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Autosomal dominant cerebellar ataxias: a systematic review of clinical features

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Background and purpose: To assess, through systematic review, distinctive or common clinical signs of autosomal dominant cerebellar ataxias (ADCAs), also referred to as spinocerebellar ataxias (SCAs) in genetic nomenclature.

Methods: This was a structured search of electronic databases up to September 2012 conducted by two independent reviewers. Publications containing proportions or descriptions of ADCA clinical features written in several languages were selected. Gray literature was included and a back-search was conducted of retrieved publication reference lists. Initial selection was based on title and abstract screening, followed by full-text reading of potentially relevant publications. Clinical findings and demographic data from genetically confirmed patients were extracted. Data were analyzed using the chi-squared test and controlled for alpha-error inflation by applying the Holms step-down procedure.

Results: In all, 1062 publications reviewing 12 141 patients (52% male) from 30 SCAs were analyzed. Mean age at onset was 35 ± 11 years. Onset symptoms in 3945 patients revealed gait ataxia as the most frequent sign (68%), whereas overall non-ataxia symptom frequency was 50%. Some ADCAs often presented non-ataxia symptoms at onset, such as SCA7 (visual impairment), SCA14 (myoclonus) and SCA17 (parkinsonism). Therefore a categorization into two groups was established: pure ataxia and mainly non-ataxia forms. During overall disease course, dysarthria (90%) and saccadic eye movement alterations (69%) were the most prevalent non-ataxia findings. Some ADCAs were clinically restricted to cerebellar dysfunction, whilst others presented additional features.

Conclusions: Autosomal dominant cerebellar ataxias encompass a broad spectrum of clinical features with high prevalence of non-ataxia symptoms. Certain features distinguish different genetic subtypes. A new algorithm for ADCA classification at disease onset is proposed.

Introduction

Autosomal dominant cerebellar ataxias (ADCAs) are a group of clinically and genetically heterogeneous neurodegenerative disorders distributed worldwide, characterized by progressive ataxia but also often associated with a broad spectrum of neurological or other clinical findings [1]. Currently, ADCAs are classified under different genetic subtypes known as spinocerebellar ataxias (SCAs). Mutations described are most often the result of polyglutamine repeat expansions, conventional mutations and large rearrangements in genes with diverse functions [2]. A large group of pedigrees with ADCA have still not had their loci determined, suggesting that the number of SCAs will continue to increase [3,4].

Genetic classification can be confusing, as numbering is non-continuous (e.g. 9 and 24 are vacant), possible allelic variants exist (e.g. SCA15-16-29 and

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SCA19-22) and some subtypes have not been assigned any number, such as dentatorubro-pallidoluysian atrophy (DRPLA) [5]. Harding's classification based mainly on clinical features was a practical and didactic approach to patient diagnosis in the clinical setting [6]. However, overlap of findings between different subtypes, difficulty in identifying familial inheritance, as well as the considerable range of phenotypic characteristics found within pedigrees makes diagnosis based on a clinical classification a real challenge [7]. Furthermore, distinctive clinical manifestations present at disease onset in the absence of ataxia can remain the predominant, or sometimes the only, symptom observed during disease progression. On occasion, patients may present cerebellar symptoms exclusively, resembling 'pure' clinical forms at disease onset and then progressively developing other neurological symptoms [8].

For all these reasons, an updated ADCA clinical–genetic classification summarizing SCA subtypes is needed, particularly as a growing number of subtypes are constantly being reported and more pedigree groups are being detected without identifiable loci [9].

The exact prevalence of the diverse clinical manifestations of SCAs is hard to estimate, since large series of patients presenting common subtypes are scantily described and many infrequent subtypes rely solely on isolated pedigree reports. In addition, only a reduced number of studies were specifically designed to determine the frequency of clinical features; most described patients' features only partially or included only the most common SCA subtypes [10].

In an attempt to overcome some of these limitations, a systematic review was conducted of clinical ADCA phenomenology to determine what clinical features are associated and how often they present, as well as to establish whether distinctive or common signs can be identified in different genetic SCA subtypes.

Methods

Search strategy

A comprehensive structured search (Data S1) was undertaken by two independent reviewers (MR and LD), started in October 2011 and updated throughout September 2012. Original articles, clinical notes, case reports, letters, congress abstracts, review articles or any other kind of publications potentially containing clinical feature descriptions or proportions published in English, Spanish, French, German, Italian or Portuguese were extracted. Sources included MEDLINE, EMBASE, MD-Consult, LILACS, Global Health, Orphanet and NORD. In some cases, authors were contacted to identify gray literature. Back-search of reference lists from retrieved publications was conducted to identify potentially relevant publications undetected during the structured search. No time restrictions were applied since some of the patients only described at a clinical level before genetic diagnosis became available were subsequently tested.

Study selection

A two-step sequence was independently applied to study selection by the same reviewers mentioned above to determine whether material retrieved contained clinical descriptions or rates of ADCAs. First, publications were considered potentially relevant after titles and abstracts were screened. If no abstract was available, the publication was still selected for a second review, in which full-text reading was undertaken to identify publications reporting clinical feature descriptions or rates. Data quality was secured by excluding patients without genetic confirmation or duplicate cases (only the most complete description or recent publication was included). In addition, rare cases with two different genetic subtype mutations or in which ADCA was present together with other neurological diseases (e.g. multiple sclerosis), and therefore overlap between clinical features could occur, were also excluded. First authors were contacted when clinical feature descriptions were unclear or age at onset uncertain, or eventually if duplicate case reporting was suspected.

Data extraction

Non-episodic ADCA patients with genetic SCA confirmation (including linkage analysis) of any age, sex, ethnicity, illness duration or degree of severity were included when clinical features were described or prevalence rates reported. The most recent physical examination was considered to calculate age at examination. If provided, other demographic data were also extracted. Presence or absence of clinical features was recorded on a standardized data sheet only when explicitly reported, and extracted exactly as described in the text. For further analysis, a synonym list was developed to unify different clinical terms used synonymously (e.g. appendicular ataxia, limb ataxia, dysmetria or over-/under-shooting) after considering which terms could be reasonably combined. Disagreements between reviewers at any stage during selection were resolved jointly by consensus.

Statistical analysis

Descriptive data were presented as mean ± standard error of the mean or proportions. Between-group comparisons of quantitative variables were conducted using ANOVA with Brown–Forsythe correction when variances were not homogeneous. For $P < 0.01$, *post hoc* tests were performed using pairwise t tests. The chi-squared test with Yates' correction was applied for categorical variable analysis. If overall $P < 0.01$, chi-squared test pairwise comparisons were run. Experiment-wise alpha-error was maintained at 0.05 by employing the Holms step-down procedure [11]. Sample size adequacy for detection of clinical feature prevalence differences between SCA groups was evaluated. Absolute percentage difference between SCA groups most frequently or least frequently affected was calculated for each clinical feature. The minimum sample size needed to detect significant differences in prevalence of each clinical feature, as large as the one calculated before with 80% power, was obtained by the arc sin transformation formula [12]. When the calculated minimum sample size was smaller than the observed group size, clinical features were not analyzed further as power was considered insufficient. Similarly, clinical features described in fewer than two publications by different authors or working groups were also excluded from further analysis. IBM SPSS software version 20 (Chicago, IL, USA) was used for statistical analysis.

Results

In all, 11 150 publications were screened through literature search. A flow diagram showing publications yielded by the search is shown in Fig. 1. Data from 12 141 genetically confirmed patients amongst 30 SCA subtypes are presented. Clinical feature descriptions or proportions for novel provisional locus names assigned to SCA32, SCA33 and SCA34 were not available.

Demographic and clinical features

No major differences were found between males and females (52% vs. 48%, respectively). The geographical distribution is shown in Fig. S1. Mean age at onset, at time of examination and disease duration until examination for all SCA subtypes are described in Fig. S2. Mean age at time of death in 417 patients was 52 ± 1 years.

Clinical characteristics at onset

It was possible to ascertain 35 different clinical features at onset, reported in 3945 patients. Gait or truncal ataxia was the most frequent sign (68%), followed by dysarthria (14%), not otherwise specified ataxia (16%), diplopia (7%), dizziness (8%), intention or postural tremor, limb ataxia or impaired hand skills, and parkinsonism (all 4%) (Table 1). Overall ataxia or non-ataxia symptom frequency at onset was 84% and 50%, respectively (many patients began with more than one symptom, increasing the total frequency of clinical features above 100%). SCA3 was the most heterogeneous subtype at onset, with 22 different clinical features reported, whereas SCA4, SCA18, SCA19–22, SCA21, SCA25, SCA26, SCA28 and SCA30 were the most 'pure', starting exclusively with ataxia. Some subtypes began more often with non-cerebellar symptoms, such as SCA7 with visual impairment (49%); SCA14 with myoclonus (8%);

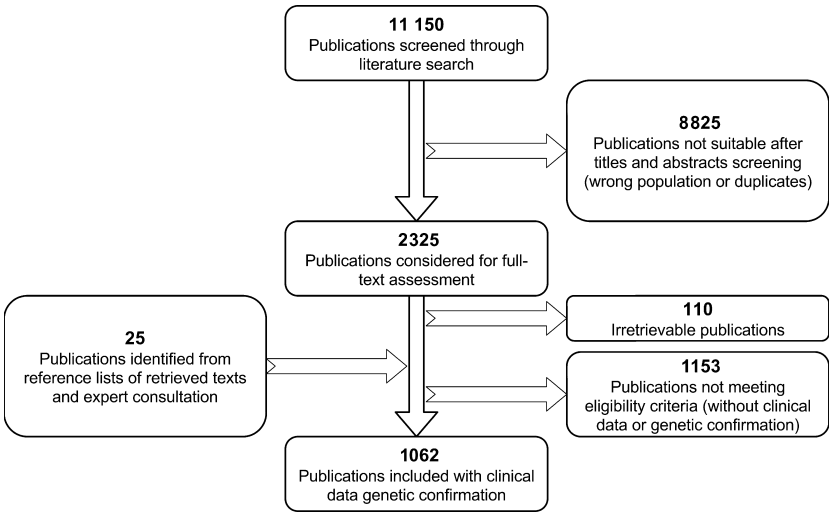

Figure 1 Flow diagram of the study selection process.

Table 1 Genetic subtypes with significantly higher or lower rates of corresponding clinical features at onset

Clinical feature at onset	*n*[a]	Genetic subtypes with significantly higher proportion of the corresponding clinical feature than other subtypes [b]	Genetic subtypes with significantly lower proportion of the corresponding clinical feature than other subtypes [b]
Gait or truncal ataxia	2634 (68%)	SCA1; SCA2; SCA6; SCA14; SCA28; SCA31; SCA36	SCA7; SCA11; SCA12; SCA17; SCA27; DRPLA
Dysarthria	528 (14%)	SCA6; SCA10; SCA20; SCA35	SCA1; SCA2; SCA3; SCA7
Ataxia (NOS)	498 (16%)	SCA2; SCA4; SCA21; SCA25; SCA26; SCA30	
Diplopia	315 (7%)	SCA6	SCA7; SCA3
Dizziness	268 (8%)	SCA6	SCA1; SCA2; SCA3; SCA7
Limb ataxia	151 (4%)	SCA6; SCA23; SCA28; SCA36	SCA2; SCA3
Intention or postural tremor	150 (4%)	SCA8; SCA12; SCA27; SCA15–16	SCA2; SCA3; SCA6
Visual impairment	146 (7%)	SCA7	SCA1; SCA2; SCA6
Parkinsonism[c]	101 (4%)	SCA17	SCA6
Seizures	68 (5%)		
Cognitive impairment	53 (2%)	SCA17; DRPLA	SCA2; SCA3
Psychiatric alterations	45 (1%)	SCA17; DRPLA	
Delayed development	42 (2%)	SCA13; SCA29; DRPLA	
Dystonia	35 (1%)		
Vomiting	34 (6%)		
Cramps	25 (2%)	SCA2; SCA3	
Pain	21 (1%)		
Chorea-dyskinesia	19 (6%)		
Spastic paraparesis	17 (1%)		
Head titubation	13 (1%)		
Myoclonus	13 (1%)	SCA14	SCA2
Sensation alterations	10 (1%)		
Dysphagia	8 (0.1%)		
Nystagmus	8 (1%)	SCA5	SCA6
Weakness	8 (0.01%)		
Autonomic dysfunction[d]	6 (0.01%)		
Ophthalmoparesis	4 (0.1%)		
Hearing loss – tinnitus	4 (0.1%)		
Headache	4 (1%)		
Sleep disorders[e]	4 (0.1%)		
Spasticity	2 (0.01%)		
Fasciculations	2 (0.01%)		
Fatigue	2 (1%)		
Akathisia	1 (0.01%)		
Restless legs	1 (0.01%)		
Microcephaly	1 (5%)		

DRPLA, dentatorubro-pallidoluysian atrophy; NOS, not otherwise specified. [a]Total *n* reported was different for all clinical features; [b]all with $P < 0.001$; [c]parkinsonism includes bradykinesia, rigidity or rest tremor; [d]autonomic dysfunction includes orthostatic hypotension, sexual or urinary dysfunction; [e]sleep disorders include daytime sleepiness, insomnia and rapid eye movement behavior.

SCA17 with parkinsonism (12%), psychiatric alterations (19%) and cognitive impairment (13%); SCA13 and DRPLA with developmental delay (61% and 7%, respectively); and the latter also with psychiatric alterations (4%) and cognitive impairment (15%); all presented *P* values <0.001.

Clinical characteristics of overall disease course

The total number of different clinical characteristics ascertained was 121, with insufficient power for prevalence comparison detected in 59. Statistically significant clinical features present above or below the general rate for different genetic subtypes are listed only in table form for simplification and clarity (Tables S1 and 2). The latter were not compared further but some are nevertheless described in Table S2.

Discussion

In this systematic review rates for a large number of clinical features covering several genetic SCA subtypes are reported, identifying certain specific differences between them. Although two earlier systematic reviews on SCA have been published, these focused only on SCA7 and DRPLA [13,14].

Table 2 Genetic subtypes with significantly higher or lower proportion of the corresponding clinical feature than other subtypes during overall disease course

	Genetic subtypes with significantly higher proportion of the corresponding clinical feature than other subtypes	Genetic subtypes with significantly lower proportion of the corresponding clinical feature than other subtypes
Gait or truncal ataxia		SCA12; SCA27
Limb ataxia	SCA2	SCA13; SCA29
Dysarthria	SCA2	SCA3; SCA4; SCA14; SCA18; DRPLA
Intention or postural tremor	SCA2; SCA12	SCA3; SCA6
Hypotonia	SCA2; SCA31	SCA6
Dizziness		SCA36
Ophthalmoparesis	SCA2; SCA3	SCA5; SCA6; SCA13; SCA36; DRPLA; **SCA10**; **SCA31**; **SCA35**
Saccadic eye movement alterations	SCA2; SCA6	SCA1; SCA3; SCA5; SCA11; SCA28
Nystagmus	SCA3; SCA6; SCA10; SCA15–16	SCA1; SCA2
Diplopia	SCA1; SCA2; SCA3; SCA6; SCA31	SCA36; **SCA10**
Pseudoexophthalmos	SCA1; SCA2; SCA3	SCA6; SCA7; SCA10; **SCA31**
Eyelid ptosis	SCA7; SCA28	SCA6
Visual impairment	SCA7	SCA2; SCA3; **SCA10**; **SCA20**; **SCA15–16**
Retinal degeneration	SCA7	SCA1; SCA2; SCA3
Hearing loss	SCA36	
Dysphagia – bulbar signs		
Pyramidal signs[a]	SCA1; SCA3; SCA7; SCA17; SCA31; DRPLA; SCA28 (only for hyperreflexia)	SCA2; SCA6; SCA10; SCA28 (only for spasticity); SCA 29; SCA31
Parkinsonism[b]	SCA2; SCA17; SCA21	SCA1; SCA6; SCA7; **SCA10**
Chorea-dyskinesias	SCA17; SCA27; DRPLA	SCA1; SCA2; SCA3
Myoclonus	DRPLA	SCA1; SCA6
Dystonia	SCA3; SCA17; DRPLA	SCA1; SCA2; SCA6
Myokymia	SCA2	
Head titubation	SCA2	
Cognitive impairment	SCA8; SCA13; SCA17; SCA2; DRPLA	SCA3; SCA6; SCA7; SCA31; **SCA18**
Psychiatric alterations	SCA2; SCA17; DRPLA	
Delayed development	SCA29; DRPLA	SCA2
Neuromuscular disorder [c]	SCA1 (only for sensation alterations); SCA2; SCA3 (only for cramps); SCA21 (only for hypo-areflexia); SCA36, **SCA4**, **SCA18 and SCA25** (only for hypo-areflexia and deep sensation alterations)	SCA1 (only for hypo-areflexia); SCA8; SCA3 (only for hypo-areflexia); SCA6; SCA7 (only for sensation alterations); SCA10; SCA15–16; SCA31; **SCA20** (only for deep sensation alterations)
Seizures	DRPLA	
Autonomic dysfunction[d]	SCA2; SCA3 (only for urinary dysfunction); SCA17 (only for urinary dysfunction)	SCA3 (only for orthostatic hypotension); SCA6; SCA36 (only for urinary dysfunction); **SCA7**; **SCA15–16**

[a]Pyramidal signs include hyperreflexia, extensor plantar response or spasticity; [b]parkinsonism includes bradykinesia, rigidity or rest tremor; [c]neuromuscular disorder includes hypo-areflexia, superficial or deep sensation alterations, weakness, cramps, limb or tongue fasciculations, or atrophy; [d]autonomic dysfunction includes orthostatic hypotension or urinary dysfunction. DRPLA, dentatorubro-pallidoluysian atrophy. The items in bold are SCAs with clinical features with 100% (first column) or 0% (second column) frequency.

Before further discussion, it should be pointed out that the main strengths of this systematic review are that the search is not restricted to a single database or to publications published in English only and that a large population was ascertained, with varied origins from a wide range of publications, thus increasing power for between-group difference detection. Consideration of $P < 0.01$ values as statistically significant and extraction of data only from genetically confirmed patients, excluding relatives with possibly the same but unproven disorder, further strengthen our findings. Furthermore, strict statistical methods were followed to avoid alpha-error inflation and insufficient power, thus allowing for valid prevalence estimates and statistical inferences. Indeed, great effort was put into maintaining experiment-wise alpha error at the 0.05 level by controlling alpha-error inflation and reducing the critical P level to 0.01 in global comparisons. Similarly, power calculations were used to detect and exclude clinical features

for which between-comparisons were not possible due to insufficient sample size.

The study also has limitations to acknowledge. First, it was not possible to retrieve almost 4% of full-text publications, mostly because they were published in the 1970s or 1980s and therefore not available electronically. Considering that 45% of retrieved publications contained clinical data, the proportion of publications with probable clinical descriptions of genetically confirmed patients that were missed is reduced to less than 1%, and corresponded only to the most frequent SCA subtypes. Second, various non-ataxia symptoms reported in the original publications lack clear definitions and standardization; some publications might have used different diagnostic tools to evaluate certain clinical signs, such as cognitive impairment, or described only commonly examined or noticeable clinical features without thorough screening for others, like psychiatric symptoms. Nevertheless, most other clinical characteristics would be so obvious that under-reporting bias in these cases would seem unlikely. Moreover, absence of clinical manifestations was recorded only when explicitly mentioned as absent, to gain in accuracy. However, this may have generated inadequate reporting of infrequent symptoms or features not evidenced at a clinical level. Also, some non-statistically significant features of several SCA subtypes could be attributable to this drawback. Finally, publications reporting demographics only, without clinical descriptions, were excluded, and consequently demographic data were not represented exactly. In addition, the mean age at disease onset and the mean age at time of death are imprecise because these calculations are flawed by selection bias.

Gait ataxia was the most common symptom at onset and other non-ataxia features accounting for 50% of the total cases were highly frequent, as previously described [15]. In particular, dysarthria, diplopia, dizziness, intention or postural tremor, limb ataxia or impaired hand skills, visual impairment and parkinsonism are clinical features that should be investigated during examination of patients with suspected ADCA. Sometimes, clinical features at onset can offer a clue on the underlying genotype, such as visual impairment (SCA7), myoclonus (SCA14), parkinsonism (SCA17), developmental delay (SCA13 and DRPLA), and psychiatric alterations or cognitive impairment (SCA17 and DRPLA). On other occasions, clinical features such as limb ataxia or impaired hand skills and intention or postural tremor were not as common at onset as gait ataxia but became more frequent during disease course. The mean age at onset was not useful to distinguish between the different SCAs, although some genetic subtypes such as SCA5, SCA7, SCA13, SCA18, SCA19–22, SCA21, SCA25, SCA27 and SCA28 may be observed in patients whose age at onset was before their 30s, or others such as SCA6, SCA11, SCA20, SCA23, SCA31, SCA35 and SCA36 started usually at the fifth or sixth decade.

SCAs without statistically significant non-cerebellar features, in which the phenotype during overall disease course was restricted to cerebellar dysfunction, were SCA5, SCA6, SCA10, SCA11, SCA12, SCA14, SCA19–22, SCA20, SCA23, SCA26, SCA30 and SCA31. Some of these subtypes were described in isolated patients, so caution must be taken before considering them 'pure' forms. SCA10 and SCA17, usually mentioned as associated with seizures, did not show a statistically significant rate of seizures, possibly because, as in the case of SCA10, seizures were rare in one large study [16]. Higher frequency in altered saccadic eye movements, nystagmus, intention or postural tremor and hypotonia distinguished SCA6, SCA10, SCA12 and SCA31, respectively, from other 'pure' subtypes. The remaining SCA subtypes combined cerebellar syndrome with other neurological features ('mixed' forms). Most could be distinguished from one another by the higher or lower frequency of several clinical features (Tables S1 and 2; Fig. 2). Some discrepancies between clinical experience and published papers have been found. In clinical practice diplopia is common at early stages in SCA3; however, the literature showed a high frequency of diplopia during overall disease course, but not at onset. Likewise, amyotrophy is a frequent sign in the late phases of SCA1 but was not statistically different from other SCA subtypes during overall disease course.

The findings in the present study support associations between certain clinical features and different SCA subtypes classically described in previous unstructured reviews [1–3,5,7,8,17,18] with the added value of relying on a structured search and quantitative data analysis.

Marras *et al.* [9] clearly expressed the concern of community clinicians at large over difficulties encountered when using the current state of classification of neurodegenerative disorders, in which genetics play an important role as causal or predisposing factors. The same list of locus symbols is used by both clinicians and researchers, who have different needs. The authors recommended that the list shows clinicians known clinical spectra of genetically determined disorders associated with particular phenotypes, to guide clinical evaluation and diagnostic testing [9]. In an attempt to better organize SCA subtypes according to our systematic analysis results, SCA subtypes were

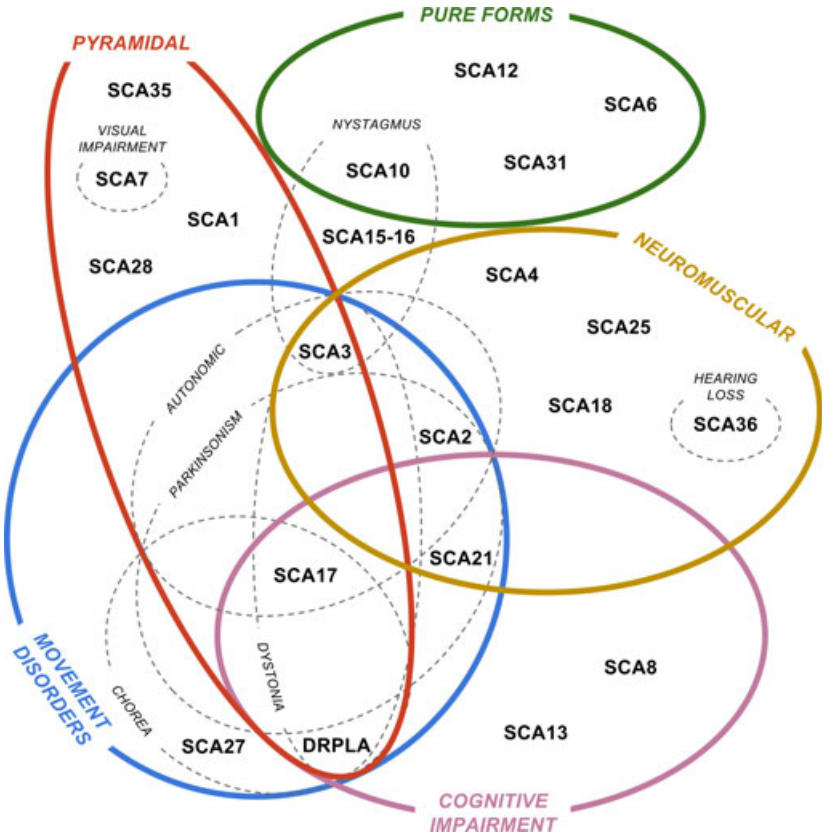

Figure 2 Organization of SCAs according to main clinical features. The SCAs without clinical features reaching statistical significance are not shown.

divided into two main groups based on Harding's classification of ADCAs [6], depending on clinical features at disease onset: 'pure ataxia forms' in which the phenotype corresponds almost exclusively to ataxia and 'non-ataxia forms' in which other clinical features than ataxia are predominant at disease onset (Table 3).

Both groups proposed may differ not only with respect to the presence or absence of non-ataxia features. Faster disease progression in the most frequent 'mixed forms' such as SCA1, SCA2 and SCA3 has been reported in a prospective multicenter study, compared with SCA6, the most prevalent 'pure form' [19]. Although a clinical–genetic classification is useful to summarize diverse clinical features linked to different genetic subtypes, it should not be used to categorize single patients, given the high level of phenotype–genotype overlap and occasional unusual clinical presentations. It has been proposed that this might be overcome with proposed predictive algorithms, in which the definition of pure or mixed form is followed by the presence or absence of movement disorders, cognitive dysfunction and neuromuscular symptoms [7,20]. In addition, the use of the proposed clinical algorithm at disease onset might help orient selection of which commercially available genetic tests for SCAs to use in patients with suspected ADCA. However, clinical diagnosis of genetic subtypes even with algorithms might still be difficult in clinical practice.

In conclusion, ADCAs remain a clinically heterogeneous group of neurodegenerative disorders. Descriptions of main clinical features and their frequency of presentation, as well as distinction between genetic subtypes, will be useful for neurologists trying to predict SCA subtypes in patients with suspected ADCA. Larger prospective studies systematically evaluating a full list of non-ataxia features are required to improve current SCA subtype distinctions and their classification into the two ADCA groups as proposed. Classification into these two main groups may help better classify future novel SCA subtypes, which will surely continue to be identified, by linking phenotype to genotype.

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Table 3 Proposed clinical algorithm for ADCA classification at disease onset

ADCA groups	Other clinical features	SCA- HGNC symbol
A 'Pure' ataxia	No	SCA1-ATXN1 SCA4- PLEKHG4 SCA11- TTBK2 SCA18 SCA19–22 SCA20 SCA21 SCA23 SCA25 SCA26 SCA28-AFG3L2 SCA30 SCA31 SCA36- NOP56
B Mainly non-ataxia	Intention or postural tremor	SCA8-ATXN8OS SCA12-PPP2R2B SCA15-16-ITPR1 SCA27-FGF14
	Dysarthria	SCA10-ATXN10 SCA20 SCA35-TGM6
	Dysarthria diplopia Dizziness	SCA6-CACNA1A
	Nystagmus	SCA5-SPTBN2
	Cramps	SCA2-ATXN2[a]SCA3-ATXN3
	Myoclonus	SCA14-PRKCG[a]
	Visual impairment	SCA7-ATXN7
	Parkinsonism Cognitive impairment Psychiatric alterations	SCA17-TBP
	Cognitive impairment Psychiatric alterations Delayed development	DRPLA-ATN1
	Delayed development	SCA13-KCNC3 SCA29

HGNC, Human Gene Nomenclature Committee; DRPLA, dentatorubro-pallidoluysian atrophy. [a]Also ataxia at onset.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. MEDLINE (PubMed) search strategy.
Table S1. Clinical features with significantly higher or lower average rates for different genetic subtypes during overall disease course.
Table S2. Demographic and clinical feature rates of SCA subtypes.
Figure S1. Geographical distribution of publications with clinical data.
Figure S2. Age-related SCA subtype demographic features (years ± SEM). It was not possible to calculate some data of SCA4, SCA26, SCA27 and SCA30.

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