Movement Disorders
CLINICAL PRACTICE

REVIEW

The Geographic Diversity of Spinocerebellar Ataxias (SCAs) in the Americas: A Systematic Review

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ABSTRACT: Background: The frequency and presentation of each of the most common forms of spinocerebellar ataxias (SCAs) varies widely. In the case of the Americas, this diversity is particularly dynamic given additional social, demographic, and cultural characteristics.
Objective: To describe the regional prevalence and clinical phenotypes of SCAs throughout the continent.
Methods: A literature search was performed in both MEDLINE and LILACS databases. The research was broadened to include the screening of reference lists of systematic review articles for additional studies. Investigations dating from the earliest available through 2019. Only studies in English, Portuguese, and Spanish were included. We analyzed publications with genetically confirmed cases only, ranging from robust samples with epidemiological data to case reports and case series from each country or regions.
Results: Overall, SCA3 is the most common form in the continent. Region-specific prevalence and ranking of the common forms vary. On the other hand, region-specific phenotypic variations were not consistently found based on the available literature analyzed, with the exception of the absence of epilepsy in SCA10 consistently described in a particular cluster of cases in South Brazil.
Conclusion: Systematic, multinational studies analyzing in detail the true frequencies of SCAs across the Americas as well as distinct clinical signs and clues of each form would be ideal to look for these potential variations.

Spinocerebellar ataxias (SCAs) represent a clinically heterogeneous group of disorders characterized by autosomal dominant degeneration and dysfunction of the cerebellum and its afferent and efferent connections.[1] Despite their heterogeneity, some SCAs can be grouped according to a common molecular pathological mechanism, for example, expansion of polyglutamine encoding CAG repeats within their respective genes, expansion of intronic repeats, or molecular changes in other noncoding regions.[2,3] From a clinical perspective, SCAs present with a variable combination of cerebellar ataxia syndrome features.[1–5] In addition, patients with SCAs can present with extracerebellar motor and nonmotor symptoms and signs, such as movement disorders, ocular dysfunctions, pyramidal tract signs, peripheral neuropathy, cognitive dysfunction, seizures, sleep disorders, olfactory loss, dysautonomia, and mood disorders.[6–11] Finally, systemic findings may be part of the phenotype of certain SCAs.[6,11]

The worldwide prevalence of SCAs is in the range of 4/100.000 (from 2/100.000 to 43/100.000).[1,2,12] To date, more than 40 SCA subtypes have been characterized (Table 1); however, the prevalence of specific subtypes depends on ethnic and geographical variables. A review published 15 years ago by Schöls and colleagues[3] showed that despite 30% of SCAs remaining undiagnosed at the time, SCA3 was the most common form worldwide, representing 21% of all SCAs, followed by SCA2 and SCA6 (15% each), SCA1 (6%), SCA7 (5%), and SCA8 (3%), whereas SCA10, 12, 14, 17, and dentatorubro-pallidoluysian atrophy (DRPLA) were considered

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TABLE 1 *SCAs–summary of genetic characteristics*

SCA	Locus	Gene	Mutation (Expansion)
SCA1	6p22-23	*ATXN1*	CAG
SCA2	12q23-24.1	*ATXN2*	CAG
SCA3	14q32.1	*ATXN3*	CAG
SCA4	16q22.1	*SCA4*	–
SCA5	11q13.2	*SPTBN2*	–
SCA6	19p13	*CACNA1A*	CAG
SCA7	3p21.1-p12	*ATXN7*	CAG
SCA8	13q21	*ATXN80S*	CAG/CTG
SCA10	22q13.31	*ATXN10*	ATTCT
SCA11	15q15.2	*TTBK2*	–
SCA12	5q32	*PPP2R2B*	CAG
SCA13	19q13.33	*KCNC3*	–
SCA14	19q13.4	*PRKCG*	–
SCA15	3p26.1	*ITPR1*	Allelic to SCAs 16, 29
SCA16	3p26.1	*ITPR1*	Allelic to SCAs 15, 29
SCA17	6q27	*TBP*	CAG
SCA18	7q22-q32	*IFRD1*	–
SCA19	1p13.2	*KCND3*	Allelic to SCA22
SCA20	11p11.2-q13.3	*SCA20*	Multiple gene duplication
SCA21	7p21.3-p15.1	*SCA21*	–
SCA22	1p13.2	*KCND3*	Allelic to SCA19
SCA23	20p13	*PDYN*	–
SCA24	–	–	–
SCA25	2p21-p15	*SCA25*	–
SCA26	19p13.3	*EEEF2*	–
SCA27	13q34	*FGF14*	–
SCA28	18p11	*AFG3L2*	–
SCA29	3p26.1	*ITPR1*	Allelic to SCAs 15, 16
SCA30	4q34.3-q35.1	*SCA30*	–
SCA31	16q22	*SCA31*	TGGAA
SCA32	7q32-q33	*SCA32*	–
SCA33	–	–	–
SCA34	6q12.3-q16.1	*ELOVL4*	–
SCA35	2Op13	*TGM6*	–
SCA36	20p13	*NOP36*	GGCCTG
SCA37	1p32	*SCA37*	–
SCA38	6p12.1	*ELOVLE5*	–
SCA39	–	–	–
SCA40	14q32	*CCDC88C*	–
SCA41	4q27	*TRPC3*	–
SCA42	17q21.33	*CACNA1G*	–
SCA43	3q25.2	*MME*	–
SCA44	6q24.3	*GRM1*	–
SCA45	5p33.1	*FAT2*	–
SCA46	19q13.2	*PLD3*	–
SCA47	1p35.2	*PUM1*	–
SCA48	16p13.3	*STUB1*	–
DRPLA	12p13.31	*ATN1*	CAG

SCA, spinocerebellar ataxia; DRPLA, dentatorubro-pallidoluysian atrophy.

TABLE 2 *Main ethnic origins of the countries with the highest number of patients with spinocerebellar ataxias*

Regions and Countries	Main Ethnic Origins
North America	
Canada	European: British, French, Irish, German, Italian, Slav, Dutch Native American Indian and Inuit Asian: Indian, Chinese, Philippian, Jew
United States	European: British, Irish, German, Italian, French, Dutch, Slav, Scandinavian African Native American Indian Asian: Chinese, Indian, Philippian, Jew
Mexico	Native American Indian European: Spanish, British, Irish, Italian, German, French, Dutch Asian: Arabian, Chinese, Korean, Jew
Central America	
Cuba	African European: Spanish, French, Portuguese, Italian, Slav, Dutch, Greek Native American Indian Asian: Chinese, Japanese
South America	
Venezuela	European: Spanish, Portuguese, Italian, German Native American Indian African
Colombia	European: Spanish, Italian, German Native American Indian African Asian: Arabian, Chinese, Japanese, Jew
Peru	Native American Indian European Spanish, Austrian, British, French, German, Croatian Asian: Chinese, Japanese, Arabian African
Chile	European: Spanish, German, Croatian, Greek Native American Indian Asian: Arabian, Chinese, Japanese
Argentina	European: Spanish, Italian, German, Slav, French Native American Indian Asian: Arabian, Jew
Brazil	European: Portuguese, German, Italian, Spanish, Slav, Dutch African Native American Indian Asian: Arabian, Japanese, Chinese, Jew

exceedingly rare. Although rare, SCA10 proved to be one of the most common in certain geographic areas such as Peru, Mexico, and Brazil.[12]

The Americas represent a unique continent with regard to its ethnic, social, demographic, and cultural diversity, with peculiar regional traits observed from the Alaska North Slope to Patagonia. The first humans in the continent, who crossed the Bering Strait from Asia in the Ice Age giving birth to the Amerindians, were later joined by the Vikings in Greenland and Atlantic Northeast, followed by the European settlers and later the Africans and European-Arabian-Asian immigrants (Table 2). The result is a melting pot, forming a diverse genetic landscape.[13] This, among other factors, may play an important role and influence in the wide range of epidemiological and phenotypic diversity emerging from studies showing population-specific and region-specific aspects of SCAs in the continent. Recognizing that several questions remain unanswered on this topic, the aim of this study is to review the available published data and expert opinion on the geographic and phenotypic diversity of SCAs in the Americas.

Methods

A literature search was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in both

MEDLINE and LILACS databases using "spinocerebellar ataxia," "ataxia," or specific SCA subtypes as search terms along with "epidemiology" and with the geographic designations "North America," "Central America," "Caribbean," "South America," and the individual names of all countries of the American continent in the medical subject headings, title, abstract, or author-supplied keywords. The research was broadened to include screening of reference lists of systematic review articles for additional studies initially missed or presented only in abstract form. No restrictions were predetermined on the year of the study, with investigations dating from earliest available through 2019. Only studies in English, Portuguese, and Spanish were included. We analyzed publications with genetically confirmed cases only, ranging from robust samples with epidemiological data to case reports and case series from each country or regions. Figure 1 shows the flow diagram for inclusion of articles.[14]

Results

An overall assessment of the frequency of SCAs in North, Central, and South America shows that the most common subtype is SCA3, followed by SCA2, 10, and 7 (Fig. 2). SCAs subtypes 1 and 6 were generally less prevalent.[2,12]

The results for each individual country are described in the following sections (Table 3).

North America

In Canada, only 1 clinical study, a single-center retrospective chart review with a total of 21 SCA families, was found in the literature.[15] The study showed that SCA3, found in 23.8% of the families, was the most common molecular diagnosis, followed by SCA2 (14.3%) and SCA6 (9.5%), whereas SCA1 and SCA8 were identified in 1 family (4.8%) each. In terms of clinical profile, the presentations of the core features described in the study are typical, although more subtle details (ie, bulging eyes in SCA3) are not presented for comparison. Recently, ataxia with erythrokeratodermia as a result of *ELOVL4* gene mutations (SCA34) was primarily described and characterized in a large French–Canadian family.[11]

In the United States, a study of 109 SCA cases with confirmed genetic diagnoses published more than 20 years ago found that the most common subtype was SCA3 detected in 33.9%, followed by

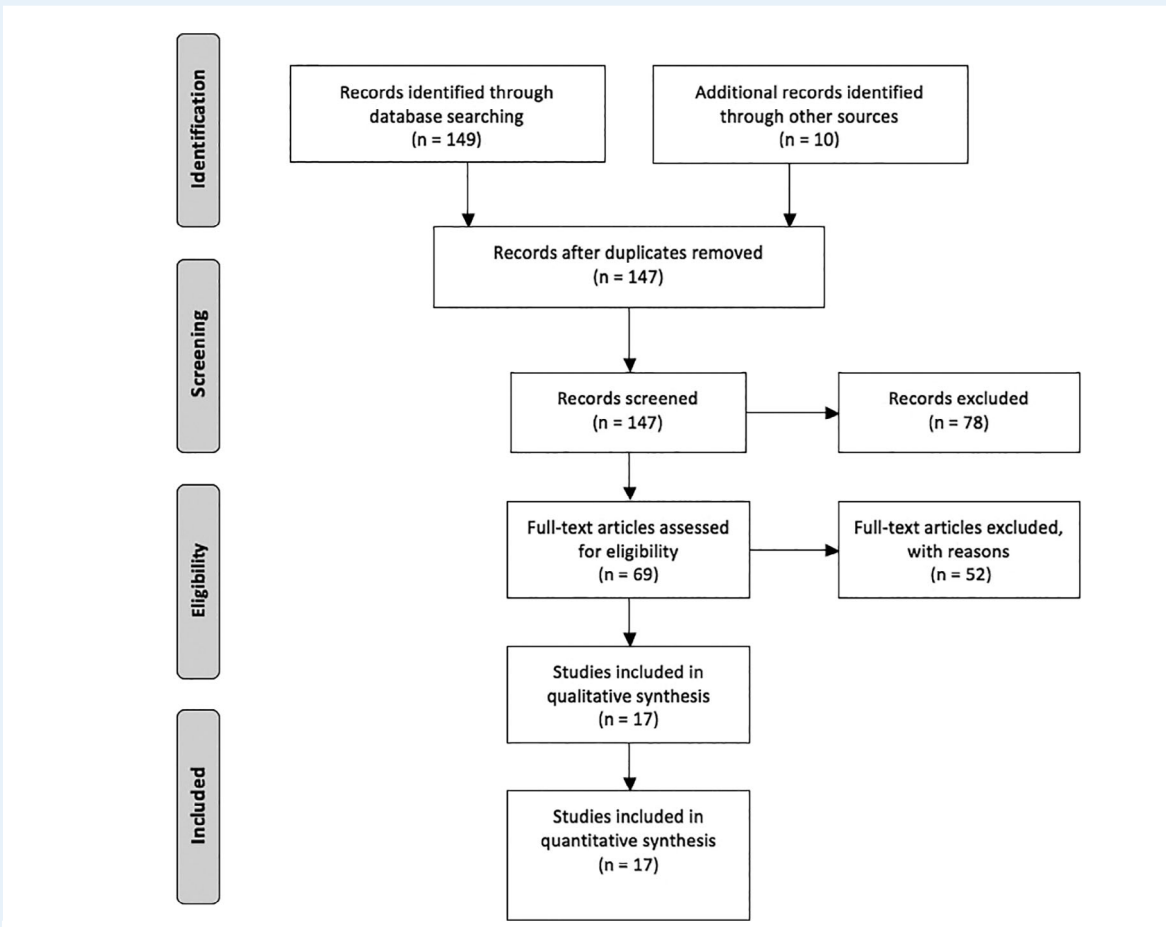

FIG. 1. Inclusion of articles by Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram.[14]

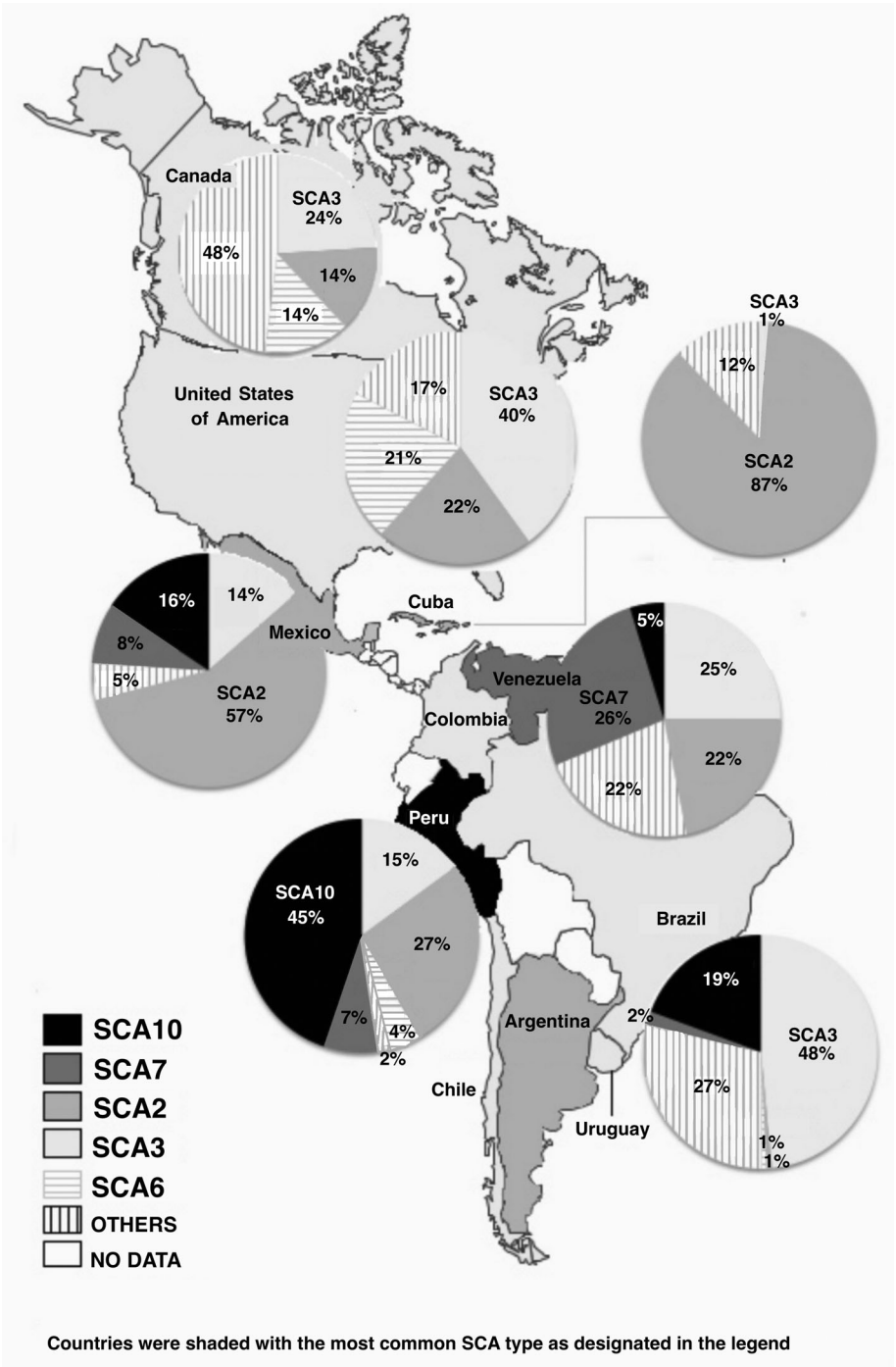

FIG. 2. Most frequent SCAs in the Americas. Drawn from data in Table 3 by one of the authors (C.H.F.C.). SCA, spinocerebellar ataxia.

both SCA2 and SCA6 in 24.8%, then SCA1 in 9.2%, and SCA7 in 7.3%.[16] Similar figures were confirmed later in a broader 12-center study of 345 patients in which SCA3 accounted for 40%, followed by SCA2 in 21.7%, SCA6 in 21%, and SCA1 in 17.4%.[17] This study was able to perform an assessment of the phenotypes and rates of longitudinal progression, comparing their data with those from an earlier methodologically similar European study, finding no significant difference for any of the subtypes and variables. Despite the relatively large number of Americans who are Mexican immigrants or of Mexican heritage, SCA10 has only been rarely described in the United States, and its prevalence remains unknown. Case reports describe cases of Mexican Americans presenting seizures as part of

TABLE 3 *Frequency of SCA in the Americas—main studies*

Country/Year	Patients (n)	Most common SCA	Other SCAs	Reference
North America				
Canada, 2005	69	SCA3	SCAs 2, 6, 1, and 8	Kraft et al[15]
United States (Minnesota), 1998	178	SCA3	SCAs 2, 6, 1, and 7	Moseley et al[16]
United States, 2013	345	SCA3	SCAs 2, 6, and 1	Ashizawa et al[17]
	123	SCA2	SCAs 10, 3, 7, and 17	Alonso et al[25]
Mexico (Gulf Coast), 2014	64	SCA7	SCA2	Magaña et al[27]
Central America				
Cuba, 2009	753	SCA2	SCAs 3 and 1	Velázquez-Pérez et al[28]
South America				
Argentina, 2015	19	SCA2	SCAs 3, 1, 6, and 7	Rodriguez-Quiroga et al[59]
Brazil, 1997	328	SCA3	SCAs 2 and 1	Lopes-Cendes et al[50]
Brazil (South), 2006	66	SCA3	SCAs 7	Jardim et al[51]
Brazil (South), 2012	150	SCA3	SCAs 10, 2, 7, 1, and 6	Teive et al[52]
Brazil, 2014	544	SCA3	SCAs 2, 7, 1, 10, and 6	de Castilhos et al[55]
Brazil (Sao Paulo state), 2014	320	SCA3	SCAs 7, 1, 2, 6, 8, and 10	Cintra et al[54]
Brazil (South), 2018	460	SCA3	SCAs 10, 2, 7,1, and 6	Camargo et al (personal communication)
Chile, 2015	50	SCA3	Not reported	Miranda[47]
Chile, 2018	63	SCA3	Not reported	Saffie Awad et al[48]
Peru, 2018	258	SCA10	SCAs 2, 3, 7, 6, and 1	Cornejo-Olivas et al (personal communication)
Venezuela, 2016	115	SCA7	SCAs 3, 2, 1, 10, and DRPLA	Paradisi et al[37]

SCA, spinocerebellar ataxia; DRPLA, dentatorubro-pallidoluysian atrophy.

their phenotype, but also a patient of Sioux Native American ancestry in whom no seizure was documented.[18,19] Still in the United States, SCA13 and SCA36 were tested in large samples of patients with undiagnosed sporadic or familial cerebellar ataxia, identifying 4 positive families each (<1%) from 2 distinct ethnic groups: white European and Asian (Japanese and Vietnamese).[20,21] SCA14, SCA18, and SCA20 have been described in single families.[22–24]

In Mexico, the largest published study analyzed SCA1–3, 6–8, 10, 12, and 17 and DRPLA on a total of 682 individuals, 559 of them belonging to 108 autosomal dominant families and 123 sporadic cases in which Friedreich's ataxia or a secondary cause were excluded.[25] All cases were Mestizos, born in Mexico, as well as their parents and grandparents. The most frequent molecular diagnosis was SCA2 (45.4%), followed by SCA10 (13.9%), SCA3 (12%), SCA7 (7.4%), and SCA17 (2.8%). No cases of SCA6, 8, or 12 or DRPLA were found. In terms of clinical profile, although most of the SCAs were found to be rather typical, it is important to highlight the fact that SCA10 was originally described in Mexico with a phenotype of pure cerebellar ataxia and seizures, occasionally added by mild pyramidal and neuropsychiatric signs.[26] A case-finding study restricted to the genetic analysis of SCA1, 2, 3, 6, and 7 in 5 communities of Veracruz State identified 64 SCA cases from 10 families, most of them (8 families, 55 individuals) with SCA7 in addition to 2 families with SCA2, but none with the other forms tested.[27]

Central America

Our review did not find any publications, including case reports, describing SCAs in continental Central America: Guatemala, Belize, El Salvador, Honduras, Nicaragua, Costa Rica, and Panama.

In insular Central America, literature is also sparse, except for Cuba where the SCAs, particularly SCA2, have been well studied. These studies include a nationwide epidemiological survey for SCAs showing that SCA2 represents 86.8% of all SCAs, followed by SCA3 in 4.1% and rare (<1%) cases of SCA7 and SCA1.[28,29] The molecular, pathologic, and phenotypic profiles of the Cuban SCA2 patients have been thoroughly explored and are consistent with the typical presentation and longitudinal progression described elsewhere. In the case of SCA3, the subphenotype III with peripheral signs seems to be more common than previously reported in other series.[29]

A total of 3 unrelated SCA2 families were described in Martinique (French West Indies) in 2 publications by the same group, outlining typical features (ataxia, supranuclear ophthalmoplegia, and hyporeflexia) but also intrafamilial phenotypic heterogeneity.[30,31] Recently, a large family from Antigua with SCA3 was well documented, including affected individuals who moved to Barbados and Trinidad-Tobago.[32] Gwinn-Hardy and colleagues[33] also described an Antiguan SCA3 family of sub-Saharan African descent, whereas Giunti and colleagues[34] described SCA3 families from Jamaica living in the United Kingdom.

South America

Ecuador, Paraguay, Uruguay, Suriname, and Guyana have no published cases of SCAs. One SCA3 family from French Guiana was described as part of a large worldwide study. In this case, the disease was probably the result of independent mutation based on the presence of a unique intragenic haplotype not found in other populations.[35] Similarly, only 1 reference was found in the literature describing SCAs in Bolivia, a unique report of a family with 3 ataxic patients, all with SCA10 mutations, and 2 of them also presenting molecular diagnosis of SCA2. Of the SCA10 cases, 2 had epilepsy, and both affected by SCA2 had supranuclear ophthalmoplegia.[36]

In Venezuela, a nationwide study found 115 unrelated SCA families. SCA7 was the most frequent subtype (26.6%), followed by SCA3 (25%), SCA2 (21.9%), SCA1 (17.2%), SCA10 (4.7%), and DRPLA (3.1%); no cases of SCA6, 8, or 17 were found, and in 43% of the families, a specific diagnosis was not identified.[37] SCA7 mutations displayed strong geographic aggregation in 2 independent founder foci, and SCA1 showed a very remote founder effect for a subset of families. Most of the SCA10 present seizures similar to cases initially described in Mexico.

In Colombia, no systematic SCA study was found. An early retrospective study of 38 patients with "inherited ataxias" did not find cases of dominant inheritance or diagnoses of any form of SCAs.[38] However, a unique SCA10 case of an adopted Colombian patient of mixed Amerindian (mother)/white European Australian descent presenting initially with epilepsy and ataxia has been described.[39] This case later developed chorea and had a concomitant molecular diagnosis of Huntington's disease. Also, 2 adopted Colombian brothers diagnosed with SCA21 have recently been reported, presenting with a complex combination of ataxia, postural tremor, parkinsonism, myoclonus, motor and mental development delay, behavioral abnormalities, and early-onset cataracts, broadening the clinical spectrum of this disorder previously only described in European and Asian families.[40] As in Colombia, there are no studies on the prevalence of SCAs in the population of Uruguay. Despite this, it is believed that the most common SCA in both countries is SCA3 in view of unpublished data from specialized outpatient clinics (personal communication).

In Peru, information on specific forms of SCAs and their prevalence is becoming more appreciable during the past years. SCA10 seems to be the most frequent form, occurring in more than 20% of cases,[41,42] followed by either SCA2, detected in 7.8% of a sample of 231 cases, or SCA3, diagnosed in 9.7% of a smaller sample of 31 patients with dominant ataxias.[43] The cases of SCA2 present with features common to what has been described worldwide; however, the SCA10 cases present much less frequently with epilepsy (if compared with Mexican cases), and no evidence of peripheral neuropathy (similar to Brazilian patients).[43,44] SCA7 and SCA6 have been described in 2 Peruvian kindreds each; SCA1 has been described in 1 family; all presenting phenotypes consistent with what has been described in the literature.[44,45] One Peruvian SCA10 family of Amerindian ancestry living in Italy presenting with ataxia and epilepsy was described in 2014.[46]

A total of 2 studies in preparation have also looked at nonpathogenic large normal alleles in *ATXN1*, *ATXN3*, *CACNA1A*, and *ATXN10*, a factor associated with disease prevalence in SCAs1, 3, 6, and 10 among healthy mestizo Peruvians. These studies, however, did not confirm the hypothesis of an association of the frequency of these diseases with mutation-prone alleles (personal communication).

In Chile, 2 retrospective studies with limited data are available. The first was published in 2015, describing 50 patients with "inherited ataxias," 10 (20%) of them with a molecular diagnosis of SCA3 belonging to 5 different families; no details of the diagnoses on the remaining cases are presented.[47] Another more recent retrospective study of 22 patients presenting with "genetic ataxias" identified 14 with a molecular diagnosis of SCA3, and the remaining presenting recessive or X-linked forms.[48] One case of SCA1 has also been reported as an abstract.[49]

In Brazil, the most common forms of SCAs have been described in detail. However, because of the significant differences in terms of ethnic background from 1 state to another and even within the same state, the frequencies of each form cannot be generalized. For example, the first study that performed a genetic analysis of SCAs in Brazil was published in 1997 and was restricted to SCA1, SCA2, SCA3, and DRPLA, including 328 patients from the Southern states, finding mutations in 39%: SCA3 in 30% of them, followed by SCA2 in 9%, and SCA1 in 6%.[50] Another early study including 66 patients from the Southern state of Rio Grande do Sul found an overwhelming frequency of SCA3 (92%), followed by SCA7 in 2%. One single case of SCA8 was found, and only 6% remained undiagnosed. The authors attribute the high prevalence of SCA3 to a probable Azorean founder effect.[51] Still in South Brazil, a study based on a tertiary center in the state of Parana analyzed a total of 150 patients from 104 families with SCAs.[52] This study confirmed that SCA3 was the most prevalent type (72.46%), but in this population, SCA10 represented the second most common form (11.60%), followed by SCA2 (7.25%), SCA7 (4.34%), SCA1 (2.90%), and SCA6 (1.45%). No cases were positive for SCA8, SCA12, SCA17, or DRPLA. Interestingly, this study and another by the same group created the notion that the Brazilian form of SCA10 did not typically present with seizures, as opposed to Mexican SCA10 cases.[52,53] A study from Ribeirão Preto, state São Paulo with 320 patients with dominant ataxias found a molecular diagnosis in 265 (82.8%) belonging to 131 unrelated families.[54] SCA3 was by far the most common (70.7%), followed by SCA7 (6%), SCA1 (5.3%), SCA2 (2.7%), SCA6 (1.3%), SCA8 (0.7%), and SCA10 (0.7%). No cases of SCA12, SCA17, or DRPLA were found.[53] The largest Brazilian study published so far included 544 SCA patients from 359 families from 11 tertiary urban centers from the South, Southeast, North, and Northeast states.[55] Overall, SCA3 was the most common form, accounting for 59.6% of the whole sample, followed by SCA2 in 7.8%, SCA7 in 5.6%, SCA1 in 4.2%, SCA10 in 3.3% and SCA6 in 1.4%. Regional differences were evident; for example, SCA7 was the second most common in parts of the Southeast, whereas Sao Paulo had the highest prevalence of SCA2 and all cases of SCA6. Although the clinical and genotypic markers of these disorders were, for the most part, consistent with what was described elsewhere in the world, 1 striking exception was the fact that seizures were actually part of the phenotype among the SCA10 families, similar to what was described among Mexican cases.[55] Finally, in a large sample of 167 SCA3 patients belonging to 68 pedigrees, Moro and colleagues[7] studied the frequencies of SCA3 subphenotypes. Subphenotype 2 was the most common, with ataxia and pyramidal findings (67.5%), followed by subphenotype 3 with ataxia and peripheral signs (13.3%), and subphenotype 6 with pure cerebellar syndrome in 7.2%.[7] Only 1 family with DRPLA has been reported in Brazil, among 487 patients with autosomal dominant ataxias (0.2%).[56] This family had 6 affected members, all with late-onset ataxia and associated with dementia in 2. A DRPLA case of Japanese ancestry has been confirmed in a report currently submitted for publication by our group. Finally, a family with SCA31 and a sporadic case of SCA34 with erythrokeratodermia were published recently.[57,58]

In Argentina, a prospective study based on a center of neurogenetics found a total of 20 cases of SCAs, including 8 (40%)

with SCA2, followed by SCA1 and SCA3, both with 5 cases each (20%), and the remaining being 1 case of SCA6 and 1 case of SCA7.[59] SCA10 has also been described in an Argentinean family presenting a phenotype similar to that described in Mexicans[60] (Table 2).

Discussion

Several assumptions can be made in view of the data presented in this review. The high frequency of SCA7 in the Mexican State of Veracruz and in Venezuela, both close to Caribbean, is quite intriguing because the disease is more commonly found in patients from countries such as Finland, Sweden, the Netherlands, and South Africa.[27,37] The Mexican cluster could be explained by the fact that the Mexican communities analyzed, founded by Spanish landowners and populated by Native Americans, were settled in a region in which the geography may have undermined communication with other populations and limited human migration. Of importance, the phenotype of the large group of SCA7 cases described in this study is quite typical when compared with other cases with this diagnosis elsewhere. Thus, it is likely that an ancestral mutation spread over the communities of Veracruz because of their geographical isolation as well as cultural habits, such as consanguineous marriages.[27] In other words, a cluster of SCA7 patients as the result of a founder effect. In the case of Venezuelan families, 1 study showed that the mutations presented a strong geographic aggregation in 2 separate founder foci, but their correlation with the haplotype described in other populations, particularly the Mexican, has not been determined so far.[37] Interestingly, SCA7 has been described with relatively high prevalence in the state of Ceara, Northeastern Brazil, also near the Caribbean.[57]

The highest prevalence of SCA2 worldwide is in the province of Holguin, Cuba, particularly in the municipality of Baguanos, also the place where the first description was performed.[28] The majority of these cases are of Spanish Caucasian ancestry, consistent with the fact that SCA2 tends to be more prevalent among a few countries colonized by the Spanish throughout the Americas. On the other hand, an independent founder effect cannot be ruled out as Cubans also have the highest worldwide prevalence of what is designated "large normal SCA2 alleles," a well-defined factor linked to the expansion of CAG repeats and a higher prevalence of SCA2.[61]

The fact that pathogenic expansions of the SCA6 locus are associated with a common *CACNA1A* haplotype worldwide may indicate that cases of SCA6 across the globe are indeed eventually linked to a common founder in Japan. North and Latin America have the largest Japanese community outside Japan, especially in the United States, Brazil, Peru, and Mexico.[62] Accordingly, Canada, the United States, Brazil, and Peru have documented cases of SCA6, as outlined previously in this review.[15,17,55] In Brazil, cases are concentrated in the states of Parana and Sao Paulo, the 2 areas that received more dense immigration from the Japanese at the turn of the 20th century.[55,63]

In the case of SCA3, the ancestral origin and spreading routes of mutational events were relatively well delineated using haplotype studies. As such, 2 independent de novo mutations have been identified, generating lineages with implications to the population of the Americas.[64] The most ancient (Joseph lineage) first occurred in Asia around 7000 years ago, diffused throughout Europe much later, leading to founder effects in the Azorean island of Sao Miguel and Portugal's Northeastern mainland. The second, the Machado lineage, probably originated in the Island of Sao Miguel and along the Tagus river valley in the heart of the mainland about 1500 years ago. Worldwide, most affected families share the intragenic haplotypes of 1 of these lineages: Machado lineage dispersed almost exclusively by Portuguese emigration, whereas the Joseph lineage dispersed to additional parts of the world before the Portuguese founder effect occurred (Asia, Oceania, East Europe, etc.).[64] On the other hand, both lineages converge in the Americas, more so, obviously, throughout Brazil with a particular high frequency in the coastal cities of the Santa Catarina state in the south. This area received a large wave of Portuguese immigrants during the middle of the 18th century, coming specifically from the islands of Madeira and Azores because of the serious economic difficulties and constant seismic activity.[65]

In theory, the presence of different lineages or the occurrence of SCA3 clusters in specific geographic areas could lead to different proportions of SCA3 subphenotypes or a more random presence of phenotypic variability in certain areas of the globe. Although the distribution of subphenotypes has not been consistently compared between different SCA3 populations, a cursory look at the most important studies of larger SCA3 samples does not reveal any major discrepancy, except for the proportionately higher frequency of subphenotype III among Cubans described in 1 study.[7,29] Other phenotypic variables, however, may present with different frequencies in different populations. One such example is the presence of "bulging eyes" (BE; Fig. 3). Although

FIG. 3. Spinocerebellar ataxia type 3–"bulging eyes." From a personal collection (H.T.), with appropriate approvals.

a single-center study of 167 SCA3 from Brazil, most of the participants from the Santa Catarina state with families who originated from the Azorean island of São Miguel, found that almost two thirds had BE,[10] other Brazilian studies with different populations of SCA3 found much lower frequencies, ranging from 27% to 30%,[51,55] figures similar to those described in Portugual.[66] Interestingly, BE seems to be unusual among samples from countries such as Germany and France.[67,68]

SCA10 may be the 1 form of SCAs primarily originated in the Americas. Almeida and colleagues[69] were the first to perform a detailed haplotype study in Brazilian and Mexican families showing several evidences of an ancestral common origin for SCA10 in Latin America, probably from an ancestral Amerindian population. Later, however, single families from China and Japan were identified, indicating that the original mutation may have occurred before the migration of Amerindians from East Asia to North America.[70] Screenings for SCA10 among other populations are so far negative.

SCA10 was first described in 1998, and ensuing studies confirmed a phenotype combining ataxia and epilepsy.[71,72] The first Brazilian description done by our group, however, did not detect epilepsy as part of the clinical presentation, a finding that was later confirmed on a different study.[53,73] The later study found a 3.75% prevalence of epilepsy among this cluster of Southern Brazilian SCA10 cases,[53] differing from patients from Mexico (72.2%), Argentina (100%), Venezuela (80%), and even among other regions of Brazil (65%).[55,74] Peruvian cases seem to present with epilepsy much less frequently, but the exact frequency is part of data currently been organized for publication (personal communication). So far, several potential variables that could influence this phenotypic discrepancy have been studied and proved to be irrelevant, including age, age of onset, and size of the pathogenic ATTCT expansion.[74] One exception is the presence of a penta or heptanucleotide interruption motif, designated "ATCCT interruption" found within the SCA10 ATTCT expansions. So far, the most consistent study on this specific issue showed that cases with more "pure" expanded repeat mutations (ATCCT negative) had a lower likelihood for the development of seizures, whereas the ATCCT-positive patients had a 6.3-fold increased risk of presenting seizures and a 13.7-fold greater chance of seizures within their first-degree relatives.[75]

Conclusion

The heterogeneous and mixed ethnic background characteristic of the Americas is not the only challenge for a review of any topic related to genetic disorders in the continent. In addition to the existence of several geographically circumscribed clusters of specific SCA subtypes and founder effects, access to tertiary medical centers, genetic testing, dedicated specialists, and means to disseminate scientific data can markedly differ among neighboring areas in the subcontinent or even within the same country. As a result, several countries have no or poorly detailed published data related to this topic, a problem that is not exclusive to the least scientific or economically developed.

Despite these limitations, it seems evident that SCA3 is the most common form in the continent overall, although country-specific prevalence and ranking of the common forms vary. Notable examples are the following: (1) SCA2, the most common form in Cuba and Mexico, whereas it is the second most common in Canada, the United States, Peru, Venezuela, and Brazil; (2) SCA10 is the most common SCA in Peru, the second most common subtype in Mexico, and part of Southern Brazil; (3) SCA7 seems to be the most common form in Venezuela.

In addition to guiding differential diagnosis and molecular testing by ranking the most common forms of SCAs in different parts of the continent, the other main objective of this review was to identify region-specific phenotypic variations. To be noteworthy, these variations should be unique or at least peculiar, in contrast to the classic description, as consequences of molecular or, less commonly, environmental modifiers. Unfortunately, with the exception of what was already discussed with regard to the presence or absence of epilepsy in SCA10, no other evident differences could be observed for other forms of SCA based on the available literature. A systematic, multinational study analyzing in detail the discerning clinical signs and clues of each form (bulging eyes, other movement disorders, oculomotor abnormalities, etc.) would be ideal to look for these potential variations.

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Author Roles

1. Research project: A. Conception, B. Organization, C. Execution. 2. Manuscript preparation: A. Writing of the first draft, B. Review and Critique

H.A.G.T.: 1A, 1B, 1C, 2A
A.T.M.: 1C, 2A
C.H.F.C.: 1A, 1C, 2B
R.P.M.: 1B, 2A, 2B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board is not necessary for this review paper. The authors confirm that the patient consent to disclosure of his picture (Figure 3) was acquired. There was no human or animal research in this review study. Informed consent

was not necessary. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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