Portuguese and Amerindian ancestry. In the 28 patients, the age of onset was 34.8 ± 7.7 years (range from 23 to 46 years) and all patients had a pure cerebellar ataxia, with gait ataxia, dysarthria, and nystagmus. Remarkably, none of these patients had seizures, or other accompanying disorders described in Mexican SCA10 patients, such as polyneuropathy and hepatic, cardiac, or hematologic abnormalities. Only a few Brazilian SCA10 patients had mild pyramidal signs. Neuroimaging studies (brain magnetic resonance imaging and computed tomography) showed cerebellar atrophy without overt brainstem or cerebral atrophy. Eighteen patients from the five families who were genotyped showed expanded SCA10 alleles containing 1,350–2,400 ATTCT repeats [3, 10]. The SCA10 repeat size inversely correlates with the age of onset in these Brazilian patients.

SCA10—Comparison Between Mexican and Brazilian Patients

Studies of additional families confirmed the low frequency (3.75 %) of epilepsy in Brazilian SCA10 patients [3, 11]. Although the mean size of the ATTCT repeat expansion in Brazilian patients (1,820) was smaller than that in Mexican patients (2,838), the repeat size cannot explain the phenotypic difference because the range of the repeat size showed a large overlap between Brazilian and Mexican patients with and without seizures. On the other hand, interrupting sequences within the expanded ATTCT repeat of SCA10 may be a disease modifier that could explain the phenotypic difference between the Brazilian and Mexican series of patients, as hypothesized by Matsuura et al. [12] and supported by extensive data from McFarland et al. [13], who found that the presence of repeat interruptions within the SCA10 expansion confers a 6.56-fold increase in the risk of an SCA10 patient developing epilepsy and a 12.92-fold increase in an SCA10 patient having a family history of epilepsy. McFarland et al. [13] concluded that the presence of repeat interruptions in SCA10 repeat expansions indicates a significant risk for the epilepsy phenotype.

SCA10 in Latin America

SCA10 has also been found in patients from Argentina, Venezuela, Colombia, and recently Peru [14–16]. No SCA10 cases have been reported from Europe, Asia, or North America (Caucasians). Like in Mexican SCA10 patients, these patients from Argentina, Venezuela, and Peru with SCA10 showed cerebellar ataxia associated with epilepsy. The ethnic origin (by oral history) of most patients with SCA10 from Latin America showed an Amerindian ancestry. Almeida et al. [17] studied the ancestral origin of the ATTCT repeat expansion in SCA10. They concluded that there is a common ancestral origin for SCA10 in Latin America, which might have arisen in an ancestral Amerindian population and later spread to the mixed populations of Mexico, Brazil, and probably other countries in Latin America.

SCA10—One Hypothesis

Currently available data suggest that the SCA10 mutation probably arose in one of the Amerindian populations south of the US–Mexican border [18–20]. Historically, several studies support the hypothesis that Amerindian and Native American ancestors migrated from eastern central Asia across the exposed Bering land bridge to North America, and then spread to Central America and South America. It may be worthwhile investigating SCA10 ATTCT repeat alleles in the native American populations originating from areas north of the US–Mexican border.

Conclusion

In conclusion, SCA10 is a rare form of autosomal dominant cerebellar ataxia found predominantly in patients from Latin America, with Amerindian ancestry.

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