Discovery and characterisation of spinocerebellar ataxia type 36 or "Costa da Morte ataxia"

M. Arias

Neurology Department. Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain.

ABSTRACT

This study presents a chronological account of how and when a variety of degenerative ataxia was identified in Costa da Morte (a region on the Atlantic coast of Galicia, Spain); the disease was named spinocerebellar ataxia type 36 (SCA36) following the discovery of the causal genetic mutation, and it now represents the most prevalent autosomal dominant hereditary ataxia in Galicia. The same disease was described in the region of the river Asida (Chugoku, Japan) early in the second decade of the 21st century, with no knowledge or relationship between the two groups.

Patients present imbalance, usually slowly progressive and with onset in the fifth decade of life; other clinical features include hearing loss and dysarthria with atrophy and fasciculations of the tongue. Some patients present a discrete cognitive and affective cerebellar syndrome, which may precede motor symptoms.

Structural neuroimaging shows atrophy of the vermis, extending to the rest of the cerebellum and brainstem; ^{18}F-FDG PET has detected hypometabolism in the right cerebellar hemisphere in preataxic patients.

SCA36 is caused by a $(TG_3C_2)_n$ hexanucleotide expansion in intron 1 of the *NOP56* gene, resulting in intranuclear inclusions (RNA foci) and aberrant synthesis of dipeptides, which cause neuronal dysfunction, and particularly the loss of Purkinje cells. SCA36 and *C9orf72* mutations (the main cause of amyotrophic lateral sclerosis and frontotemporal dementia) are caused by hexanucleotide expansions, a peculiarity that has led to several concomitant research projects studying both entities: the elimination or silencing of these expansions by gene therapy may enable us to slow or cure both conditions.

KEYWORDS

SCA36, *NOP56*, MRI, PET, cerebellum

Introduction

The Greek word *αταξία* evokes disorder and discoordination; in today's medicine, it is used to refer to a disorder of voluntary movement characterised by titubation, imprecision, and dysrhythmia, due to dysfunction of the cerebellum and its connections: thus, we may refer to gait ataxia, appendicular ataxia, ataxic dysarthria, and ocular dysmetria. The cerebellum functions in parallel with the brain (both contain a similar number of neurons, approximately 40-50 billion): while the brain is responsible for planning and decision-making, the cerebellum acts through learned patterns to guide, monitor, and adjust voluntary movement; it is also involved in controlling executive functions, language, emotion, and social cognition. While the term ataxia is used to refer to a relevant neurological symptom or sign in a patient's clinical picture, the main definition

Corresponding author: Dr Manuel Arias
E-mail: manuel.arias@usc.es

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of the term refers to hereditary degenerative cerebellar diseases.

Unlike the cardiocentric philosopher Aristotle (384-322 BCE), Hippocrates of Kos (460-370 BCE), the father and pioneer of protoscientific medicine, was fully aware of and defended the important functions of the brain; he himself used the word ataxia to emphasise the tendency to chronicity of the disease causing the disorder. In later centuries, the concept of ataxia expanded and, true to its origins, became imprecise, with references to numerous diseases and symptoms (fever, chorea, tremor, etc), and perhaps only the angels being spared.[1] In 1984, Duchenne de Boulogne[2] used the term "locomotor ataxia" to describe gait abnormalities caused by tabes dorsalis. In 1863, Freidreich[3] described the most frequent variety of autosomal recessive degenerative ataxia, which bears his name. Over the latter half of the 19th century and the first seven decades of the 20th, clinical and neuropathological findings led to the description of new varieties of familial and sporadic degenerative ataxia: some forms present purely cerebellar involvement, whereas different parts of the nervous system are affected in others (basal ganglia, pons, olivary nucleus, posterior funiculi, spinocerebellar tracts, peripheral nerves). In the early 1980s, the talented researcher Anita Harding, who was sadly lost too young, established a degree of order and coherence in the field of degenerative ataxias, among her many other contributions. Regarding autosomal dominant cerebellar ataxias (ADCA), Harding[4] distinguished between three main types: *i)* ADCA I (cerebellar syndrome plus other symptoms: cognitive impairment, ophthalmoplegia, abnormal movements, optic neuropathy, hearing loss, peripheral neuropathy, amyotrophy); *ii)* ADCA II (cerebellar syndrome associated with retinal degeneration); and *iii)* ADCA III (pure cerebellar syndrome). With the description of the first genetic loci and subsequently the causal genes responsible for autosomal dominant ataxias,[5-10] the term ADCA came to be replaced by SCA, modified with a number indicating the chronological order in which each subtype was genetically characterised. To date, 48 SCAs have been described, although the locus of the causal gene has only been identified for 45.[11,12]

This article describes the results of different studies into SCA36 and recounts the discovery of the disease, which is also known as "Costa da Morte ataxia" after the Galician coastal region where the majority of patients originate. In chronological order, the review is structured as follows: *a)* first patients; *b)* characterisation of the clinical phenotype; *c)* search for the genetic locus, gene, and mutation; *d)* molecular and cellular biology: SCA36 and *C9orf72*; *e)* cognitive and affective cerebellar syndrome; *f)* present and future perspectives; and *g)* conclusions.

Development

First patients: Hospital Provincial de Conxo (Santiago de Compostela)

Hospital Provincial de Conxo, which was initially administrated by the provincial government of A Coruña, was inaugurated in 1985. It was equipped with state-of-the-art technology (the second hospital in Spain, and the first public hospital, to have a magnetic resonance imaging [MRI] scanner; digital angiography; lithotripsy; and hyperbaric chamber). As it had not been allocated a specific healthcare district, the centre often received patients from throughout the province, as well as other parts of Galicia and Spain, perhaps attracted by the novelty of the MRI scanner.

In 1992, I attended a 70-year-old man, born in the town of Borneiro (belonging to the municipality of Cabana de Bergantiños in the Costa da Morte region [A Coruña]), who presented more than 15 years' history of progressive symptoms of midline ataxia and, to a lesser extent, appendicular ataxia and dysarthria. After this first patient, other patients visited from Cabana, but also from Malpica and Ponteceso; all these municipalities are located close to the estuary of the river Anllóns (Figure 1). During the last decade of the 20th century, ten patients consulted with clinical manifestations of late-onset degenerative ataxia, initially presenting with pure cerebellar syndrome and subsequently developing sensorineural hearing loss and tongue atrophy with fasciculations; they did not present retinopathy, dementia, epilepsy, involuntary movement, or peripheral neuropathy. Some patients presented vitiligo, which I initially considered may constitute part of the clinical spectrum. Many of these patients were close relatives (siblings, cousins, uncles/aunts, parents and children), and analysis of the inheritance pattern showed unequivocally that this was an autosomal dominant disease.

According to Harding's classification, I classified these patients' disease as ADCA III progressing to "light" ADCA I (ataxia, hearing loss, and focal motor neuron disease). As mentioned previously, the discovery of the

first genetic loci associated with autosomal dominant ataxias led to the acronym ADCA gradually being replaced by SCA plus a number indicating the order in which each variant was discovered. At the beginning of the 21st century, with the creation of the Fundación Pública Galega de Medicina Xenómica (Galician Public Foundation of Genomic Medicine) and the first genetic studies, we discovered that none of these patients had any of the known SCAs. With the creation of the Galician Healthcare Service, all hospitals in Santiago de Compostela came to be run under this body; therefore, the neurology department of the Hospital Provincial de Conxo, where the first patients were studied (clinical examination, MRI, neurophysiology, and CSF analysis) and the peculiar "Costa da Morte ataxia" was identified, was integrated into the neurology department of the Hospital Clínico in 2004.

Characterisation of the clinical phenotype

In 2003, during the Annual Meeting of the American Neurological Association, in San Diego (USA), I suggested to Dr María Jesús Sobrido Gómez (who would lead the molecular-genetic studies), a neurologist who trained in Santiago de Compostela and completed a neurogenetics fellowship at the University of California, Los Angeles, that a team should be established to continue research into SCA–Costa da Morte ataxia and to identify its genetic and molecular basis.

We began this work in 2005, with a modest but effective economic grant from the Galician regional government to begin an initial research project. We scheduled visits, often on weekends and public holidays, to healthcare centres and homes, where we met and diagnosed patients and their family members, some of whom also presented or were at risk of developing the disease. A member of the research team would provide, explain, and collect informed consent forms developed specifically for the project; another would collect blood samples for molecular-genetic testing; and three senior neurologists would examine the patients, using a structured data log book to record the findings; individuals were classified as affected (symptomatic) or asymptomatic (carriers or non-carriers of the mutation) (Figure 2). Some of the affected individuals, with different disease progression times, agreed to travel to Santiago to be studied with MRI, positron emission tomography (^{18}F-FDG PET), evoked potentials, electromyography, and several otological examinations.

Figure 1. A) Map of the Costa da Morte region. B) Estuary of the river Anllóns

By 2006, we had studied 28 patients from two families, all of whom presented homogeneous clinical manifestations overlapping with those described previously; vitiligo was ruled out as a manifestation of the disease, as it was absent in one family and did not present in all clinically affected members of the other family. Susana Arias-Rivas presented the clinical and paraclinical findings in the project she presented for her Diploma in Advanced Studies, pending the results of the molecular-genetic study, and the term Costa da Morte ataxia gained academic recognition and official status.

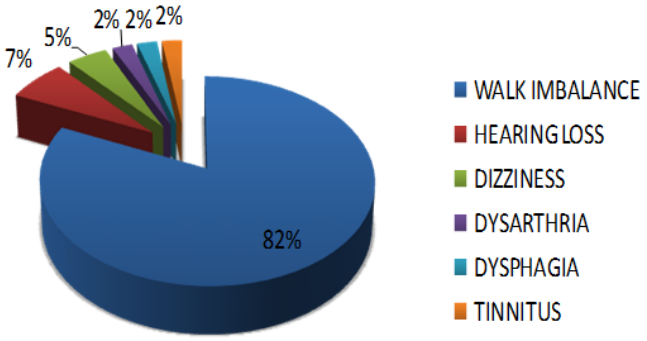

Figure 2. A) Symptoms at onset (%).

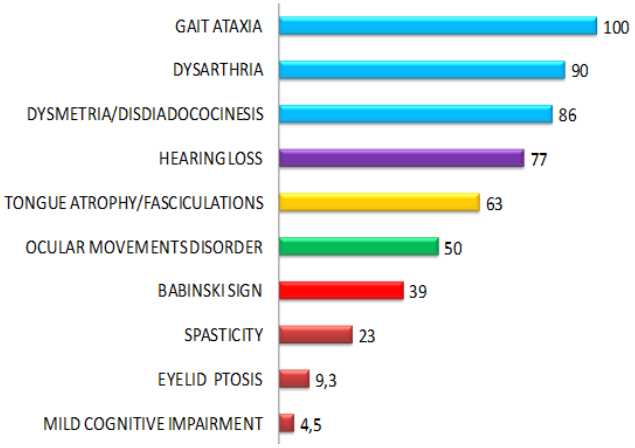

Figure 2. B) Clinical findings.

In 2008, after examining 167 individuals from 10 families, from whom we also collected blood samples for the molecular-genetic study, the phenotypic study was complete. Of the 167 participants, we considered 44 to be clinically affected (24 women and 20 men); mean age of onset was 53.2 years, and mean age at the time of clinical examination was 63.8 years. The balance disorder was the first symptom in 82% of patients, and all patients presented midline ataxia. Figure 2 provides more detail on the clinical phenotype. With respect to the complementary studies carried out in selected patients, laboratory tests detected no abnormalities in samples of blood (complete blood count, biochemistry, immune and metabolic panel) or CSF (cells, protein, glucose). In the neurophysiological studies, motor and sensory nerve conduction velocity results were normal, whereas needle electromyography only revealed denervation restricted to the muscles of the tongue (focal motor neuron disease). We also observed alterations in somatosensory evoked potentials: specifically, increased latency and decreased amplitude when the lower limbs were stimulated, a finding indicative of central neuropathy. The brainstem auditory evoked potentials study revealed reduced amplitude or absence of waves I and II, suggesting auditory neuropathy, whereas in the audiometry examination, many patients presented considerable binaural hearing impairment, with a loss greater than 40 dB above 2500 Hz. Brain MRI studies of patients at different stages of progression identified a pattern of progressive cerebellar atrophy, beginning at the superior cerebellar vermis and subsequently extending throughout the cerebellum and finally, in older patients, to the brainstem. No relevant white matter disease or cortical atrophy was detected (Figure 3). Oral communications were presented at the Annual Meetings of the Galician Society of Neurology (A Coruña, 2008), the Spanish Society of Neurology (Barcelona, 2008),[13] and the European Federation of Neurological Sciences (Stockholm, 2012)[14] to raise awareness of the clinical phenotype of Costa da Morte ataxia.

Genetic locus, gene, and characteristics of the causal mutation

The first linkage studies, using short tandem repeat (STR) markers in DNA samples obtained from patients with SCA–Costa da Morte ataxia, enabled us to locate a candidate region with a logarithm of the odds (LOD) score of 10 in chromosome 20p13. Subsequently, a study with single nucleotide polymorphism (SNP) markers further narrowed this region, finding that affected patients shared a region of 2 cM (0.8 Mb; 19 genes) (Figure 4). With these data, we had discovered a new SCA (clinical profile and demonstrated genetic locus), although we opted not to publish the findings, as we expected the identification of the specific gene and causal mutation to be a simple task that could be resolved in a matter of months.

At the time, no causal gene had been identified for SCA23, characterised in 2004 with a linkage study that identified the 20p13-12.3 region (6 Mb; 97 genes)[15]; SCA23 presents with a late-onset, slowly progressive

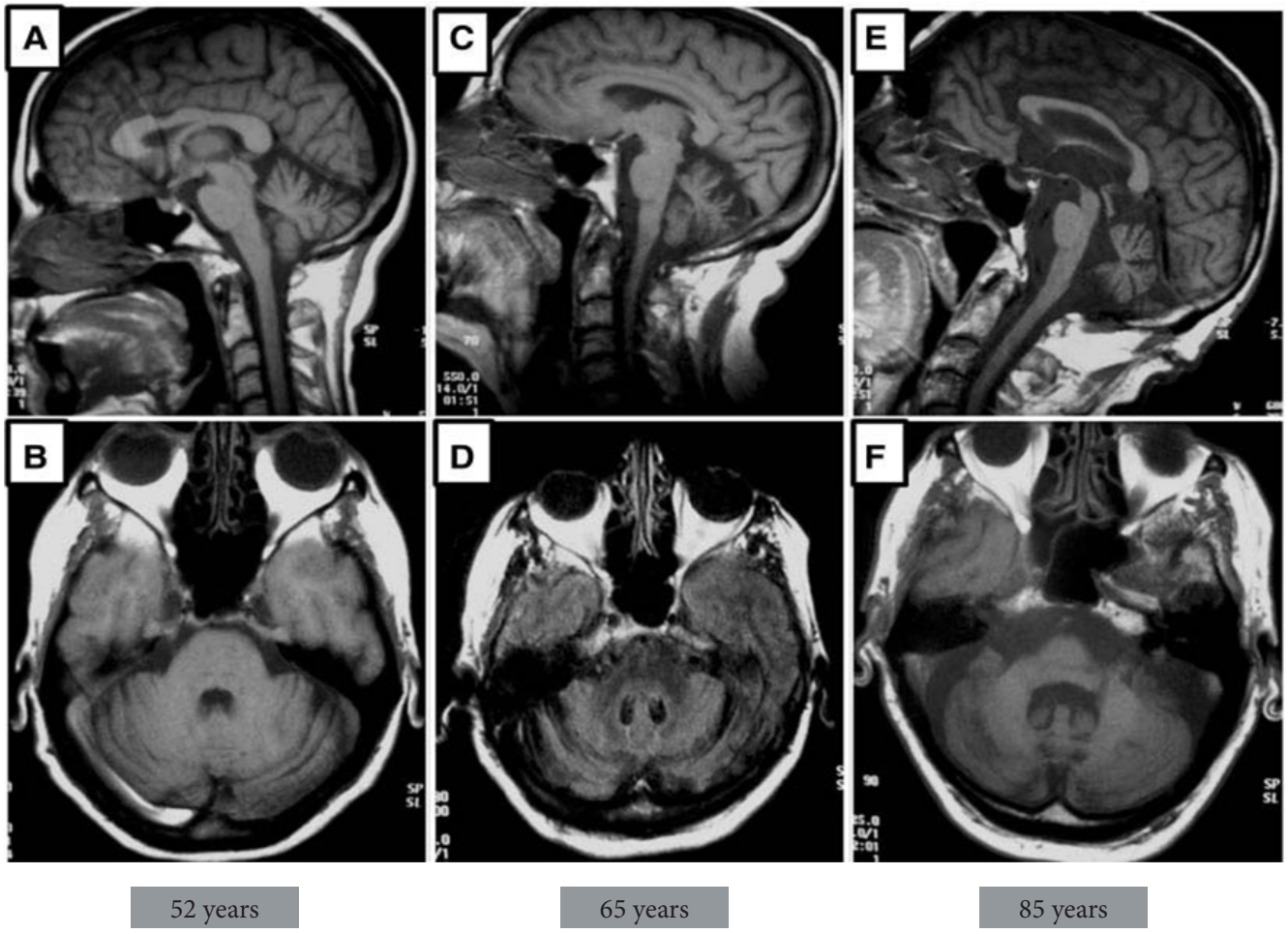

Figure 3. T1-weighted brain MRI studies: A and B) Early stage (vermis atrophy); C and D) intermediate stage (pancerebellar atrophy); E and F) late stage (cerebellar and brainstem atrophy).

pure cerebellar syndrome and is not associated with hearing loss or tongue fasciculation. A study published in late 2010 reported that it was caused by mutations in the *PDYN* gene, which was not included in the 2-cM region identified in our patients.[16] SCA35 was also described in 2010; this ataxia is caused by mutations in *TGM6*,[17] one of the 19 genes in our candidate region. However, direct and repeated sequencing of this gene, as well as the other 18, did not demonstrate a genetic alteration in our patients' DNA. We suspected that the causal mutation was a repeat expansion, although it could not be identified as we did not have access to Southern blot technology (special authorisation is needed due to the use of radiation). This caused significant delays in the characterisation of the disease, although we were eventually able to demonstrate that all the patients analysed presented an intronic expansion in one allele of the *NOP56* gene (Figure 4). Several months later, as we were preparing the publication, we were overtaken by a Japanese research group,[18] who were the first to publish the genetic cause of SCA36. The clinical phenotype was obviously very similar to that observed in our patients, although the description did not identify hearing loss; however, these authors did report hearing loss after our publication.[19,20]

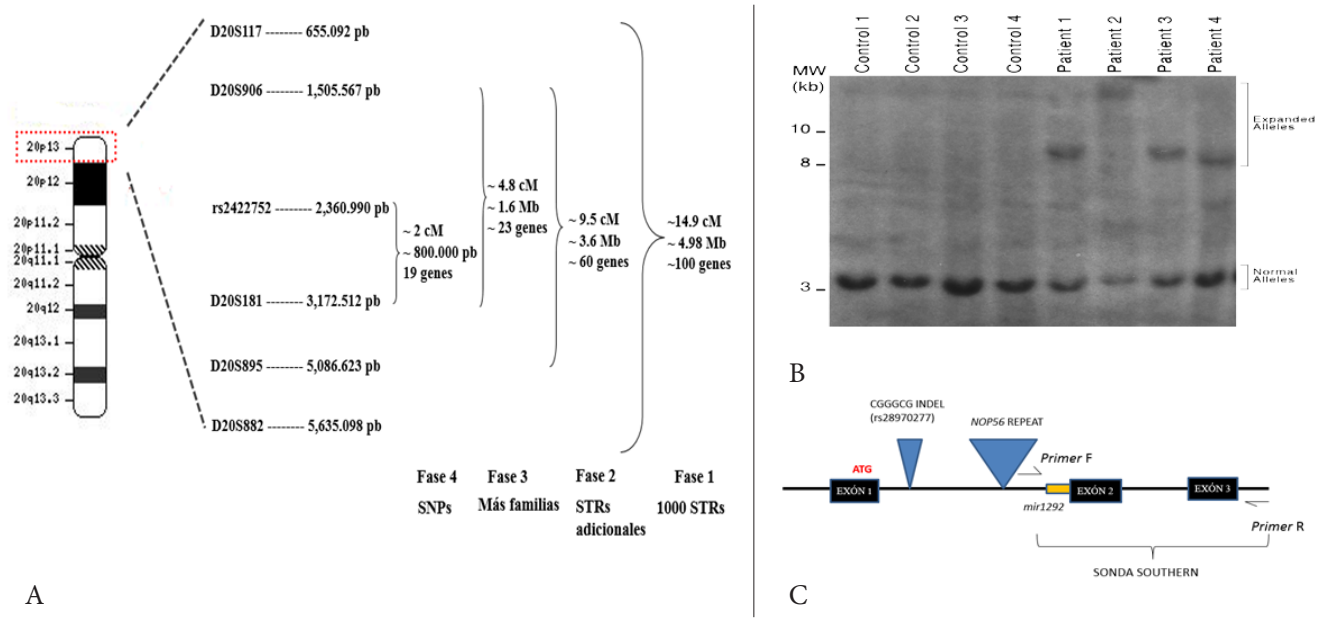

Figure 4. Phases of the molecular-genetic study (images provided by Dr M.J. Sobrido). A) Linkage study. B) Southern blot. C) Diagram of the *NOP56* gene.

Molecular biology: SCA36 and *C9orf72*

The *NOP56* gene codes for a 56-kD protein that interacts with those encoded by *NOP1* and *NOP58* to form the 60S ribosomal subunit. SCA36 is caused by a mutation in the *NOP56* gene consisting of a heterozygous expansion of the GGCCTG hexanucleotide $(TG_3C_2)_n$ repeat in intron 1 of the gene.[18,19] The presence or absence of this pathological expansion confirms or excludes the diagnosis of SCA36, both in symptomatic individuals and those at risk of developing the disease, as well as in apparently sporadic cases. PCR testing with appropriate primers can identify the expansion in heterozygosis; precise quantification of the size of alleles with large expansions requires more complex tools. Normal alleles present 3-14 CGCCTG repeats in white populations[19] and 3-8 repeats in Japanese populations.[18] Mutant alleles usually present 650 or more repeats, although some patients present shorter expansions. Diagnosis of SCA36 in asymptomatic individuals, as well as preimplantation and prenatal studies, first requires the identification of the mutation in a family member. We are not aware of any other allelic disorders caused by *NOP56* mutations with a phenotype other than that described. It is unclear whether the size of the expansion is correlated with the onset and severity of clinical manifestations.[19,21]

Studies with lymphoblasts have shown that the CGCCTG expansion in *NOP56* causes focal intranuclear accumulation of RNA (RNA foci) in neurons.[19] Similar findings have been reported in other SCAs caused by repeat expansions, as well as in Huntington disease and Steinert disease. The role of RNA in these diseases is currently a highly active field of research. A related disease does exist: the most frequent hereditary cause of amyotrophic lateral sclerosis and frontotemporal dementia, as with SCA36, is an intronic hexanucleotide repeat expansion $(G_4C_2)_n$; in this entity, the expansion is located in an open reading frame portion of DNA on chromosome 9, denominated *C9orf72*.[22] These expansions give rise to canonical translations (SCA36) and repeat-associated non-ATG (RAN) translations, which generate potentially toxic proteins composed of repeated dipeptides. RAN translation is the predominant form in *C9orf72*, and gives rise to insoluble forms of polypeptides.[23,24] Studies are being conducted with

induced pluripotent stem cells and the construction of organoids obtained from cutaneous fibroblasts from Galician patients with SCA36; research groups from several countries, including one from the University of Emory (Atlanta, USA) and another from the Mayo Clinic neuroscience department (Jacksonville, USA), have participated in these studies. Some of the results of these studies with living cells and autopsy material from patients with SCA36 and *C9orf72* expansions were published very recently in *Neuron*[23] and *Cell Reports*.[24]

Neuropsychological study and functional neuroimaging

A comprehensive clinical, neuropsychological, and functional neuroimaging (^{18}F-FDG PET) study was conducted in the group of individuals carrying the SCA36 mutation. Some participants did not yet present imbalance (preataxic) and others had different degrees of ataxia. In the preataxic individuals, we identified: *i)* reduced phonological verbal fluency, correlated with hypometabolism in the right cerebellar hemisphere in the functional neuroimaging study, whereas structural MRI findings were normal; *ii)* symptoms of anxiety and depression.[25,26] These findings confirm that, from an early stage, SCA36 progresses with a cognitive and affective syndrome, and reaffirm the role of the cerebellum as a coordinator/driver, contributing both to motor function and to cognition and affect. In her doctoral thesis, Rocío Martínez-Regueiro[27] studied in detail the cognitive and affective syndrome in SCA36–Costa da Morte ataxia and conducted a preliminary validation of the Spanish-language version of the Schmahmann syndrome scale, previously developed in English for detection of this syndrome.[28]

Present and future perspectives of SCA36

The incidence and prevalence of SCAs vary considerably between countries, ranging from one to four cases per 100 000 population. SCA3 is the most frequent type of SCA worldwide, with SCA10 being the most frequent type in Mexico, SCA7 in Scandinavian countries, and SCA2 and SCA3 in Spain.[29-33] SCA36 is currently the most prevalent type of SCA in Galicia, accounting for 21.3% of all cases of autosomal dominant ataxia in adults according to the database of the Galician Public Foundation of Genomic Medicine.[19] In addition to the families in Galicia and Japan, SCA36 has been diagnosed in several other countries; in Spain, a significant cluster has been discovered in Albacete, whose connection with Costa da Morte ataxia is yet to be established. In a joint meeting with neurologists from Albacete, we were fortunate enough to examine some of the patients, finding that the upper and lower motor neuron involvement was more prominent in this cluster.

With over 150 patients with molecular diagnosis of SCA36 in Spain, and an additional 400 at risk of developing the condition, we are considering the possibility of a therapeutic trial with riluzole or troriluzole.[34-36] This would be the first trial of patients affected with a single genetic variety of ataxia.

Due to the presence of patients with SCA36 in such other countries as Japan, where significantly more resources are available to continue with this research, as well as the pathophysiological connection between amyotrophic lateral sclerosis and the *C9orf72* gene, we are hopeful that new forms of gene therapy may become available in the near future that may enable the elimination or silencing of the pathological expansion in order to cure or at least to slow the progression of this degenerative disease.

To date, two international symposia on SCA36 have been held (in Tomonoura [Japan] in 2016 and in Cabana de Bergantiños [Spain] in 2019; Figure 5), with the participation of clinicians and researchers from around the world: experience was shared and new projects and collaborations were discussed; without a doubt, these will help to deepen our understanding of this disease and to find a cure. A third international symposium, to be held in Albacete, has been proposed, but plans have not yet crystallised.

Conclusions

It has now been more than 25 years since I visited the first patients with SCA36–Costa da Morte ataxia; in this time, the causal mutation has been discovered and a diagnostic technique has been implemented that can detect the disease at any time of life. We have learned more details about the clinical profile and better understand some of the more specific manifestations, such as the cognitive/affective syndrome, and the results of functional neuroimaging studies. Clear advances have been made in cell biology and basic research into the effects of the mutation, but the definitive step of identifying an effective treatment is yet to be made.

Figure 5. I and II SCA36 International Symposia.
Figure 6. Consultations at patients' homes.

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I am grateful to all of our patients and their family members who provided us with the opportunity to perform the different studies, for their enthusiastic collaboration, and for their trust in us (welcoming us into their homes to perform clinical examinations) (Figure 6), and to all the physicians who have participated in this research, most of whom contributed to some of the studies reviewed.[13,19,22,25,26] I am also grateful to the patient Ramón Moreira for his significant contribution to the creation of family trees and for encouraging participation in our research. I would like to thank the municipal council of Cabana de Bergantiños for its help and for making available municipal facilities to hold meetings and the II SCA36 International Symposium. I am also grateful to AGA (Galician Ataxia Association) and FEGEREC (Galician Federation of Rare and Chronic Diseases) for their constant support. Finally, I would like to thank the writer and journalist Manuel Rey for his contribution to raising awareness of SCA36–Costa da Morte ataxia.[37]

Conflicts of interest

The author has no conflicts of interest to declare.

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