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Movement Disorders in Autosomal Dominant Hereditary Ataxias: A Literature Review

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Movement Disorders in Autosomal Dominant Hereditary Ataxias: A Literature Review

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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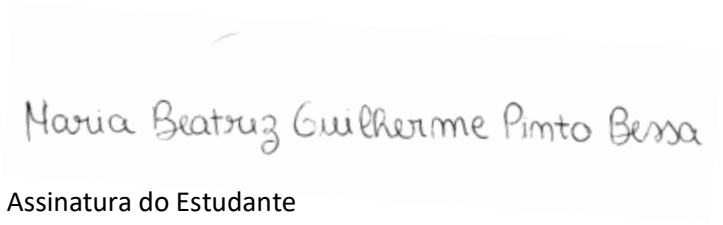

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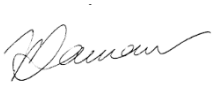

Assinatura do Orientador

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DEDICATÓRIA

Aos meu Pais e aos meus Irmãos, pelo vosso constante incentivo, apoio incondicional e infinita paciência. Todas as conversas e momentos partilhados convosco foram e serão sempre uma enorme parte de mim, disso estou certa.

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RESUMO

Introdução: As ataxias hereditárias autossómicas dominantes (ADHAs) são um grupo heterogéneo de doenças neurodegenerativas geneticamente classificadas como ataxias espinocerebelosas (SCAs) seguidas por um número. Caracterizam-se por uma síndrome cerebelosa associada ou não a sintomas não-cerebelosos. As doenças do movimento encontram-se descritas em algumas SCAs, podendo constituir a forma de apresentação, sintoma dominante ou mesmo sintoma único da doença.

Objetivos: Realização de uma revisão sistemática da frequência das doenças do movimento nas SCAs e caracterização dos seus subtipos.

Métodos: Foi efetuada uma pesquisa estruturada na PubMed®, até outubro de 2019, de artigos sobre doenças do movimento nas SCAs. Foram selecionados artigos em Inglês ou Português com base na relevância do título e resumo, seguido da sua leitura integral. Registaram-se dados relativos ao subtipo da SCA, tipo e frequência das doenças do movimento, assim como dados demográficos e clínicos.

Resultados: Foram identificados 1794 artigos na pesquisa inicial, dos quais 1664 foram excluídos. Foram incluídos 23 artigos obtidos através de listas de referências, sendo considerados 153 para análise final. Na SCA1, as doenças do movimento mais frequentes foram distonia e tremor postural; na SCA2 o tremor postural, distonia e Parkinsonismo; na Doença de Machado-Joseph (MJD) a distonia e Parkinsonismo; na SCA14 a distonia e mioclonias; na SCA17 a distonia, Parkinsonismo e coreia/coreoatetose; na DRPLA a coreia/coreoatetose e mioclonias.

Conclusão: As doenças do movimento são manifestações comuns de várias SCAs. A sua presença pode associar-se à neurodegeneração generalizada em certas SCAs, particularmente de estruturas extra-cerebelosas como os gânglios da base. Contudo, as doenças do movimento também podem ocorrer em SCAs sem degeneração extra-cerebelosa evidente, o que poderá realçar o papel do cerebelo na patogenia destas doenças.

Palavras-Chave: Ataxias espinocerebelosas; Ataxia cerebelosa; Ataxia autossómica dominante; Doenças do movimento.

ABSTRACT

Background: Autosomal dominant hereditary ataxias (ADHAs) are a heterogeneous group of neurodegenerative disorders classified genetically as spinocerebellar ataxias (SCAs) followed by a number. SCAs are mainly characterized by cerebellar ataxia, with non-cerebellar symptoms being also present. Movement disorders have been reported in some patients, as the presenting, dominant, or even isolated feature of the disease.

Aims: To perform a systematic review of the frequency of movement disorders in SCAs, and further characterize its subtypes.

Methods: A structured PubMed® search of articles on movement disorders in SCAs, up to October of 2019, was performed. Publications written in English or Portuguese were selected based on title and abstract relevance, followed by a full-text reading. Data concerning SCA subtype, type and frequency of movement disorders were extracted, along with demographics and clinical features.

Results: The initial search yielded 1794 papers, of which 1664 were excluded. Twenty-three additional articles obtained from reference lists were included, with 153 being considered for final analysis. In SCA1, the most frequent movement disorders were dystonia and postural tremor; in SCA2 postural tremor, dystonia and Parkinsonism; in MJD dystonia and Parkinsonism; in SCA14 dystonia and myoclonus; in SCA17 dystonia, Parkinsonism, and chorea/choreoathetosis; in DRPLA chorea/choreoathetosis and myoclonus.

Conclusion: Movement disorders are common features of many SCAs. Its presence can associate with widespread neurodegeneration in certain SCAs, particularly of extracerebellar structures such as the basal ganglia. Nevertheless, movement disorders may also occur in SCAs without evidence of extracerebellar degeneration, which could emphasize the role of the cerebellum in the pathogeny of movement disorders.

Keywords: Spinocerebellar ataxias; Cerebellar ataxias; Autosomal dominant ataxias; Movement disorders.

LIST OF ABBREVIATIONS

ADHA – Autosomal Dominant Hereditary Ataxia

ATXN1 – *Ataxin-1* gene

ATXN2 – *Ataxin-2* gene

ATXN3 – *Ataxin-3* gene

CACNA1A - *Calcium voltage-gated channel subunit alpha1 A* gene

CT – Computerized tomography

DAT – Dopamine transporter

DBS – Deep brain stimulation

DRPLA – Dentatorubral-pallidoluysian atrophy

DRT – Dopamine replacement therapy

ET – Essential tremor

GPi – Globus pallidus internus

HD – Huntington's disease

MJD – Machado-Joseph disease

MRI – Magnetic resonance imaging

NII – Neuronal intranuclear inclusions

PD – Parkinson's disease

PET - Positron emission tomography

POE – Progressive external ophthalmoplegia

PRKCG - *Protein kinase C gamma* gene

SARA - Scale for assessment and rating of ataxia

SCA – Spinocerebellar ataxia

SPECT - Single-photon emission computed tomography

TBP - *TATA-box binding protein* gene

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Introduction

Autosomal dominant hereditary ataxias (ADHAs) are a genotypically and phenotypically diverse group of neurodegenerative disorders that mainly affect the cerebellum and its afferent and efferent pathways.[1]

Molecular diagnosis has established more than 40 different subtypes of ADHAs, a number that is currently expanding.[2] ADHAs are classified as spinocerebellar ataxias (SCAs), followed by a number, which is assigned according to the order of detection of the genetic locus involved.[2]

SCAs are typically adult-onset, slowly progressive disorders.[1-3] Notwithstanding, age of onset and progression rate were found to have a high variability amongst different SCAs and even within the same type of SCA.[1-3] SCA2, SCA7, SCA17, and dentatorubral-pallidoluysian atrophy (DRPLA) may present a childhood-onset and rapidly progressively phenotype, due to its marked anticipation phenomenon.[4,5]

The relative frequency of different SCAs has also been found to vary amongst geographic locations. Machado-Joseph Disease (MJD) is the most common SCA worldwide, followed by SCA1, SCA2, SCA6, and SCA7.[2] In Portugal, the population-based survey established MJD as the most frequent SCA, with an overall prevalence of 3,1 per 100.000 population, followed by DRPLA and ataxia due to point mutations in *Calcium voltage-gated channel subunit alpha1 A* (*CACNA1A*) gene.[6]

The relationship between the Portuguese genetic background and MJD is of unavoidable reference. The official history of MJD started with the first description of the Machado family in 1972.[7] In the same year, the Thomas family was described,[8] and four years later the Joseph family was reported.[9] To note, all three families were originally from the Azores and emigrated to the United States of America.[7-9] In the following years, other families were described in the Azores, mainland Portugal, and several different countries, some with connections to the Portuguese expeditions.[10,11]

Although ataxia is usually the most prominent feature, non-cerebellar features may also be present in these patients.[2] Oculomotor dysfunction, peripheral neuropathy, cognitive impairment, deafness, epilepsy, sleep disturbances, and movement disorders, amongst others, have been reported.[1-4] In fact, movement disorders are frequently associated with various SCAs, being described as the presenting, dominant, or even isolated feature of the disease.[12,14] The presence of movement disorders in SCA patients may provide important clues to the underlying genotype, pathology and might even be associated with different disease progression rates.[2,12-14]

Objectives

This study aims to analyse the frequency and type of movement disorders in SCAs and to explore movement disorders' features and eventual association with SCA subtypes.

Methods

A structured MEDLINE (PubMed®) search was performed up to October 2019. Search terms employed included "Spinocerebellar ataxia", OR "Dominant cerebellar ataxia" AND "Movement disorders", OR "Extrapyramidal signs", OR "Dystonia", OR "Parkinsonism", OR "Chorea", OR "Myoclonus", OR "Tremor", OR "Tics". Time restrictions were not applied, in order to guarantee maximal coverage. Original articles, case reports, short communications, letters, congress abstracts, reviews, and all other publications written in English or Portuguese were extracted.

Inclusion criteria were defined as studies on movement disorders in SCAs and studies on SCAs containing clinical descriptions of movement disorders. Exclusion criteria comprised publications describing episodic SCAs; SCAs with less than ten papers describing movement disorders; cases in which SCAs were present along with another neurological disorder, resulting in possible overlap of clinical features; and studies on cell/animal models.

Publications were initially selected based on title and abstract relevance, followed by a full-text reading.

A standardized data sheet was created to collect information on SCA subtype, type and frequency of movement disorders, age of onset of ataxia and movement disorders, and individual patient data, such as movement disorder's characteristics, imaging studies, neuropathological studies and treatments (*Figure 1*).

Back-searching from retrieved publications reference lists was performed, allowing to scan for relevant publications missed in the initial search. Relevant books and thesis chapters were also considered.

Results

The initial search yielded a total of 1794 publications. After a thorough title and abstract screening, 1664 were excluded:

- 919 reported on other neurologic disorders or recessive ataxias (as Huntington's disease, ataxia-telangiectasia, Friedreich's ataxia, Parkinson's disease, amongst others);
- 519 did not concern movement disorders;
- 77 were studies on cell or animal models;
- 72 were not in English or Portuguese;
- 37 were on SCAs with less than ten studies concerning movement disorders (nine papers referred to SCA6, eight to SCA7 and SCA8 each, seven to SCA12, six to SCA10, three to SCA5, SCA15, and SCA27 each, two to SCA16, SCA21, SCA19/22, and SCA36 each, and one to SCA18, SCA35, SCA37, SCA42, and SCA48 – some of these papers addressed movement disorders on more than one SCA subtype);
- 29 were unobtainable for full-text reading;
- six described episodic SCAs;
- five consisted of case reports of patients with SCA and other neurological disorder simultaneously.

Therefore, 130 articles were examined, and 23 additional studies were identified through reference lists. In total, 153 publications were analysed: 51 referred to MJD, 50 to SCA2, 26 were on SCA1, 24 on SCA17, sixteen on SCA14, and fifteen on DRPLA. Some articles reported on more than one SCA (*Figure 2*).

SCA1

SCA1 is caused by an abnormal expansion of the CAG-trinucleotide repeat in the *Ataxin-1* gene (*ATXN1*), located on chromosome 6p22.[1,15,16] Normal alleles bear less than 35 CAG-repeats and are interrupted by one to three CAT trinucleotides.[1,16] In alleles carrying 36 to 44 trinucleotide-repeats, pathogenicity seems to depend on whether CAT repeat interruption is

present.[16,17] Typically, expansions with over 39 repeats without interruptions are considered to have full penetrance.[16-18]

Age of onset is usually during the fourth decade of life,[12,13,18] with some authors describing onset in adolescence.[18] From one generation to the next, affected individuals usually have an earlier onset and more severe phenotype, in a phenomenon called genetic anticipation.[18,19] This is often a result of progressively longer trinucleotide expansions, as it happens in many other polyglutaminopathies and is particularly relevant in cases of paternal transmission.[14,19,20]

Clinical features comprise cerebellar ataxia, oculomotor abnormalities, such as hypermetric saccades and nystagmus, and brisk deep tendon reflexes.[16,18] Executive dysfunction, dysphagia, movement disorders and polyneuropathy, may also be present in later stages.[1,16,18] Disease progression seems to be severe in SCA1 when compared to SCA2 or MJD.[21] On brain MRI there is usually cerebellum and brainstem atrophy, particularly affecting the pons. Olivopontocerebellar and white matter atrophy has also been described.[22,23] Neuropathological studies reveal severe depletion of Purkinje cells, degeneration of the dentate nucleus, inferior olives, pontine nuclei of the IX, X, and XII cranial nerves, spinocerebellar tracts, and posterior columns.[16] Besides neuronal loss, neuronal intranuclear inclusions (NII) of mutated ataxin-1 were also found, mostly in severely affected areas such as the pons but also the cortex and striatum.[24]

In neuropathology and neuroimaging studies, the involvement of the extrapyramidal system seems to be variable. Generally, basal ganglia degeneration is not described.[22] Still, Kish et al. reported seven out of eleven SCA1 patients exhibiting marked reduction of putaminal dopamine levels due to nerve terminal degeneration with only mild nigrostriatal neuron loss.[25]

Movement disorders in SCA1

Fifteen papers described movement disorders in SCA1 patients: eleven identified dystonia, six chorea/choreoathetosis, four postural/action tremor, two Parkinsonism, and two myoclonus. Tics were not reported in any article.

From the fifteen publications, 437 patients were described: dystonia was reported in 37, postural/action tremor in 30, chorea/choreoathetosis in fourteen, bradykinesia in five, rigidity in two, resting tremor in eight, and myoclonus in six (*Table I*).

Dystonia

In the largest available cohort of 117 SCA1 European patients, Schmitz-Hubsch et al. reported dystonia in 12,8%.[21]

It was described as either focal, segmental, or generalized. Focal forms were more common: two patients had dystonic posturing of the extremities,[26,27] one of which was task-induced hand dystonia (writer's cramp),[27] and one had blepharospasm.[18] Wu et al. presented a case of segmental dystonia, comprising blepharospasm, oromandibular, and cervical dystonia,[28] and generalized dystonia was described twice.[29,30]

Dystonia was always present in association with cerebellar syndrome, usually months to years after disease onset. [26,27,29,30] It has not been reported as an isolated feature of SCA1. It was described as the presenting symptom in one patient: Wu et al. reported a 39-year-old man, with 49 CAG-repeats, presenting blepharospasm, oromandibular dystonia, and retrocollis at onset and later developing ataxia.[28] The authors suggested the presence of dystonia could result from a more selective involvement of the basal ganglia.[28]

Kuo et al. described the *TATA-Box Binding Protein* gene (*TBP*) as a possible genetic modifier of SCA1, as the authors found patients with longer repeats in the *TBP* gene had a lower frequency of dystonia.[31]

Treatment was described in two patients: one had mild retrocollis improvement with baclofen, trihexyphenidyl, and botulinum toxin (had been previously treated with clonazepam, without any improvement).[28] The other had temporary benefit with botulinum toxin, eventually becoming non-responsive as the disease progressed.[30] This patient was then submitted to deep brain stimulation (DBS) of the globus pallidus internus (GPi) with almost complete resolution of dystonic movements, having only residual cervical dystonia which responded well to botulinum toxin.[30]

Postural/action tremor

Postural/action tremor was more difficult to analyse since it was inconsistently addressed either as part of the cerebellar syndrome or as a specific and independent movement disorder.

Nevertheless, Lai et al. reported a frequency analysis of postural tremor in SCA1, identifying it in 5,6% of 54 patients.[32] In contrast, Dragasević et al. identified postural tremor frequency to be of 60,6%, in 33 Serbian patients.[33] Most retrieved studies did not explore its characteristics. Yet, Gan et al. found that SCA1 patients with postural tremor had slower rates of ataxia progression.[34]

Chorea/choreoathetosis

Schmitz-Hubsch et al. studied chorea and dyskinesia together and identified a frequency of 6,8% amongst 117 patients.[21] The second-largest cohort considering chorea was reported by Dragasević et al., reporting a frequency of 3% in 33 patients.[33] Chorea was carefully analysed in a single case, being present at an advanced stage of disease: Namekawa et al. provided a report of a 38-year-old patient at onset, with a 50 CAG expansion, who presented slowly progressive cerebellar syndrome with choreoathetoid movements of upper and lower limbs emerging ten years after disease onset, alongside dystonic posturing of the toes.[25]

Parkinsonism

Parkinsonism was not common in SCA1 patients, and both retrieved papers reported on Parkinsonian features individually. Schmitz-Hubsch et al. identified resting tremor in 6,8% of 117 patients and rigidity in 1,7%,[21] while Jhunjhunwala K et al. described bradykinesia in 12,5% in a series of 40 SCA1 patients.[35]

Myoclonus

Myoclonus had a frequency of 4,3% in 117 patients from the Schmitz-Hubsch et al. series,[21] and 8% in twelve patients from Schols et al.[12] There were no further characterizations of myoclonus in SCA1.

SCA2

SCA2 is caused by an abnormal CAG-repeat expansion in the *Ataxin-2* gene (*ATXN2*), located on chromosome 12q24.[36,37] Normal alleles carry fourteen to 31 CAG-repeats and are interrupted by one to three CAA-repeats, which appear to provide stability to the CAG expansion.[38] The pathological forms harbour over 34 CAG-repeats and are not always interrupted by CAA-repeats.[38]

Typically, SCA2 presents as an adult-onset progressive ataxia, during the fourth decade of life.[36,38-40] Nonetheless, age of onset is widely variable and childhood-onset forms have been described in patients with marked anticipation phenomenon, usually in paternal transmission.[37,39,41] As in other polyglutamine disorders, repeat expansion size correlates inversely with age of onset.[14,38,39,41]

Clinically, SCA2 comprises dysarthria, oculomotor dysfunction, with early slow saccades and nystagmus, dysphagia, peripheral neuropathy, and could also encompass cognitive impairment, amyotrophy, and movement disorders.[38-40]

Imaging studies reveal cerebellum, brainstem, and olivopontocerebellar atrophy.[42]

On neuropathological examination, there is atrophy of the cerebellum, brainstem, frontal lobes, and cranial nerves, as well as widely diffuse neuronal loss, which especially affects the substantia nigra pars compacta, the ventral anterior and ventral lateral thalamic nuclei, internal and external pallidum, pedunculopontine nucleus and the subthalamic nucleus.[20,40] Cytoplasmatic deposits and widespread NII, especially in the pontine nuclei, were also found.[43]

Movement disorders in SCA2

Forty-four papers described movement disorders in SCA2 patients: 25 reported Parkinsonism, 24 dystonia, fifteen postural/action tremor, eight chorea/choreoathetosis, and seven myoclonus. None of the articles described tics.

From the 44 articles, there were a total of 967 patients: postural/action tremor was reported in 131 patients, dystonia in 115, Parkinsonism in 108 (resting tremor *per* se was described in another 28 patients, rigidity in sixteen, and bradykinesia in six patients), myoclonus in 37, and chorea/choreoathetosis in 32 (*Table II*).

Postural/action tremor

Postural tremor seems to be more frequent in SCA2 than in SCA1 or MJD.[12,14,32,34,41] Cancel et al. presented the largest cohort with frequency analysis on postural tremor, describing it in 21% of 111 patients,[38] whereas Gan et al. found it in 27,5% amongst 69 SCA2 patients.[34]

There were not many descriptions of the clinical features of postural tremor, however, Freund et al. reported a case of a rapidly progressive debilitating postural tremor of the head, trunk, and upper limbs.[44] DBS of the thalamus and subthalamus presented remarkable benefit for this patient.[44] Postural tremor seemed to associate with higher Scale for Assessment and Rating of Ataxia (SARA) scores and faster rates of ataxia progression.[32,34]

Dystonia

Schmitz-Hubsch et al. presented the largest cohort of SCA2 patients and described a frequency of 14,2% of dystonia amongst 163 European SCA2 patients.[21] Cancel et al. observed it in 9% of 111 patients.[38]

Focal dystonia was described in 27 patients. It presented as cervical dystonia in seventeen patients,[33,44-49] hand dystonia in five,[33,37,50] oromandibular in two,[51,52] foot dystonia in also in two,[53,54], and truncal dystonia in one.[55] There were no descriptions of segmental or generalized forms.

Dystonia has not been described as an isolated feature of SCA2, being usually present in patients with cerebellar syndrome, manifesting years after disease onset.[45,47] It was also described in SCA2 patients having Parkinsonism as the most prominent feature.[53,54] Notwithstanding, there are reports of dystonia as the presenting symptom: cervical dystonia was described in three cases,[45,48,49] oromandibular dystonia in one,[52] and writer's cramp in one as well.[50] In the case report of oromandibular dystonia at onset, the patient was 58 years old, had 40 CAG-repeats, and developed Parkinsonism in two months.[52]

Several authors found a relation between the presence of dystonia and an earlier onset, larger expansions, and a higher SARA score.[38,45] In contrast, Kuo et al. did not identify an association between dystonia and larger expansions but found a correlation with higher SARA scores.[31]

Treatment options for dystonia were described in fourteen patients: dopamine replacement therapy (DRT) was used in four cases,[47,50,52,55] exhibiting benefits only in one patient with cervical dystonia.[47] Anticholinergics (trihexyphenidyl) were used in four cases,[47,50,52,55] showcasing positive results in one.[47] Baclofen was also reported in one patient and was not effective.[52] Benzodiazepines (clonazepam and diazepam) were used in two cases, without benefit.[52,55] Botulinum toxin was reported in one patient with writer's cramp with no benefit.[50] DBS was not a common practice amongst dystonic SCA2 patients and has had controversial results. Cheng et al. reported one case of DBS of the GPi with promising results and significant improvement of writer's cramp without worsening of cerebellar symptoms,[50] while Beaulieu-Boire et al. described one patient in which benefits were modest and the overall disability worsened.[56]

Parkinsonism

Schmitz-Hubsch et al. reported Parkinsonian features individually and identified rigidity in 7,4% and resting tremor in 14,9% of 163 European patients,[21] whereas Stezin et al. described Parkinsonism in 10,9% of 73 Indian patients.[57]

Parkinsonism clinical spectrum was wide, ranging from mild Parkinsonian signs alongside marked cerebellar syndrome to a levodopa-responsive, almost classic Parkinson's Disease (PD)-like phenotype without any cerebellar signs. Parkinsonism with predominant cerebellar syndrome was reported in seventeen patients,[35,41,54,58] Parkinsonism as the most prominent feature in association with mild cerebellar signs was found in ten,[36,46,54,59-62] and PD-like phenotype was identified in 65.[36,37,49,52-54,59-61,63-68]

Different studies have discussed the association of Parkinsonism, age of onset, and length of CAG repeats, obtaining contradictory results. Some studies linked Parkinsonism to later onset and smaller CAG-repeat expansions (33 to 43 repeats, interrupted by CAA-repeats that were stably transmitted.).[37,65,68] In its turn, Monte et al. reported an association with early age of onset and longer expansions.[45] Pedroso et al. found that SCA2 patients with Parkinsonism had significantly longer disease duration and higher SARA scores.[58]

Positron Emission Tomography (PET) scan and Single-Photon Emission Computed Tomography (SPECT) studies revealed that pronounced presynaptic dopaminergic deficits and largely unaffected postsynaptic D2 receptors, predominantly affecting the putamen and caudate nucleus, were not specific of Parkinsonian SCA2 patients, as it was also present in patients with a predominant cerebellar syndrome.[66,69,70] In fact, Schols et al. found putaminal dopamine transporter (DAT) deficit in five out of six SCA2 patients, with only one having Parkinsonism.[69] These findings could be indicative that basal ganglia involvement alone might not explain the high frequency of movement disorders in SCA2 patients.[69]

DTR was reported in 44 cases: 39 had complete response to it,[36,37,49,53,54,60,61,63,64,66,68,69] 3 showed only mild improvement[54,61] and two did not respond.[37,62] Typically, Parkinsonian phenotypes resembling classic PD had better responsiveness to DRT.[36,52-54,62-64,68] Dopaminergic-related motor complications, such as motor fluctuations and dyskinesia, were described in five cases.[37,49,52,60,63] Amantadine was used in ten patients[54,59,63] and anticholinergics (trihexyphenidyl and benztropine) were reported in four patients.[54,63,64] Both had temporary benefits and were usually associated with DRT.[54,59,63] Clonazepam was used for over ten years in one patient, with rigidity improvement.[54]

Myoclonus

Myoclonus is more frequent in SCA2 than in SCA1 and MJD, according to some authors.[14,41] Schmitz-Hubsch et al. reported it in 13,7% of 163 patients.[21]

There was a single report of a patient, carrying a 46 CAG expansion, with cerebellar syndrome at onset who developed severe continuous multifocal myoclonus ten years later.[71]

Treatment with valproate, clonazepam, and levetiracetam was attempted with no benefit. However, piracetam provided a complete response and marked improvement.[71]

Results on a possible correlation between myoclonus and repeat length were discordant. While Schmitz-Hubsch et al. did not associate it with CAG-repeat length,[21] Cancel et al. described a positive relation between myoclonus and longer expansions in SCA2 patients.[38]

Chorea/choreoathetosis

Chorea was not a common feature in SCA2. As mentioned before, Schmitz-Hubsch et al. did not differentiate chorea and dyskinesia, therefore the two had a combined frequency of 6,8% amongst 163 patients.[21] In its turn, Stezin et al. found chorea in 2,7% of 73 SCA2 patients.[57] Only two papers provided further characterization of chorea/choreoathetosis. In both studies, it was presented in association with cerebellar syndrome, years after disease onset,[72,73] and was described as choreoathetosis of the upper and lower limbs[72] and as generalized chorea.[73]

Schmitz-Hubsch et al. associated chorea with longer CAG-repeat expansions.[21]

Treatment was only described in one patient, with an atypical antipsychotic (risperidone) but had poor response.[72]

MJD

MJD, also referred to as SCA3, is caused by an abnormal CAG expansion in the *Ataxin-3* gene (*ATXN3*), located on chromosome 14q32.[74,75] Normal alleles harbour 12 to 44 CAG-repeats and alleles of affected individuals have over 60 repeats.[75,76]

Age of onset varies widely, being more commonly within the fourth or fifth decade of life and ranging from 7 to 70 years old[10,13,74,76,77] Earlier onset has been associated with larger CAG-expansions and anticipation phenomenon, more clear in paternal transmission[10,14,21,74,78]

MJD phenotype is of one the most variables amongst SCAs. Progressive cerebellar ataxia and oculomotor abnormalities, such as eyelid retraction, nystagmus, progressive external ophthalmoplegia (PEO), ophthalmoparesis, and bulging eyes, are frequently identified.[10,74] Pyramidal signs, peripheral neuropathy, facial and tongue fasciculations, sleep disorders and movement disorders may also be present.[10,74]

Its vast phenotype has motivated researchers to classify MJD into clinically defined subtypes, that have been largely debated over the years.[10,11,76] Coutinho and Andrade described three main clinical types: type 1 ("type Joseph") had early-onset, predominant pyramidal and extrapyramidal signs, and fast disease progression; type 2 ("type Thomas") had intermediate

onset, dominant cerebellar syndrome, and could progress to type 1 or type 3; type 3 ("type Machado") had later onset, with distal amyotrophy being the most important finding.[11] Cerebellar ataxia was the most common sign at onset.[74]

Correlations between repeat length and clinical features of the disease have been identified: Maciel et al. associated larger CAG-expansions with marked pyramidal and extrapyramidal features, and smaller expansions with prominent ataxia, ophthalmoplegia, and peripheral involvement.[79] Schmitz-Hubsch et al. identified similar correlations but suggested that peripheral motor signs were age-dependent and not associated with CAG-expansion length.[21]Intrafamilial clinical variability was a frequently explored characteristic even in family members sharing a common number of CAG-repeats, suggesting many factors besides expansion length could be of influence.[80]

On imaging studies there is an early cerebellar atrophy, with disease progression affecting also supratentorial and infratentorial structures.[81] Volumetric MRI identified a significant reduction of the cerebellum, brainstem, basal ganglia, and cerebral cortex, particularly at the frontal and temporal regions.[81]

Neuropathological findings consisted of neuronal degeneration of the cerebellum, brainstem, subthalamic nucleus, pallidum, substantia nigra, and peripheral nervous system, establishing MJD as a rather widespread neurodegenerative disease.[10,74,82] As described in other polyglutaminopathies, the mutated protein accumulates in NII, predominantly in the ventral portion of the pons but also in the remaining affected brain areas.[83]

Movement disorders in MJD

Forty-one papers described movement disorders in MJD patients: 28 reported dystonia, 21 Parkinsonism, eight chorea/choreoathetosis, seven postural/action tremor, and five myoclonus. Tics were not described.

From the 41 articles, there was a total of 1640 patients: dystonia was reported in 199 patients, Parkinsonism in 75 (bradykinesia *per se* was described in 28, rigidity in another 26, and resting tremor in ten), postural/action tremor in 50, chorea/choreoathetosis in 22, and myoclonus in twelve (*Table III*).

Dystonia

Dystonia had a frequency of 3,67% amongst the largest available cohort of 381 Brazilian patients[84] and of 7,8% in another 167 patients, also of Brazilian ancestry.[51] Contrasting to these two studies, others identified a much higher frequency of dystonia in MJD. Schmitz-Hubsch et al. reported it in 23,9% out of 139 MJD European patients,[21] whereas Vale et al. identified it in 29,8% of 57 Portuguese patients.[13]

It either presented as focal, segmental, or generalized. Focal dystonia was present in 41 patients: eighteen had blepharospasm,[51,84,85] nine oromandibular dystonia,[46,51,84] nine foot dystonia,[29,51,85,87-90] three cervical dystonia,[84,91] and two hand dystonia. [51,92] Twenty-one patients had multifocal dystonia with various combinations of oromandibular dystonia, cervical dystonia, and upper or lower limb dystonia.[11,46,72,84,88,93-95] Segmental dystonia was present in three involving the neck, trunk, and upper limbs.[51,56,95] Generalized dystonia was described in sixteen patients.[51,82,84-86,96,97] Two patients with suspected homozygosity developed generalized dystonia.[82,87]

Although less common, dystonia was reported as the onset symptom in four patients: two had facial dystonia,[85] one cervical dystonia,[91] and one lower limb dystonia.[88] The latter patient was 40 years old at onset and presented dystonia with diurnal fluctuations and remarkable responsiveness to low-dose DRT, bearing resemblance to dopa-responsive dystonia.[88] In most reports, dystonia was associated with cerebellar syndrome, being also described as an isolated symptom in two patients, as writer's cramp and as cervical dystonia.[91,92]

Dystonia was linked to earlier onset, longer CAG expansions and higher SARA scores,[12,13,31,85] but no correlation to progression rate was identified.[31]

On volumetric MRI studies, dystonic patients had pre- and paracentral cortical atrophy and severe volumetric reduction at the basal ganglia.[85]

DRT was used in nineteen patients, ten of which with significant improvement.[85,88-91] Nunes et al. suggested dopaminergic dysfunction might play an important role at least in some dystonic patients.[85] An association of DRT and trihexyphenidyl was successfully used in one case, although the improvement was only temporary.[96] Botulinum toxin was used to treat fifteen patients, with dystonia improvement in twelve.[46,56,85,91] Adverse effects, such as dysphagia, ptosis, and diplopia were reported in five patients.[46,85] DBS was used in two cases: Beaulieu-Boire et al. described one case in which DBS provided dystonia improvement and aggravated overall disability,[56] whereas Muglan et al. described a patient with cervical dystonia in which DBS did not provide benefits.[91]

Parkinsonism

Schmitz-Hubsch et al. reported rigidity in 10,3% and resting tremor in 3,6%, amongst 139 patients,[21] while Moro et al. found Parkinsonism in 6,6% in a total of 167 patients.[51] Out of 57 Portuguese patients, Parkinsonism had a frequency of 5,3%.[13]

As in SCA2, clinical presentation ranged from Parkinsonian signs in association with cerebellar syndrome to a classic PD-like phenotype with levodopa-responsiveness. Mild Parkinsonism with prominent cerebellar signs was present in nineteen patients,[61,80,86,93,94,99] predominant Parkinsonism in 35,[12,51,66,67,77,80,94,98,100,101] and PD-like phenotype in seventeen.[55,61,67,80,87,93,98,100]

Parkinsonism correlation with CAG expansion is debatable. Gwinn-Hardy et al. correlated it with smaller expansions and late disease onset.[87] Jardim et al. did not find an association between expansion length and rigidity and/or bradykinesia.[99]

Imaging studies revealed similar results to those on SCA2, as PET scans reveal marked presynaptic dopaminergic deficits and unaffected postsynaptic D2 receptors whether or not Parkinsonism was present.[69,98] Notwithstanding, severe putamen and caudate nucleus DAT deficit was identified in Parkinsonian patients.[69,98,101]

Schols et al. reported a single Parkinsonian MJD patient displaying degeneration of the substantia nigra pars compacta and well-preserved subthalamic nucleus, whereas the remaining patients showed degeneration of both structures and had no evidence of Parkinsonism during lifetime.[69] These results could help elucidate why some patients develop Parkinsonism while others do not, when degeneration of the dopaminergic pathways is a common finding in MJD.[69]

DRT was used in 39 patients: it had marked benefit in 32 patients,[12,55,61,67,69,87,93,94,100,101] mild improvement in two,[67,80] and a poor response in five patients.[77,100] Dopaminergic-related motor complications, namely motor fluctuations without dyskinesia, were observed in three patients.[87,94]

Baclofen was the initial treatment in one patient with a PD-like phenotype and showed minor rigidity improvement, being later switched to DRT.[87] Trihexyphenidyl was used in three patients[80,101] and amantadine in two,[98] all in association to DRT.

Postural/action tremor

Moro et al. registered postural tremor in 2,4% of 167 patients,[51] whereas Gan et al. found a frequency of 12,4% in a cohort of 129 patients,[34] and Lai et al. identified it in 14,3% of 126 patients.[32]

There were not many descriptions of this movement disorder, yet tremor was reported as the onset symptom by Tan et al.[102] A patient with a 59 CAG-repeat presented with an essential

tremor (ET)-like phenotype, poorly responsive to propranolol.[102] Abnormal oculomotor signs developed years after disease onset.[102]

The presence of postural tremor was associated with longer repeat expansions[34] and Lai et al. associated it with higher SARA scores.[32]

Chorea/choreoathetosis

Schmitz-Hubsch et al. reported chorea/dyskinesia in 10,1% of 139 MJD patients,[21] whereas Moro et al. did not find chorea in the series.[51] Vale et al. identified it in 1,8% of 57 Portuguese patients.[13]

Although its frequency was analysed in several cohorts, its characteristics were only described in four patients. Chorea/choreoathetoid movements appeared in three patients alongside a cerebellar syndrome.[29,72,78] In one patient, chorea and cognitive dysfunction were the main features of the disease, suggesting an Huntington's disease (HD)-like phenotype, with cerebellar ataxia having a later onset.[89] Chorea was not reported as an isolated feature on MJD.

Treatment was described in two cases: clonazepam in one patient, and haloperidol in the HD-like phenotype, in both providing no benefit.[72,89]

Myoclonus

Myoclonus was found to have a frequency of 4,4% in 139 MJD patients.[21] Moro et al. described it in 0,6% of 167 patients,[51] and Vale et al. did not find myoclonus in the Portuguese series.[13]

Myoclonus was further characterized on rare occasions. Coutinho and Andrade found facial myoclonus in four patients, and palatal myoclonus in one.[11] Schols et al. reported two patients, with 70 and 73 repeats, presenting myoclonus of the proximal limbs after 20 years of disease onset.[78]

SCA14

Unlike previously described ADHA, SCA14 is caused by conventional mutations in *Protein Kinase C Gamma* gene (*PRKCG*), located on chromosome 19q13.[103-106] Reported cases were mostly due to missense mutations, with deletions, nonsense mutations, and splicing variants being also described.[103,105,107-111]

It is usually detected in the fourth decade of life as a slowly progressive pure cerebellar ataxia with dysarthria and nystagmus,[104,106,112] although age of onset may range from childhood

to 60 years old.[104,108,109,111,114] Some authors speculated about the occurrence of anticipation, with an earlier age of onset and more severe phenotypes ensuing in subsequent generations.[104,105] SCA14 phenotype has expanded to include movement disorders, pyramidal syndrome, cognitive impairment, and sensory loss.[104,105,108,109,111]

Mutations in the catalytic domain of *PRKCG* were found to relate to more complex and severe SCA14 phenotypes.[108,113] Affected families had a wider range of age of onset, higher rates of cognitive dysfunction, movement disorders and sensory loss.[108,113]

On imaging studies, there is an almost exclusive marked midline cerebellar atrophy.[106,108,111,112,115]

Neuropathological studies identified selective loss of Purkinje cells, without changes in any other brain areas.[106] Thus, it remains unclear why some patients do not present a pure cerebellar disorder.[116]

Movement disorders in SCA14

Twelve papers described movement disorders in SCA14 patients: seven reported myoclonus, six dystonia, five postural/action tremor, two Parkinsonism, and one chorea/choreoathetosis. Tics were not reported in any article.

From the twelve papers, there was a total of 114 patients: myoclonus was reported in thirteen patients, dystonia in twelve, postural/action tremor in eleven, chorea/choreoathetosis in two, and Parkinsonism in one (rigidity solely was described in one, and bradykinesia and resting tremor were not found) (*Table IV*).

Myoclonus

In the 25 patients' cohort reported by Chelban et al., myoclonus was identified in 12%, usually in patients with complex phenotypes.[113]

In the original report of the disease, Yamashita et al. described a Japanese family with two different phenotypes of the disease. In this family, five out of nine affected members presented early-onset axial myoclonus, three to sixteen years before developing ataxia. The remaining patients had later onset pure cerebellar ataxia.[104] There are three additional descriptions of patients with myoclonus and early age of onset, presenting mild generalized myoclonus,[114] myoclonic jerks of the head, trunk, and upper limbs,[117] and a combination of myoclonus and epilepsy.[111] In the remaining studies, three patients had mild myoclonus affecting the face, trunk, and upper limbs,[113] one truncal and upper limb myoclonus,[116] and one myoclonus of the neck and lower limbs in association with cognitive impairment[109]

Imaging studies of the original Japanese family disclosed marked atrophy of the cerebellar vermis in patients with myoclonus and minimal cerebellar signs[104] whereas, in patients with pure cerebellar ataxia, the atrophy pattern extended to the upper part of the cerebellar hemisphere.[104]

Treatment was reported in seven patients: six used clonazepam and valproic acid, with clinical improvement in five;[104] one patient, with combined mild cervical dystonia and myoclonus of the head, trunk, and upper limbs, was successfully treated with clonazepam.[117]

Dystonia

Chelban et al. described dystonia in 8% of 25 patients,[113] whereas in nine patients from German families, Ganos et al. calculated dystonia frequency in 55,6%.[116] It has been described as focal and segmental. Focal dystonia was reported in ten patients: writer's cramp in seven,[105,113,116,118] cervical dystonia in three,[115,116,117] and hand dystonia in one.[114] Cervical dystonia with dystonic tremor of the head was present in two patients.[113,116] Segmental dystonia was present in one patient, a combination of cervical dystonia and dystonic posturing of the upper limbs.[116]

In most descriptions, dystonia surfaced years after cerebellar syndrome onset. Notwithstanding, it was found to be the initial symptom in two patients, as writer's cramp and cervical dystonia.[115,118]

Imaging studies in dystonic SCA14 patients demonstrated that atrophy was restricted to the vermis and cerebellar hemispheres.[105,113]

Treatment was reported in six patients: four patients were successfully treated with botulinum toxin injections.[113,115,118] Etizolam was used in one patient in association with botulinum toxin, with a great response.[115] Clonazepam was used in another patient with dystonia and myoclonus, providing significant improvement.[117]

Postural/action tremor

Postural/action tremor had a frequency of 33,3% amongst fifteen patients described by Klebe et al.[109] It was reported as head tremor in eight patients[108,109,112,115] and mild postural tremor of the hands in one.[109] Head tremor was also found as the onset symptom twice, with cerebellar ataxia developing years later.[109,112]

Chorea/choreoathetosis

Chorea was only reported in one paper. Stevanin et al. described choreic movements of the hands in two of eighteen (14,3%) patients from a French family with a missense mutation of the catalytic domain.[108] Both patients were 40 years old at disease onset.[108]

Parkinsonism

Parkinsonism was infrequent. Nonetheless, Klebe et al. identified isolated rigidity in one patient [109] and Chelban et al. described a patient with early-onset, predominant cerebellar syndrome, and non-progressive Parkinsonism, which did not require treatment.[113] True PD-like phenotypes were not described in SCA14.

SCA17

SCA17 is caused by a coding CAG/CAA expansion in the *TBP* gene, located on chromosome 6q27, which encodes the TATA-binding protein.[119] The cut-off point for the pathologic repeat expansion in SCA17 is still heavily discussed. Normal SCA17 alleles were reported to range from 25 to 42 repeats,[120,121] whereas affected alleles tend to harbour more than 43 to 45 CAG/CAA-repeats.[119,122,123] Despite, Origone et al. recently documented a SCA17 patient with a full-phenotype and solely 41 CAG/CAA repeats.[124]

Age of onset is typically in the fourth decade of life, ranging from three to 60 years old.[120,125,126] Some authors described a correlation between larger expansions and earlier onset.[120,122,125,127] Nevertheless, SCA17 expansions appeared to be particularly stable during parent-child transmission and CAA interruptions were speculated to have a stabilizing role.[124] Maltecca et al. described a family with stable transmissions in all affected members but one, revealing loss of CAA interruptions and subsequent intergenerational instability.[120] This patient had a longer repeat expansion, distinctive young onset, and severe phenotype.[120]

Clinical features comprised progressive cerebellar ataxia, cognitive impairment, psychiatric features, and movement disorders.[120,128] Epilepsy and pyramidal signs were also described.[122,126,129,130] Cerebellar ataxia was the most common onset symptom.[120] The absence of peripheral nerve involvement can provide an important clue in distinguishing SCA17 from other ADHA.[129] Phenotypic variation was common even within families with similar expansion lengths.[131] In fact, Koutsis et al. reported a family with three affected members: two sisters, both with 54 CAG-repeats, one presenting ataxia, dementia, dystonia, chorea, and epilepsy, whilst the other had mild slowly progressive ataxia and minor cognitive and psychiatric problems. Their

father had an HD-like phenotype (no data available on the size of the expansion).[131] Therefore, the length of the repeat expansion appeared to have limited influence over phenotype.[130,131]

MRI studies revealed marked cerebellar and occasional mild cerebral cortex atrophy.[12,132,133] On one patient a putaminal rim hyperintensity on T2-weighted images was also identified.[128] DaTSCAN revealed a reduction of presynaptic dopamine transporters in the striatum, with postsynaptic dopamine D2 receptor binding capacity being only slightly reduced.[122,124]

Neuropathological studies disclosed mild atrophy of the caudate nucleus and putamen, as well as neuronal loss in the cerebral cortex, neostriatum, Purkinje cell layer, parahippocampal gyrus, and inferior olivary nucleus.[122,126,132] Degeneration of the locus coeruleus and substantia nigra was also described.[122,130] Immunohistochemistry revealed that NII formation was restricted to the cerebral cortex, putamen, and midbrain reticular formation.[126,132]

Movement disorders in SCA17

Twenty papers described movement disorders in SCA17: thirteen reported chorea/choreoathetosis, eleven Parkinsonism, ten dystonia, three postural/action tremor, and two myoclonus. There were no tics reports.

From the twenty articles, a total of 115 patients were described: dystonia was identified in 37 patients, Parkinsonism in 34 (isolated rigidity was described in fifteen, whilst bradykinesia and resting tremor were not identified), chorea/choreoathetosis in 34, myoclonus in three, and postural/action tremor in three (*Table V*).

Dystonia

Dystonia was a typical finding. In two cohorts of fifteen patients, dystonia was identified in 53,3%[129] and 46,7%.[134]

Focal dystonia was the most characterized form, with three patients developing foot dystonia,[120,125,135] two cervical dystonia,[131,135] one writer's cramp,[135] and one blepharospasm.[134] Generalized dystonia was reported in one patient.[133] Dystonic posturing of the upper limbs were described in four patients, usually in combination with choreic movements.[128,131,136] Generalized dystonia was present in one patient.[133]

Dystonia usually developed years after cerebellar syndrome onset, being only described as the initial symptom in four individuals. Hagenah et al. described three patients from a German family, with 53 to 55 repeat expansions, who presented focal dystonia at onset and later

developed cerebellar ataxia, pyramidal, and other extrapyramidal signs.[135] Maltecca et al. identified a patient with foot dystonia at onset.[120]

Dystonia appeared to be more common in patients with larger repeat expansions, ranging from 50 to 60 repeats.[131]

Treatment was only reported in two cases. Both patients had focal dystonia and were successfully treated with botulinum toxin.[135]

Parkinsonism

Nethisinghe et al. reported Parkinsonism in 45% of a series of 20 patients,[127] whilst Mariotti et al. described it in 53,3% of fifteen individuals of Italian ancestry,[129] and Rolfs et al. in 13,3% amongst fifteen German patients.[134]

Parkinsonism was associated to cerebellar syndrome, rapidly progressive dementia, and psychiatric symptoms in fifteen patients.[62,121,125,127,134] In ten patients it presented as a PD-like phenotype.[62,121,127,137] It seemed to be related to smaller expansions with CAA interruptions.[137]

DRT was used in ten patients: seven had significant improvement,[62,121,137] two mild improvement,[62] and one had no benefit.[62] The PD-like phenotype was usually levodopa-responsive.[121,137] Dopaminergic-related motor complications were reported in four patients, namely, peak-dose dyskinesia and fluctuation.[62,121]

Chorea/choreoathetosis

Chorea/choreoathetosis was a frequent finding in SCA17. Nethisinghe et al. calculated it in 20% of 20 patients, whereas Mariotti et al. reported a frequency of 66,7% of choreic movements amongst the fifteen patients[129] and Rolfs et al. identified it in 26,7%.[134]

The combination of different clinical features may result in major disease phenotypes. The association of generalized chorea, cognitive, and psychiatric disturbances might mimic HD, and SCA17 has been considered an HD-like syndrome, more specifically HDL4.[122] An HD-like phenotype was reported in six patients,[125,130,131,133] whereas eight patients were described as having several combinations of choreic/choreoathetoid movements and cerebellar syndrome.[128,131,136,138,139] The HD-like phenotype was found in patients carrying low range expansions, from 43-48 CAG/CAA repeats.[123,125,131,133]

There were no treatment descriptions for chorea/choreoathetosis.

Myoclonus

Oda et al. reported a frequency of 25% amongst eight patients,[138] whilst Choubtum et al. identified it in 12,5% of eight patients.[125] The two patients described by Oda et al. presented myoclonus as the initial symptom, shadowed by cerebellar signs and cognitive dysfunction.[138]

Postural/action tremor

Postural/action tremor was not frequent. Rolfs et al. recounted a frequency of 6,7%, [134] whilst Choubtum et al. described it in 12,5%.[125]

Mehanna et al. presented a patient with 44 repeat-expansion and rapidly progressive cerebellar ataxia, cognitive dysfunction, and a minimal irregular postural tremor at physical examination.[140]

DRPLA

DRPLA is caused by an expanded CAG-repeat in *DRPLA* gene, located on chromosome 12p13, which encodes atrophin-1.[141] Normal alleles harbour five to 28 CAG-repeats, with pathological expansions bearing more than 48 repeats.[142,143]

Age of onset is one of the most variables amongst SCAs. Although the mean age of onset is around 28-29 years old in Portuguese families, it ranged from the first to seventh decade,[6,13] and anticipation appeared to occur throughout generations,[5,142,143,146,147] particularly linked to paternal transmission.[5,142,144,147]

DRPLA phenotype is diverse, encompassing different combinations of cerebellar ataxia and cognitive impairment, with epilepsy and movement disorders.[144-146]

Several studies defined significant correlations between expansion length, age of onset, and clinical features. Larger expansions were associated with juvenile-onset ataxia, progressive myoclonic-epilepsy, and cognitive deterioration.[144,147,148] Smaller expansions frequently resulted in adult-onset forms, either the pseudo-Huntington type with chorea, dementia, and psychiatric symptoms, or the ataxo-choreoathetoid type, characterized by progressive ataxia, choreoathetosis, and dementia.[141,142,144,146,147]

Brain MRI may include atrophy of the cerebellum, brainstem and/or of the cortical and subcortical cerebral structures.[143,145,149]

Pathological findings in DRPLA comprised marked neuronal loss in the dentate nucleus and external segment of the globus pallidus and their respective projections to the red and subthalamic nuclei.[144,145] The dentatorubral system was usually more severely affected than the

pallidoluysian complex, yet the combined degeneration of both systems is the hallmark of DRPLA.[145] Atrophy of the caudate, putamen, substantia nigra, inferior olivary nucleus, and thalamus were also described, but to a lesser extent.[144,145] NII containing the mutated protein were rather widespread.[150]

Movement disorders in DRPLA

Twelve papers described movement disorders in DRPLA: ten reported chorea/choreoathetosis, nine myoclonus, six postural/action tremor, five dystonia, one Parkinsonism, and one tics.

From the twelve articles, a total of 111 patients were described: chorea/choreoathetosis was reported in 52, myoclonus in 33, dystonia in sixteen patients, postural/action tremor in eight, Parkinsonian traits in two (rigidity in one and resting tremor in two), and tics in two (*Table VI*).

Chorea/choreoathetosis

Chorea was a common finding in DRPLA. It was described in 28% of a series with 25 patients[13] and 42,1% in another series with nineteen patients.[141] It was typically associated with a later age of onset and its combination with other symptoms defines different disease phenotypes.[146] When combined with progressive ataxia and cognitive dysfunction it results in the ataxo-choreoathetoid type, whereas the HD-like phenotype results from its association with psychiatric abnormalities and dementia. The ataxo-choreoathetoid form was present in fourteen patients,[141,143,150,151] whilst the HD-like phenotype was described in six.[141,145,146,152]

Treatment was not discussed in any report.

Myoclonus

Myoclonus was present in 24% of 25 patients.[13] Its presence associated with earlier onset and resulted in a progressive myoclonic-epilepsy phenotype.[13,146] It usually ensued after ataxia or epilepsy but was also reported as the initial symptom in one patient.[143]

Treatment for myoclonus was reported once, as an association of valproate, phenobarbital, gabapentin, and diazepam.[152] There was no information regarding the patient's response to the medication or adverse effects.

Dystonia

Dystonia was more prevalent in families of European or American ancestry.[13,141,143,145] Vale et al., reported it in 16% of 25 Portuguese patients,[13] while Nielson et al. found a frequency of 31,6% amongst nineteen Danish patients.[141]

Dystonia was often described as focal. In total, it was present in nine patients: six had cervical dystonia,[141,143,153] three hand dystonia,[141,145] and one blepharospasm.[141] One had multifocal dystonia, affecting the face, hand, and abdominal wall.[141] Generalized dystonia was reported in one patient.[141]

Although dystonia would often develop after the initial cerebellar syndrome and in combination with choreic movements, Hatano et al. described two Japanese patients with cervical dystonia as the onset and most prominent symptom.[153] Both patients also had an associated head tremor, which could be dystonic.[153] This was not the only occasion head tremor was present at onset. In fact, Ohizumi et al. reported head tremor as the initial and most prominent feature of the disease in one patient.[151] The authors hypothesised whether head tremor was, in fact, of dystonic nature or if isolated head tremor could be a cerebellar symptom.[151]

Treatment was reported in three patients: clonazepam was used in one, with modest benefit,[153] trihexyphenidyl was used on another, showing partial response,[153] and propranolol and primidone were used in the patient described by Ohizumi et al., with its efficacy being limited due to side effects. The medication was later exchanged to trihexyphenidyl, showing slight improvement.[151]

Postural/action tremor

Vale et al. reported tremor in 4% of 25 patients.[13] Although unusual, postural tremor was characterized in three patients: two of them had postural tremor of the hands[141,153] and the last had postural tremor affecting the upper limbs.[141] There were no further descriptions on postural tremor.

Parkinsonism

Parkinsonism was uncommon in DRPLA. Only Nielson et al. described mild Parkinsonian features in two patients: one had a cerebellar syndrome at onset and later developed hypomimia, rigidity and resting tremor of the hands, alongside choreic movements of the limbs and dystonia.[141] The other patient also presented ataxia, and later, hand resting tremor and blepharospasm.[141]

Tics

Tics were also uncommon in DRPLA. Nielson et al. reported two patients with facial tics years after disease onset.[141] There were no further descriptions.

Discussion

SCAs are an extensive and fairly heterogeneous group of neurodegenerative diseases, characterized by cerebellar ataxia, commonly alongside other neurological features.

Although SCA subtypes tend to present overlapping manifestations, combining information such as prevalence amongst ethnicities, clinical features, disease progression patterns, and imaging studies may provide important clues guiding towards the correct diagnosis. In fact, movement disorders are an important part of the clinical spectrum guiding towards some SCA subtypes.

Various forms of dystonia have been reported. It was frequently more associated with SCA2, MJD, SCA17, and DRPLA. It was also described in SCA1 and SCA14 to a lesser extent. Dystonia seemed to develop mainly in early onset SCA2 and MJD, being described as the presenting symptom in both. Besides, some forms of dystonia were more frequent in certain SCAs. For instance, blepharospasm and oromandibular dystonia were particularly common in MJD, whereas cervical dystonia was quite frequent in SCA2. Interestingly, although dystonia was not a very typical symptom of SCA14, writer's cramp was reported numerous times.

The presence of Parkinsonism should increase suspicion for SCA2 and MJD, primarily, but also SCA17. In these SCAs, Parkinsonism ranged from mild Parkinsonian signs combined with prominent cerebellar syndrome to a full PD-like phenotype, in which DRT was proven effective. Especially in SCA2 and MJD, Parkinsonism appeared to be associated with smaller expansions and later onset, although in SCA17 it also correlated with small repeat length. Interestingly, degeneration of the dopaminergic pathways was reported in SCA2, MJD, and SCA17, even though some patients did not present Parkinsonism. This could mean basal ganglia involvement alone may not fully explain the development of movement disorders in SCAs, and therefore, further studies may be useful to better understand the pathogenic mechanisms behind SCAs and movement disorders.

Chorea/choreoathetosis was more common in SCA17 and DRPLA but reports on other SCAs were also found. In both subtypes, the combination of choreic movements, cognitive and psychiatric disturbances could lead to misdiagnosis, mimicking HD.

SCA14 and DRPLA should be considered in SCA patients with marked myoclonus. It was frequently the onset symptom and seemed to be particularly common amongst younger patients. Furthermore, a progressive myoclonus-epilepsy phenotype should raise suspicion of DRPLA.

Lastly, postural/action tremor was a symptom of difficult approach since many authors considered it as part of the cerebellar syndrome. Notwithstanding, postural tremor was more frequently reported amongst SCA2 patients than in any other SCA.

Conclusion

It is important to consider many factors could influence SCAs phenotypic expression. The interaction of several modifying factors with the disease gene itself, involved brain circuitry, amongst other factors, could play an important role in this process, which still lacks a better understanding.

Movement disorders are common features of many subtypes of SCA. The involvement of extracerebellar structures, such as the basal ganglia seems to be a significant finding pointing towards the pathogenesis of movement disorders in SCAs. Nonetheless, neurodegeneration of these structures was also described in patients with pure cerebellar ataxia and movement disorders may also occur in SCAs without evident involvement of extracerebellar structures. These findings contribute to the debate on the development of extrapyramidal features in SCAs and the potential role of the cerebellum in movement disorders.

APPENDIX

Table I - SCA1

Reference	N	Dystonia	Parkinsonism			Chorea/ choreoathetosis	Myoclonus	Postural/action tremor	Tics
			R	B	RT				
Schols et al, 2000 [12]	12	0	0			1	1	0	0
Vale et al, 2010 [13]	1	1	0			0	0	0	0
Schols et al, 1997 [14]	10	0	0			2	0	0	0
Sasaki et al, 1996 [18]	35	1	0			1	0	0	0
Schmitz-Hubsch et al, 2008 [21]	117	15	2	0	8	8	5	0	0
Namekawa et al, 2001 [26]	1	1	0			1	0	0	0
Khwaja et al, 2016 [27]	1	1	0			0	0	0	0
Wu et al, 2004 [28]	1	1	0			0	0	0	0
Boonkongchuen et al, 2014 [29]	21	1	0			0	0	0	0
Copeland et al, 2014 [30]	1	1	0			0	0	0	0
Kuo et al, 2017 [31]	58	7	0			0	0	0	0
Lai et al, 2019 [32]	54	0	0			0	0	3	0
Dragasevic et al, 2006 [33]	33	3	0			1	0	20	0
Gan et al, 2017 [34]	52	0	0			0	0	3	0
Jhunjhunwala et al, 2013 [35]	40	5	0	5	0	0	0	4	0
Total N	**437**	**37**	**2**	**5**	**8**	**14**	**6**	**30**	**0**

Legend: B-Bradykinesia; N-Number of patients; RT-Resting tremor; R-Rigidity

Table II - SCA2

Reference	N	Dystonia	Parkinsonism			Chorea/ choreoathetosis	Myoclonus	Postural/action tremor	Tics
			R	B	RT				
Schols et al, 2000 [12]	11	0	0			0	0	6	0
Schmitz-Hubsch et al, 2008 [21]	163	23	12	0	24	11	22	0	0
Kuo et al, 2017 [31]	72	13	0			0	0	0	0
Lai et al, 2019 [32]	68	0	0			0	0	21	0
Dragasevic et al, 2006 [33]	9	4	0			0	0	7	0
Gan et al, 2017 [34]	69	0	0			0	0	19	0
Jhunjhunwala et al, 2013 [35]	28	5	4	6	4	2	0	6	0
Sun et al, 2011 [36]	16	0	6			0	0	0	0
Furtado et al, 2002 [37]	10	3	6			0	0	0	0
Cancel et al, 1997 [38]	111	10	0			0	0	23	0
Geschwind et al, 1997 [39]	16	6	0			6	0	0	0
Durr et al, 1995 [40]	31	1	0			4	2	7	0
Schols et al, 1997 [41]	21	0	1			0	6	5	0
Takao et al, 2011 [42]	1	0	1			0	0	0	0
Freund et al, 2007 [44]	1	1	0			0	0	1	0
Monte et al, 2017 [45]	48	7	16			0	0	0	0
Rezende Filho et al, 2019 [46]	20	1	0			0	0	0	0
Kitahara et al, 2009 [47]	1	1	0			0	0	0	0
Boesch et al, 2007 [48]	18	11	0			0	0	0	0
Furtado et al, 2004 [49]	4	0	4			0	0	0	0
Cheng et al, 2018 [50]	1	1	0			0	0	0	0
Moro et al, 2014 [51]	20	1	0			0	1	1	0
Woo et al, 2019 [52]	8	3	8			0	0	0	0
Simon-Sanchez et al, 2005 [53]	3	1	2			0	0	1	0
Gwinn-Hardy et al, 2000 [54]	6	1	6			0	0	0	0
Pedroso et al, 2013 [55]	2	1	0			0	0	1	0
Beaulieu-Boir et al, 2016 [56]	1	1	0			0	0	0	0
Stezin et al, 2018 [57]	73	9	8			2	4	29	0
Pedroso et al, 2016 [58]	33	9	9			5	0	0	0
Wang et al, 2015 [59]	16	0	10			0	0	0	0
Nishikawa et al, 2011 [60]	3	0	2			0	0	0	0
Socal et al, 2009 [61]	4	0	4			0	0	0	0
Yun et al, 2011 [62]	6	0	1			0	1	1	0
Lu et al, 2002 [63]	2	0	2			0	0	0	0
Payami et al, 2003 [64]	2	0	2			0	0	0	0
Charles et al., 2007 [65]	9	0	9			0	0	0	0

Shan et al, 2001 [66]	6	0	2	0	0	0	0
Wang et al, 2009 [67]	4	0	4	0	0	0	0
Kim et al, 2007 [68]	3	0	3	0	0	0	0
Schols et al, 2015 [69]	6	0	1	0	0	0	0
De Rosa et al, 2006 [71]	1	1	0	0	1	0	0
Pedroso et al, 2014 [72]	35	0	0	1	0	0	0
Bhalsing et al, 2013 [73]	1	0	0	1	0	0	0
Garcia Ruiz et al, 2002 [86]	4	1	1	0	0	3	0
Total N	**967**	**115**	**108**	**32**	**37**	**131**	**0**
			16 **6** **28**				

Legend: B-Bradykinesia; N-Number of patients; RT-Resting tremor; R-Rigidity

Table III - MJD

Reference	N	Dystonia	Parkinsonism			Chorea/ choreoathetosis	Myoclonus	Postural/action tremor	Tics
			R	B	RT				
Coutinho et al, 1978 [11]	2	2	0			0	1	0	0
Schols et al, 2000 [12]	80	8	8	24	5	2	2	6	0
Vale et al, 2010 [13]	57	17	3			1	0	0	0
Schimtz-Hubsch et al, 2008 [21]	139	33	14	0	5	14	6	0	0
Boonkongchuen et al, 2014 [29]	39	1	0			1	0	0	0
Kuo et al, 2017 [31]	134	33	0			0	0	0	0
Lai et al, 2019 [32]	126	0	0			0	0	18	0
Gan et al, 2017 [34]	129	0	0			0	0	16	0
Jhunjhunwala et al, 2013 [35]	17	3	2	4	0	0	0	3	0
Rezende Filho et al, 2019 [46]	59	13	0			0	0	0	0
Moro et al, 2014 [51]	167	13	11			0	1	4	0
Pedroso et al, 2013 [55]	1	0	1			0	0	0	0
Beaulieu-Boir et al, 2016 [56]	1	1	0			0	0	0	0
Socal et al, 2009 [61]	4	0	3			0	0	0	0
Wang et al, 2009 [67]	7	0	7			0	0	0	0
Schols et al, 2015 [69]	13	0	3			0	0	0	0
Pedroso et al, 2014 [72]	1	1	0			1	0	0	0
Takiyama et al, 1994 [74]	21	8	2	0	0	0	0	0	0
Giunti et al, 1995 [77]	22	0	2			0	0	0	0
Schols et al, 1996 [78]	42	0	0			1	2	0	0
Subramony et al, 1996 [80]	3	0	3			0	0	0	0
Coutinho et al, 1982 [82]	1	1	0			0	0	0	0
Catai et al, 2018 [84]	381	14	0			0	0	0	0
Nunes et al, 2015 [85]	75	21	3			0	0	0	0
Garcia Ruiz et al, 2002 [86]	8	1	1			1	0	2	0
Gwinn-Hardy et al, 2001 [87]	4	1	3			0	0	0	0
Wilder-Smith et al, 2003 [88]	2	2	0			0	0	0	0
Dong et al, 2013 [89]	2	1	0			1	0	0	0
Nandagopal et al, 2004 [90]	1	1	0			0	0	0	0
Muglan et al, 2016 [91]	2	2	0			0	0	0	0
Méndez-Guerrero et al, 2017 [92]	1	1	0			0	0	0	0
Bettencourt et al, 2011 [93]	2	1	2			0	0	0	0
Tuite et al, 1995 [94]	2	2	2			0	0	0	0
Yuasa et al, 1986 [95]	4	2	0			0	0	0	0
Munchau et al, 1999 [96]	1	1	0			0	0	0	0
Lang et al, 1994 [97]	1	1	0			0	0	0	0
Lu et al, 2004 [98]	3	0	3			0	0	0	0

Jardim et al, 2001 [99]	61	14	14	0	0	0	0
Subramony et al, 2002 [100]	23	0	13	0	0	0	0
Buhmann et al, 2003 [101]	1	0	1	0	0	0	0
Tan et al, 2007 [102]	1	0	0	0	0	1	0
Total N	**1640**	**199**	**75**	**22**	**12**	**50**	**0**
			26 28 10				

Legend: B-Bradykinesia; N-Number of patients; RT-Resting tremor; R-Rigidity

Table IV - SCA14

Reference	N	Dystonia	Parkinsonism			Chorea/ choreoathetosis	Myoclonus	Postural/action tremor	Tics
			R	B	RT				
Yamashita et al, 2000 [104]	9	0	0			0	5	0	0
van de Warrenburg et al, 2003 [105]	13	2	0			0	0	0	0
Stevanin et al, 2004 [108]	14	0	0			2	0	2	0
Klebe et al, 2005 [109]	15	0	1	0	0	0	1	5	0
Hiramoto et al, 2006 [111]	5	0	0			0	1	0	0
Koht et al, 2012 [112]	13	0	0			0	0	1	0
Chelban et al, 2018 [113]	25	2	1			0	3	0	0
Vlak et al, 2006 [114]	7	1	0			0	1	2	0
Miura et al, 2009 [115]	2	1	0			0	0	1	0
Ganos et al, 2014 [116]	9	5	0			0	1	0	0
Foncke et al, 2010 [117]	1	0	0			0	1	0	0
Erro et al, 2014 [118]	1	1	0			0	0	0	0
Total N	**114**	**12**	**1**			**2**	**13**	**11**	**0**
			1	**0**	**0**				

Legend: B-Bradykinesia; N-Number of patients; RT-Resting tremor; R-Rigidity

Table V - SCA17

Reference	N	Dystonia	Parkinsonism			Chorea/ choreoathetosis	Myoclonus	Postural/action tremor	Tics
			R	B	RT				
Yun et al, 2011 [62]	8	0	7			0	0	0	0
Maltecca et al, 2003 [120]	4	1	0			0	0	0	0
Chen et al, 2010 [121]	5	0	4			0	0	0	0
Origone et al, 2018 [124]	1	0	0			1	0	0	0
Choubtum et al, 2015 [125]	8	2	2			1	1	1	0
De Michele et al, 2003 [126]	11	11	11	0	0	0	0	0	0
Nethisinghe et al, 2018 [127]	20	0	9			4	0	0	0
Loy et al, 2005 [128]	1	1	0			1	0	0	0
Mariotti et al, 2007 [129]	15	8	8			10	0	0	0
Fujigasaki et al, 2001 [130]	3	0	2	0	0	1	0	0	0
Koutsis et al, 2014 [131]	3	1	0			2	0	0	0
Toyoshima et al, 2004 [132]	1	0	0			1	0	0	0
Schneider et al, 2006 [133]	3	0	0			3	0	0	0
Rolfs et al, 2003 [134]	15	7	2			4	0	1	0
Hagenah et al, 2004 [135]	3	3	0			0	0	0	0
Hire et al, 2011 [136]	2	2	2	0	0	2	0	0	0
Wu et al, 2004 [137]	1	0	1			0	0	0	0
Oda et al, 2004 [138]	8	0	1			2	2	0	0
Lee et al, 2009 [139]	2	1	0			2	0	0	0
Mehanna et al, 2011 [140]	1	0	0			0	0	1	0
Total N	**115**	**37**	**34**			**34**	**3**	**3**	**0**
			15	**0**	**0**				

Legend: B-Bradykinesia; N-Number of patients; RT-Resting tremor; R-Rigidity

Table VI - DRPLA

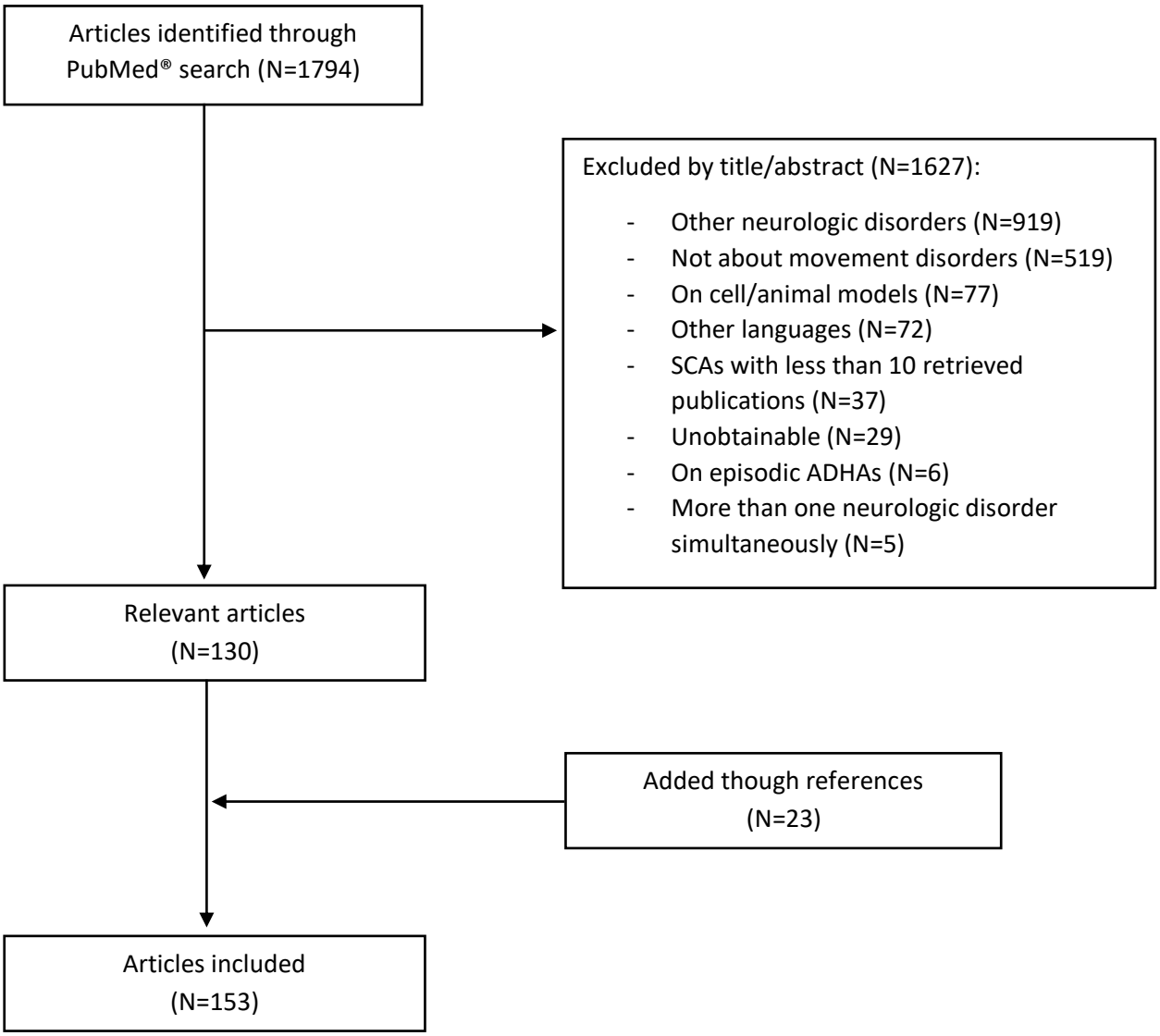
Reference	N	Dystonia	Parkinsonism			Chorea/ choreoathetosis	Myoclonus	Postural/action tremor	Tics
			R	B	RT				
Sano et al, 1994 [5]	23	0	0			13	14	0	0
Vale et al, 2010 [13]	25	4	0			7	6	1	0
Nielson et al, 1996 [141]	19	6	1	0	2	8	1	3	2
Le Ber et al, 2003 [143]	3	1	0			2	1	0	0
Warner et al, 1995 [144]	15	0	0			8	3	0	0
Warner et al, 1994 [145]	4	3	0			2	0	1	0
Ikeuchi et al, 1995 [146]	2	0	0			1	2	0	0
Lee et al, 2001 [148]	2	0	0			0	2	0	0
Munoz et al, 1999 [149]	12	0	0			8	2	0	0
Ohizumi et al, 2002 [151]	1	0	0			1	0	1	0
Licht et al, 2002 [152]	3	0	0			2	2	1	0
Hatano et al, 2003 [153]	2	2	0			0	0	1	0
Total N	**111**	**16**	**0**			**52**	**33**	**8**	**2**
			1	**0**	**2**				

Legend: B-Bradykinesia; N-Number of patients; RT-Resting tremor; R-Rigidity

Figure 1 - Standardized data sheet

Reference	SCA subtype	Total number of patients	Type of movement disorder	Number of patients with movement disorder	Estimated movement disorder frequency	Age of onset of ataxia	Age of onset of movement disorders	Movement disorders' characteristics	Imaging studies	Neuropathological studies	Treatments

Figure 2 - Flow chart of the literature search



BIBLIOGRAPHY

1. Schols L, Bauer P, Schmidt T, et al. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. Lancet Neurol 2004;3:291–304.
2. Bird TD. Hereditary Ataxia Overview. 1998 Oct [Updated 2019 Jul 25]. Seattle: University of Washington, Seattle: MP Adam, Ardinger HH, Paton RA, et al., editors. Available at http://www.genereviews.org (accessed on 18 September 2019).
3. Paulson HL. The Spinocerebellar ataxias. J Neuroophthalmol. 2009 September;29(3): 227–237.
4. Manto M, Marmolino D. Cerebellar Ataxias. Current Opinion in Neurology 2009;22:419-429.
5. Sano A, Yamauchi N, Kakimoto Y, et al. Anticipation in hereditary dentatorubral-pallidoluysian atrophy. Hum Genet 1994;93:699-702.
6. Coutinho P, Ruano L, Loureiro JL, et al. Hereditary Ataxia and Spastic Paraplegia in Portugal: A Population-Based Prevalence Study. JAMA Neurol. 2013;70(6):746-755.
7. Nakano KK, Dawson DM, Spence A. Machado disease: A hereditary ataxia in Portuguese emigrants to Massachusetts. Neurology 1972;22:49-55.
8. Woods BT, Schaumburg HH. Nigro-spinal-dentatal Degeneration With Nuclear Ophthalmoplegia: A Unique and Partially Treatable Clinico-pathological Entity. J Neurol Sci 1972;17:149-166.
9. Rosenberg RN, Nyhan WL, Bay C, et al. Autosomal dominant striatonigral degeneration: A clinical, pathological, and biochemical study of a new genetic disorder. Neurology 1976;26:703-714.
10. Coutinho P. Doença de Machado-Joseph: Tentativa de definição (Tese de Doutoramento). Porto, Universidade do Porto; 1992.
11. Coutinho P, Andrade C. Autosomal Dominant System Degeneration in Portuguese Families of the Azores Islands. A New Genetic Disorder Involving Cerebellar, Pyramidal, Extrapyramidal and Spinal Cord Motor Functions. Neurology 1978;28(7):703-709.
12. Schols L, Peters S, Szymanski S, et al. Extrapyramidal Motor Signs in Degenerative Ataxias. Arch Neurol 2000;57:1495–1500.
13. Vale J, Bugalho P, Silveira I, et al. Autosomal dominant cerebellar ataxia: frequency analysis and clinical characterization of 45 families from Portugal. European Journal of Neurology 2010;17: 124–128.
14. Schols L, Amoiridis G, Buttner T, et al. Autosomal Dominant Cerebellar Ataxia: Phenotypic Differences in Genetically Defined Subtypes? Ann Neurol 1997;42:924-932.
15. Orr HT, Chung MY, Banfi S, et al. Expansion of an Unstable Trinucleotide CAG Repeat in Spinocerebellar Ataxia Type 1. Nat Genet. 1993;4(3):221-226.
16. Opal P, Ashizawa T. Spinocerebellar Ataxia Type 1. 1998 Oct [Updated 2017 Jun 22]. Seattle: University of Washington, Seattle: MP Adam, Ardinger HH, Paton RA, et al., editors. Available at http://www.genereviews.org (accessed on 22 September 2019).
17. Zuhlke C, Dalski A, Hellenbroich Y, et al. Spinocerebellar Ataxia Type 1 (SCA1): Phenotype-Genotype Correlation Studies in Intermediate Alleles. Eur J Hum Genet. 2002;10(3):204-209.
18. Sasaki H, Fukazawa T, Yanagihara T, et al. Clinical features and natural history of spinocerebellar ataxia type 1. Acta Neurol Scand, 1996;93:64-71.

19. Dubourg O, Durr A, Cancel G, et al. Analysis of the SCA1 CAG Repeat in a Large Number of Families with Dominant Ataxia: Clinical and Molecular Correlations. Ann Neurol, 1995;37:176-180.
20. du Montcel ST, Charles P, Goizet C, et al. Factores Influencing Disease Progression in Autosomal Dominant Cerebellar Ataxia and Spastic Paraplegia. Arch Neurol, 2012;69(4):500-508.
21. Schmitz-Hübsch T, Coudert M, Bauer P, et al. Spinocerebellar ataxias types 1,2,3 and 6: Disease severity and nonataxia symptoms. NEUROLOGY, 2008;71:982-989.
22. Döhlinger S, Hauser TK, Borkert J, et al. Magnetic resonance imaging in spinocerebellar ataxias. Cerebellum. 2008;7(2):204-214.
23. Burk K, Abele M, Fetter M, et al. Autosomal dominant cerebellar ataxia type I: Clinical features and MRI in families with SCA1, SCA2 and SCA3. Brain, 1996;119:1497-1505.
24. Duyckaerts C, Dürr A, Cancel G, Brice A. Nuclear inclusions in spinocerebellar ataxia type 1. Acta Neuropathol. 1999;97(2):201-207.
25. Kish SJ, Guttman M, Robitaille Y, et al. Striatal dopamine nerve terminal markers but not nigral cellularity are reduced in spinocerebellar ataxia type 1. NEUROLOGY, 1997;48:1109-1111.
26. Namekawa M, Takiyama Y, Ando Y, et al. Choreiform movements in spinocerebellar ataxia type 1. Journal of the Neurological Sciences, 2001;187:103-106.
27. Khwaja GA, Srivastava A, Ghuge VV, et al. Writer's cramp in spinocerebellar ataxia Type 1. J Neurosci Rural Pract. 2016;7(4):584-586.
28. Wu YR, Lee-Chen GJ, Lang AE, et al. Dystonia as a presenting sign of spinocerebellar ataxia type 1. Mov Disord. 2004;19(5):586-587.
29. Boonkongchuen P, Pongpakdee S, Jindahra P, et al. Clinical analysis of adult-onset spinocerebellar ataxias in Thailand. BMC Neurol. 2014;14:75.
30. Copeland BJ, Fenoy A, Ellmore TM, Liang Q, Ephron V, Schiess M. Deep brain stimulation of the internal globus pallidus for generalized dystonia associated with spinocerebellar ataxia type 1: a case report. Neuromodulation. 2014;17(4):389-392.
31. Kuo PH, Gan SR, Wang J, et al. Dystonia and ataxia progression in spinocerebellar ataxias. Parkinsonism Relat Disord. 2017;45:75–80.
32. Lai RY, Tomishon D, Figueroa KP, et al. Tremor in the Degenerative Cerebellum: Towards the Understanding of Brain Circuitry for Tremor. Cerebellum. 2019;18(3):519-526.
33. Dragasević NT, Culjković B, Klein C, et al. Frequency analysis and clinical characterization of different types of spinocerebellar ataxia in Serbian patients. Mov Disord. 2006;21(2):187-191.
34. Gan SR, Wang J, Figueroa KP, et al. Postural Tremor and Ataxia Progression in Spinocerebellar Ataxias. Tremor Other Hyperkinet Mov (N Y). 2017;7:492.
35. Jhunjhunwala K, Netravathi M, Purushottam M, et al. Profile of extrapyramidal manifestations in 85 patients with spinocerebellar ataxia type 1, 2 and 3. J Clin Neurosci. 2014;21(6):1002-1006.
36. Sun H, Satake W, Zhang C, et al. Genetic and clinical analysis in a Chinese parkinsonism-predominant spinocerebellar ataxia type 2 family. J Hum Genet. 2011;56(4):330-334.
37. Furtado S, Farrer M, Tsuboi Y, et al. SCA-2 presenting as parkinsonism in an Alberta family: Clinical, genetic, and PET findings. NEUROLOGY, 2002;59:1625–1627.
38. Cancel G, Durr A, Didierjean O, et al. Molecular and clinical correlations in spinocerebellar ataxia 2: a study of 32 families. Human Molecular Genetics, 1997;6(5):709-715.

39. Geschwind DH, Perlman S, Figueroa CP, et al. The Prevalence and Wide Clinical Spectrum of the Spinocerebellar Ataxia Type 2 Trinucleotide Repeat in Patients with Autosomal Dominant Cerebellar Ataxia. Am J Hum Genet 1997;60:842-850.
40. Dürr A, Smadja D, Cancel G, et al. Autosomal dominant cerebellar ataxia type I in Martinique (French West Indies). Clinical and neuropathological analysis of 53 patients from three unrelated SCA2 families. Brain. 1995;118 (Pt 6):1573-1581.
41. Schols L, Gispert S, Vorgerd M, et al. Spinocerebellar Ataxia Type 2: Genotype and Phenotype in German Kindreds. Arch Neurol.1997;54:1073-1080.
42. Takao M, Aoyama M, Ishikawa K, et al. Spinocerebellar ataxia type 2 is associated with Parkinsonism and Lewy body pathology. BMJ Case Rep. 2011;2011:bcr0120113685. Published 2011 Apr 1.
43. Pang JT, Giunti P, Chamberlain S, et al. Neuronal intranuclear inclusions in SCA2: a genetic, morphological and immunohistochemical study of two cases. Brain. 2002;125(Pt 3):656-663.
44. Freund HJ, Barnikol UB, Nolte D, et al. Subthalamic-thalamic DBS in a case with spinocerebellar ataxia type 2 and severe tremor-A unusual clinical benefit. Mov Disord. 2007;22(5):732-735.
45. Monte TL, Pereira FS, Reckziegel ER, et al. Neurological phenotypes in spinocerebellar ataxia type 2: Role of mitochondrial polymorphism A10398G and other risk factors. Parkinsonism and Related Disorders, 2017;1-7.
46. Rezende Filho FM, Vale TC, Pedroso JL, et al. Facial grimacing and clinical correlates in spinocerebellar ataxia type 3. J Neurol Sci. 2019;397:138-140.
47. Kitahara M, Shimohata T, Tokunaga J, et al. Cervical dystonia associated with spinocerebellar ataxia type 2 successfully treated with levodopa: a case report. Mov Disord. 2009;24(14):2163-2164.
48. Boesch SM, Müller J, Wenning GK, et al. Cervical dystonia in spinocerebellar ataxia type 2: clinical and polymyographic findings. J Neurol Neurosurg Psychiatry. 2007;78(5):520-522.
49. Furtado S, Payami H, Lockhart PJ, et al. Profile of families with parkinsonism-predominant spinocerebellar ataxia type 2 (SCA2). Mov Disord. 2004;19(6):622-629.
50. Cheng N, Wied HM, Gaul JJ, Doyle LE, Reich SG. SCA2 presenting as a focal dystonia. J Clin Mov Disord. 2018;5:6. Published 2018 Aug 13.
51. Moro A, Munhoz RP, Moscovich M, Arruda WO, Raskin S, Teive HA. Movement disorders in spinocerebellar ataxias in a cohort of Brazilian patients. Eur Neurol. 2014;72(5-6):360-362.
52. Woo KA, Lee JY, Jeon B. Familial Spinocerebellar Ataxia Type 2 Parkinsonism Presenting as Intractable Oromandibular Dystonia. Tremor Other Hyperkinet Mov (N Y). 2019;9:611.
53. Simon-Sanchez J, Hanson M, Singleton A, et al. Analysis of SCA-2 and SCA-3 repeats in Parkinsonism: evidence of SCA-2 expansion in a family with autosomal dominant Parkinson's disease. Neurosci Lett. 2005;382(1-2):191-194.
54. Gwinn-Hardy K, Chen JY, Liu HC, et al. Spinocerebellar ataxia type 2 with parkinsonism in ethnic Chinese. Neurology. 2000;55(6):800-805.
55. Pedroso JL, Carvalho AA, Escorcio Bezerra ML, et al. Unusual movement disorders in spinocerebellar ataxias. Parkinsonism Relat Disord. 2013;19(9):834-835.
56. Beaulieu-Boire I, Aquino CC, Fasano A, et al. Deep Brain Stimulation in Rare Inherited Dystonias. Brain Stimul. 2016;9(6):905-910.
57. Stezin A, Venkatesh SD, Thennarasu K, et al. Non-ataxic manifestations of Spinocerebellar ataxia-2, their determinants and predictors. J Neurol Sci. 2018;394:14-18.
58. Pedroso JL, Braga-Neto P, Escorcio-Bezerra ML, et al. Non-motor and Extracerebellar Features in Spinocerebellar Ataxia Type 2. Cerebellum. 2017;16(1):34-39.

59. Wang C, Xu Y, Feng X, et al. Linkage analysis and whole-exome sequencing exclude extra mutations responsible for the parkinsonian phenotype of spinocerebellar ataxia-2. Neurobiol Aging. 2015;36(1):545.e1-545.e5457.
60. Nishikawa N, Nagai M, Tsujii T, et al. Three spinocerebellar ataxia type 2 siblings with ataxia, parkinsonism, and motor neuronopathy. Intern Med. 2011;50(13):1429-1432.
61. Socal MP, Emmel VE, Rieder CR, et al. Intrafamilial variability of Parkinson phenotype in SCAs: novel cases due to SCA2 and SCA3 expansions. Parkinsonism Relat Disord. 2009;15(5):374-378.
62. Yun JY, Lee WW, Kim HJ, et al. Relative contribution of SCA2, SCA3 and SCA17 in Korean patients with parkinsonism and ataxia. Parkinsonism Relat Disord. 2011;17(5):338-342.
63. Lu CS, Wu Chou YH, Yen TC, et al. Dopa-responsive parkinsonism phenotype of spinocerebellar ataxia type 2. Mov Disord. 2002;17(5):1046-1051.
64. Payami H, Nutt J, Gancher S, et al. SCA2 may present as levodopa-responsive parkinsonism. Mov Disord. 2003;18(4):425-429.
65. Charles P, Camuzat A, Benammar N, et al. Are interrupted SCA2 CAG repeat expansions responsible for parkinsonism?. Neurology. 2007;69(21):1970-1975.
66. Shan DE, Soong BW, Sun CM, et al. Spinocerebellar ataxia type 2 presenting as familial levodopa-responsive parkinsonism. Ann Neurol. 2001;50(6):812-815.
67. Wang JL, Xiao B, Cui XX, et al. Analysis of SCA2 and SCA3/MJD repeats in Parkinson's disease in mainland China: genetic, clinical, and positron emission tomography findings. Mov Disord. 2009;24(13):2007-2011.
68. Kim JM, Hong S, Kim GP, et al. Importance of low-range CAG expansion and CAA interruption in SCA2 Parkinsonism. Arch Neurol. 2007;64(10):1510-1518.
69. Schols L, Reimold M, Seidel K, et al. No parkinsonism in SCA2 and SCA3 despite severe neurodegeneration of the dopaminergic substantia nigra. Brain. 2015;138(Pt 11):3316-3326.
70. Varrone A, Salvatore E, De Michele G, et al. Reduced striatal [123 I]FP-CIT binding in SCA2 patients without parkinsonism. Ann Neurol. 2004;55(3):426-430.
71. De Rosa A, Striano P, Barbieri F, et al. Suppression of myoclonus in SCA2 by piracetam. Mov Disord. 2006;21(1):116-118.
72. Pedroso JL, de Freitas ME, Albuquerque MV, et al. Should spinocerebellar ataxias be included in the differential diagnosis for Huntington's diseases-like syndromes?. J Neurol Sci. 2014;347(1-2):356-358.
73. Bhalsing KS, Sowmya V, Netravathi M, et al. Spinocerebellar Ataxia (SCA) type 2 presenting with chorea. Parkinsonism Relat Disord. 2013;19(12):1171-1172.
74. Takiyama Y, Oyanagi S, Kawashima S, et al. A clinical and pathologic study of a large Japanese family with Machado-Joseph disease tightly linked to the DNA markers on chromosome 14q. Neurology. 1994;44(7):1302-1308.
75. Higgins JJ, Nee LE, Vasconcelos O, et al. Mutations in American families with spinocerebellar ataxia (SCA) type 3: SCA3 is allelic to Machado-Joseph disease. Neurology. 1996;46(1):208-213.
76. Paulson H. Spinocerebellar Ataxia Type 3. 1998 Oct. [Updated 2015 Sep 24] Seattle: University of Washington, Seattle: Adam MP, Ardinger HH, Pagon RA, et al., editors. Available at http://www.genereviews.org (accessed on 24 September 2019).
77. Giunti P, Sweeney MG, Harding AE. Detection of the Machado-Joseph disease/spinocerebellar ataxia three trinucleotide repeat expansion in families with autosomal dominant motor disorders, including the Drew family of Walworth. Brain. 1995;118 (Pt 5):1077-1085.

78. Schols L, Amoiridis G, Epplen JT, et al. Relations between genotype and phenotype in German patients with the Machado-Joseph disease mutation. J Neurol Neurosurg Psychiatry. 1996;61(5):466-470.
79. Maciel P, Gaspar C, DeStefano AL, et al. Correlation between CAG Repeat Length and Clinical Features in Machado-Joseph Disease. Am J Hum Genet, 1995;57:54-61.
80. Subramony SH, Currier RD. Intrafamilial variability in Machado-Joseph disease. Mov Disord. 1996;11(6):741-743.
81. Mendonça N, França MC, Gonçalves AF, et al. Clinical Features of Machado-Joseph Disease. Adv Exp Med Biol. 2018;1049:255-273.
82. Coutinho P, Guimarães A, Scaravilli F. The pathology of Machado-Joseph disease. Report of a possible homozygous case. Acta Neuropathol. 1982;58(1):48-54.
83. Paulson HL, Perez MK, Trottier Y, et al. Intranuclear inclusions of expanded polyglutamine protein in spinocerebellar ataxia type 3. Neuron. 1997;19(2):333-344.
84. Catai LMP, Camargo CHF, Moro A, et al. Dystonia in Patients with Spinocerebellar Ataxia 3 - Machado-Joseph disease: An Underestimated Diagnosis?. Open Neurol J. 2018;12:41-49.
85. Nunes MB, Martinez AR, Rezende TJ, et al. Dystonia in Machado-Joseph disease: Clinical profile, therapy and anatomical basis. Parkinsonism Relat Disord. 2015;21(12):1441-1447.
86. Garcia Ruiz PJ, Mayo D, Hernandez J, et al. Movement disorders in hereditary ataxias. J Neurol Sci. 2002;202(1-2):59-64.
87. Gwinn-Hardy K, Singleton A, O'Suilleabhain P, et al. Spinocerebellar ataxia type 3 phenotypically resembling parkinson disease in a black family. Arch Neurol. 2001;58(2):296-299.
88. Wilder-Smith E, Tan EK, Law HY, et al. Spinocerebellar ataxia type 3 presenting as an L-DOPA responsive dystonia phenotype in a Chinese family. J Neurol Sci. 2003;213(1-2):25-28.
89. Dong Y, Sun YM, Ni W, et al. Chinese patients with spinocerebellar ataxia type 3 presenting with rare clinical symptoms. J Neurol Sci. 2013;324(1-2):167-171.
90. Nandagopal R, Moorthy SG. Dramatic levodopa responsiveness of dystonia in a sporadic case of spinocerebellar ataxia type 3. Postgrad Med J. 2004;80(944):363-365.
91. Muglan JA, Menon S, Jog MS. Pearls & Oy-sters: Spinocerebellar ataxia type 3 presenting with cervical dystonia without ataxia. Neurology. 2016;86(1):e1-e3.
92. Méndez-Guerrero A, de Urabayen DUP, Llamas-Velasco S. Spinocerebellar ataxia type 3 presenting with writer's cramp without ataxia. Int J Neurosci. 2018;128(7):684-685.
93. Bettencourt C, Santos C, Coutinho P, et al. Parkinsonian phenotype in Machado-Joseph disease (MJD/SCA3): a two-case report. BMC Neurol. 2011;11:131.
94. Tuite PJ, Rogaeva EA, St George-Hyslop PH, et al. Dopa-responsive parkinsonism phenotype of Machado-Joseph disease: confirmation of 14q CAG expansion. Ann Neurol. 1995;38(4):684-687.
95. Yuasa T, Ohama E, Harayama H, et al. Joseph's disease: clinical and pathological studies in a Japanese family. Ann Neurol. 1986;19(2):152-157.
96. Münchau A, Dressler D, Bhatia KP, et al. Machado-Joseph disease presenting as severe generalised dystonia in a German patient. J Neurol. 1999;246(9):840-842.
97. Lang AE, Rogaeva EA, Tsuda T, et al. Homozygous inheritance of the Machado-Joseph disease gene. Ann Neurol. 1994;36(3):443-447.
98. Lu CS, Chang HC, Kuo PC, et al. The parkinsonian phenotype of spinocerebellar ataxia type 3 in a Taiwanese family. Parkinsonism Relat Disord. 2004;10(6):369-373.
99. Jardim LB, Pereira ML, Silveira I, et al. Neurologic findings in Machado-Joseph disease: relation with disease duration, subtypes, and (CAG)n. Arch Neurol. 2001;58(6):899-904.

100. Subramony SH, Hernandez D, Adam A, et al. Ethnic differences in the expression of neurodegenerative disease: Machado-Joseph disease in Africans and Caucasians. Mov Disord. 2002;17(5):1068-1071.
101. Buhmann C, Bussopulos A, Oechsner M. Dopaminergic response in Parkinsonian phenotype of Machado-Joseph disease. Mov Disord. 2003;18(2):219-221.
102. Tan EK, Tong J, Pavanni R, et al. Genetic analysis of SCA 2 and 3 repeat expansions in essential tremor and atypical Parkinsonism. Mov Disord. 2007;22(13):1971-1974.
103. Chen DH, Brkanac Z, Verlinde CLMJ, et al. Missense Mutations in the Regulatory Domain of PKCγ: A New Mechanism for Dominant Nonepisodic Cerebellar Ataxia. Am J Hum Genet, 2003;72:839-849.
104. Yamashita I, Sasaki H, Yabe I, et al. A Novel Locus for Dominant Cerebellar Ataxia (SCA14) Maps to a 10.2-cM Interval Flanked by D19S206 and D19S605 on Chromosome 19q13.4-qter. Ann Neurol, 2000;48:156–163.
105. van de Warrenburg BPC, Verbeek DS, Piersma SJ, et al. Identification of a novel SCA14 mutation in a Dutch autosomal dominant cerebellar ataxia family. Neurology, 2003;61:1760–1765.
106. Brkanac Z, Bylenok L, Fernandez M, et al. A New Dominant Spinocerebellar Ataxia Linked to Chromosome 19q13.4-qter. Arch Neurol, 2002;59:1291-1295.
107. Chen DH, Cimino PJ, Ranum LPW, et al. The clinical and genetic spectrum of spinocerebellar ataxia 14. NEUROLOGY, 2005;64:1258-1260.
108. Stevanin G, Hahn V, Lohmann E, et al. Mutation in the Catalytic Domain of Protein Kinase C γ and Extension of the Phenotype Associated with Spinocerebellar Ataxia Type 14. Arch Neurol, 2004;61:1242-1248.
109. Klebe S, Durr A, Rentschler A, et al. New Mutations in Protein Kinase γ Associated with Spinocerebellar Ataxia Type 14. Ann Neurol, 2005;58:720-729.
110. Shirafuji T, Shimazaki H, Miyagi T, et al. Spinocerebellar ataxia type 14 caused by a nonsense mutation in the PRKCG gene. Mol Cell Neurosci. 2019;98:46-53.
111. Hiramoto K, Kawakami H, Inoue K, et al. Identification of a new family of spinocerebellar ataxia type 14 in the Japanese spinocerebellar ataxia population by the screening of PRKCG exon 4. Mov Disord. 2006;21(9):1355-1360.
112. Koht J, Stevanin G, Durr A, et al. SCA14 in Norway, two families with autosomal dominant cerebellar ataxia and a novel mutation in the PRKCG gene. Acta Neurol Scand. 2012;125(2):116-122.
113. Chelban V, Wiethoff S, Fabian-Jessing BK, et al. Genotype-Phenotype Correlations, Dystonia and Disease Progression in Spinocerebellar Ataxia Type 14. Movement Disorders, 2018;33(7):1119-1129.
114. Vlak MHM, Sinke RJ, Rabelink GM, et al. Novel PRKCG/SCA14 Mutation in a Dutch Spinocerebellar Ataxia Family: Expanding the Phenotype. Movement Disorders, 2006;21(7):1025-1028.
115. Miura S, Nakagawara H, Kaida H, et al. Expansion of the phenotypic spectrum of SCA14 caused by the Gly128Asp mutation in PRKCG. Clin Neurol Neurosurg. 2009;111(2):211-215.
116. Ganos C, Zittel S, Minnerop M, et al. Clinical and Neurophysiological Profile of Four German Families with Spinocerebellar Ataxia Type 14. Cerebellum, 2014;13:89–96.
117. Foncke EM, Beukers RJ, Tijssen CC, et al. Myoclonus-dystonia and spinocerebellar ataxia type 14 presenting with similar phenotypes: trunk tremor, myoclonus, and dystonia. Parkinsonism Relat Disord. 2010;16(4):288-289.
118. Erro R, Cordivari C, Edwards MJ, et al. Writer's Cramp as the First Symptom of Spinocerebellar Ataxia 14. Mov Disord Clin Pract. 2014;2(1):41-42.

119. Koide R, Kobayashi S, Shimohata T, et al. A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA-binding protein gene: a new polyglutamine disease? Hum Mol Genet, 1999;8(11):2047-2053.
120. Maltecca F, Filla A, Castaldo I, et al. Intergenerational instability and marked anticipation in SCA-17. Neurology. 2003;61(10):1441-1443.
121. Chen CM, Lee LC, Soong BW, et al. SCA17 repeat expansion: mildly expanded CAG/CAA repeat alleles in neurological disorders and the functional implications. Clin Chim Acta. 2010;411(5-6):375-380.
122. Stevanin G, Brice A. Spinocerebellar ataxia 17 (SCA17) and Huntington's Disease-like 4 (HDL4). The Cerebellum, 2008;170-178.
123. Shin JH, Park H, Ehm GH, et al. The Pathogenic Role of Low Range Repeats in SCA17. PLOS ONE, 2015:10(8):e0135275.
124. Origone P, Gotta F, Lamp M, et al. Spinocerebellar ataxia 17: full phenotype in a 41 CAG/CAA repeats carrier. Cerebellum & Ataxias, 2018;5(7):1-5.
125. Choubtum L, Witoonpanich P, Hanchaiphiboolkul S, et al. Analysis of SCA8, SCA10, SCA12, SCA17 and SCA19 in patients with unknown spinocerebellar ataxia: a Thai multicentre study. BMC Neurol. 2015;15:166.
126. De Michele G, Maltecca F, Carella M, et al. Dementia, ataxia, extrapyramidal features, and epilepsy: phenotype spectrum in two Italian families with spinocerebellar ataxia type 17. Neurol Sci. 2003;24(3):166-167.
127. Nethisinghe S, Lim WN, Ging H, et al. Complexity of the Genetics and Clinical Presentation of Spinocerebellar Ataxia 17. Front Cell Neurosci. 2018;12:429.
128. Loy CT, Sweeney MG, Davis MB, et al. Spinocerebellar ataxia type 17: extension of phenotype with putaminal rim hyperintensity on magnetic resonance imaging. Mov Disord. 2005;20(11):1521-1523.
129. Mariotti C, Alpini D, Fancellu R, et al. Spinocerebellar ataxia type 17 (SCA17): oculomotor phenotype and clinical characterization of 15 Italian patients. J Neurol. 2007;254(11):1538-1546.
130. Fujigasaki H, Martin JJ, De Deyn PP, et al. CAG repeat expansion in the TATA-box binding protein gene causes autosomal dominant cerebellar ataxia. Brain, 2001;124:1939-1947.
131. Koutsis G, Panas M, Paraskevas GP, et al. From Mild Ataxia to Huntington Disease Phenocopy: The Multiple Faces of Spinocerebellar Ataxia 17. Case Reports in Neurological Medicine, 2014.
132. Toyoshima Y, Yamada M, Onodera O, et al. SCA17 homozygote showing Huntington's disease-like phenotype. Ann Neurol. 2004;55(2):281-286.
133. Schneider SA, van de Warrenburg BP, Hughes TD, et al. Phenotypic homogeneity of the Huntington disease-like presentation in a SCA17 family. Neurology. 2006;67(9):1701-1703.
134. Rolfs A, Koeppen AH, Bauer I, et al. Clinical features and neuropathology of autosomal dominant spinocerebellar ataxia (SCA17). Ann Neurol. 2003;54(3):367-375.
135. Hagenah JM, Zühlke C, Hellenbroich Y, et al. Focal dystonia as a presenting sign of spinocerebellar ataxia 17. Mov Disord. 2004;19(2):217-220.
136. Hire RR, Katrak SM, Vaidya S, et al. Spinocerebellar ataxia type 17 in Indian patients: two rare cases of homozygous expansions. Clin Genet. 2011;80(5):472-477.
137. Wu YR, Lin HY, Chen CM, et al. Genetic testing in spinocerebellar ataxia in Taiwan: expansions of trinucleotide repeats in SCA8 and SCA17 are associated with typical Parkinson's disease. Clin Genet. 2004;65(3):209-214.

138. Oda M, Maruyama H, Komure O, et al. Possible reduced penetrance of expansion of 44 to 47 CAG/CAA repeats in the TATA-binding protein gene in spinocerebellar ataxia type 17. Arch Neurol. 2004;61(2):209-212.
139. Lee WW, Kim SY, Kim JY, et al. Extrapyramidal signs are a common feature of spinocerebellar ataxia type 17. Neurology. 2009;73(20):1708-1709.
140. Mehanna R, Itin I. From Normal Gait to Loss of Ambulation in 6 Months: a Novel Presentation of SCA17. Cerebellum, 2013;12:568–571.
141. Nielson JE, Sorensen SA, Hasholt L, et al. Dentatorubral-Pallisoluysian Atrophy. Clinical Features of a Five-Generation Danish Family. Movement Disorders, 1996;11(5):533-541.
142. Koide R, Ikeuchi T, Onodera O, et al. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nat Genet, 1994;6:9-13.
143. Le Ber I, Camuzat A, Castelnovo G, et al. Prevalence of Dentatorubral-Pallidoluysian Atrophy in a Large Series of White Patients With Cerebellar Ataxia. Arch Neurol, 2003;60:1097-1099.
144. Warner TT, Williams LD, Walker RWH, et al. A Clinical and Molecular Genetic Study of Dentatorubropallidoluysian Atrophy in Four European Families. Ann Neurol 1995;37:452-459.
145. Warner TT, Lennox GG, Janota I, et al. Autosomal Dominant Dentatorubral-Pallidoluysian Atrophy in the United Kingdom. Movement Disorders, 1994;9(3):289-296.
146. Ikeuchi T, Koide R, Tanaka H, et al. Dentatorubral-Pallidoluysian Atrophy: Clinical Features Are Closely Related the Unstable Expansions of Trinucleotide (CAG) Repeat. Ann Neurol,1995;37:769-775.
147. Komure O, Sano A, Nishino N, et al. DNA analysis in hereditary dentatorubral-pallidoluysian atrophy: correlation between CAG repeat length and phenotypic variation and the molecular basis of anticipation. Neurology. 1995;45(1):143-149.
148. Lee IH, Soong BW, Lu YC, et al. Dentatorubropallidoluysian atrophy in Chinese. Arch Neurol. 2001;58(11):1905-1908.
149. Muñoz E, Milà M, Sánchez A, et al. Dentatorubropallidoluysian atrophy in a spanish family: a clinical, radiological, pathological, and genetic study. J Neurol Neurosurg Psychiatry. 1999;67(6):811-814.
150. Yamada M, Shimohata M, Sato T, et al. Polyglutamine disease: recent advances in the neuropathology of dentatorubral-pallidoluysian atrophy. Neuropathology. 2006;26(4):346-351.
151. Ohizumi H, Okuma Y, Fukae J, et al. Head tremor in dentatorubral-pallidoluysian atrophy. Acta Neurol Scand, 2002;106:319-321.
152. Licht DJ, Lynch DR. Juvenile dentatorubral-pallidoluysian atrophy: new clinical features. Pediatr Neurol. 2002;26(1):51-54.
153. Hatano T, Okuma Y, Iijima M, et al. Cervical dystonia in dentatorubral-pallidoluysian atrophy. Acta Neurol Scand, 2003;108:287–289.