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Autosomal Dominant Spinocerebellar Ataxia

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Abstract

The autosomal dominant spinocerebellar ataxias (also known as the SCAs) are a diverse and clinically heterogeneous group of disorders characterized by degeneration and dysfunction of the cerebellum and its associated pathways. Clinical and diagnostic evaluation can be challenging due to phenotypic overlap amongst numerous acquired, genetic, and idiopathic etiologies, and a stratified and systematic approach is essential. Molecular etiologies include DNA repeat expansions (both polyglutamine and non-coding repeats), ion-channel dysfunction, and disorders of signal transduction. Prompt recognition of acquired conditions or comorbidities is essential as treatment options for the genetic ataxias are currently limited. Recent advances in the field include the identification of additional genes causing dominant genetic ataxia, a better understanding of cellular pathogenesis in several disorders, the generation of new disease models which may stimulate development of new therapies, and the use of new DNA sequencing technologies, including whole exome sequencing, to improve diagnosis.

Keywords

ataxia; cerebellum; spinocerebellar; SCA; autosomal dominant

INTRODUCTION

Definition

The spinocerebellar ataxias (SCAs) are a heterogeneous group of degenerative disorders with symptoms caused by dysfunction of the cerebellum and brainstem, along with their associated pathways and connections, and with an autosomal dominant pattern of inheritance.

Symptoms and Clinical Course

- All patients exhibit cerebellar ataxia (limb, trunk, and/or gait)

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- Additional symptoms are variable and disease specific including extrapyramidal features, long tract signs, peripheral neuropathy, and, in some cases, cognitive impairment and seizures (see Table 1).
- Clinical course: The polyglutamine ataxias SCA1, SCA2, and SCA3 are progressive disorders with death resulting primarily from brain stem dysfunction [1]. In one series, median survival was in the mid-50s, 21–25 years following symptom onset [2]. The other causes of SCA tend to have a more pure cerebellar dysfunction leading to significant disability but with normal lifespan.

CLINICAL FINDINGS

Ataxia is defined as a disturbance of balance and coordination occurring in the absence of muscle weakness, and can arise from dysfunction of the cerebellum, the vestibular system, or of proprioception, alone or in combination (see Box 1) [3, 4]. The cerebellum plays a critical role in this process through the integration of multimodal sensory data with motor output predictions to yield smooth well-timed movement [5].

Box 1

Physical Examination Findings in a Patient with Ataxia*

- **Cerebellar Examination**
  - Gaze-evoked nystagmus
  - Abnormal eye movements (ocular dysmetria, impaired smooth pursuit)
  - Dysarthria (scanning)
  - Limb Dysmetria (finger-to-nose, finger chase, heel-shin testing)
  - Dysdiadochokinesis
  - Loss of check on removal of extremity resistance
  - Truncal ataxia and/or head titubation
  - Wide-based unsteady gait (“drunk” gait)
  - Inability to tandem walk
- **Vestibular Examination**
  - Spontaneous nystagmus
  - Past-pointing
  - Abnormal head thrust or Dix-Hallpike testing
- **Sensory Examination**
  - Reduced proprioception
  - Reduced vibration sense
  - Abnormal Romberg test

*Not comprehensive. Not all patients will exhibit all features.

Physical Examination

The focus of thephysical examination should be on eliciting signs specific for cerebellar dysfunction and extracerebellar findings.

- Disruption of cerebellar function manifests as impairment in coordinated muscle activity, most often observed clinically as dysarthria, dysphagia, ocular dysmetria, altered visual pursuit, direction-changing nystagmus, limb dysmetria, gait disturbance, and/or falls [3, 4].
- In slowly progressive cases, gait impairment is often seen early and is frequently associated with a sense of imbalance or feelings of generalized leg weakness.
- Exacerbation may occur when walking on uneven surfaces or under conditions of reduced sensory input, such as in low lighting. Stance often widens for additional stabilization and patients may require support to walk, especially on turning. When indoors, the practice of navigating from support to support (e.g., across items of furniture) can become a common means of ambulation.
- Depending upon the etiology of the ataxia, associated clinical features may be present and, in some cases, could be helpful to establishing the diagnosis, particularly in the case of genetic ataxias (see Table 1).

GENETICS

Despite their similarity in clinical symptoms, an array of diverse genetic causes underlie the SCAs. The genes accounting for autosomal dominant spinocerebellar ataxia are summarized in Table 1.

MOLECULAR PATHOGENESIS

Although distinct genes account for the over 30 etiologies of dominant ataxia, groups of disorders may be recognized with shared molecular mechanisms of disease. These include the polyglutamine ataxias, ataxias associated with ion-channel dysfunction, mutations in signal transduction molecules, and disease associated with non-coding repeats.

1. Polyglutamine ataxias

These include SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, SCA17, and DRPLA, where expansion within a glutamine encoding CAG repeat accounts for disease. An additional disorder, SCA8, likely arises from the combined effects of a non-coding CTG repeat expansion and the generation of a pure polyglutamine protein from the corresponding CAG repeat on the opposite strand [6].

The exact mechanism for how a polyglutamine protein causes ataxia is not understood. Potential mechanisms [7] include:

1. Protein misfolding resulting in altered function
2. Formation of toxic oligomeric complexes
3. Transcriptional dysregulation
4. Mitochondrial dysfunction
5. Impaired axonal transport
6. Aberrant neuronal signaling including excitotoxicity
7. Cellular protein homeostasis impairment

8. RNA toxicity

2. Ion-channel mutations/dysfunction

Either direct ion-channel mutations or secondary ion-channel dysfunction has been implicated in the pathogenesis of SCA5, SCA6, SCA13, SCA15/16, SCA19/22, and SCA27 [8].

A. SCA5: Mutations in the structural protein, beta-3 spectrin result in SCA5. In a mouse model of disease Purkinje neurons exhibit reduced spontaneous firing, smaller sodium currents, and dysregulation of glutamatergic neurotransmission [9].

B. SCA6: Results from a modest polyglutamine expansion in the C-terminus of a neuronal calcium channel, Cav2.1. The exact mechanism for disease pathogenesis may include calcium channel dysfunction and/or polyglutamine protein associated toxicity [10].

C. SCA13: Mutations in *KCNC3*, the gene encoding the Kv3.3 potassium channel, either suppress currents or alter channel gating in a dominant-negative manner [11]. The SCA13 mutations in Kv3.3 also reduce neuronal excitability in a zebrafish model of disease [12].

D. SCA15/16: Mutations in the inositol 1,4,5-triphosphate receptor, an intracellular ligand gated calcium channel, underlie this disorder. Decreased modulation of Purkinje neuron intrinsic firing by excitatory synaptic input is described in a mouse model of disease [13].

E. SCA19/22: Loss of function mutations in Kv4.3 cause ataxia [14, 15]. The physiologic basis for this recently identified cause of SCA is unclear.

F. SCA27: Although SCA27 does not result from an ion-channel mutation, the causative FGF14 mutations likely result in perturbed expression of voltage-gated sodium channels in cerebellar neurons [16].

3. Signal transduction

Although alterations in cellular signal transduction likely play a role in the majority of ataxias, mutations in signal transduction molecules are the direct cause of disease in SCA11, SCA12, SCA14 and SCA23.

A. SCA11: Results from loss of function mutations in TTBK2, a casein kinase 1 family member. Recent work has implicated this kinase as a dedicated regulator of the initiation of ciliogenesis [17].

B. SCA12: Results from a CAG repeat expansion in the 5’-untranslated region of protein phosphatase, PP2A. The mechanism for disease pathogenesis likely shares common features with the other non-coding repeat disorders.

C. SCA14: Results from mutations in a serine-threonine family kinase, a protein kinase C isoform, that is highly enriched in Purkinje neurons. In a mouse model of disease, mutant PKCgamma reduced long term depression at parallel fiber-Purkinje cell synapses and increased slow EPSC amplitude [18].

D. SCA23: Mutations in PDYN, the precursor protein for the opioid neuropeptides, α-neoendorphin, and dynorphins A and B (Dyn A and B) cause SCA23. Cellular models of disease suggest that alterations in Dyn A activities and/or impairment of secretory pathways by mutant PDYN may lead to glutamate neurotoxicity, underlying Purkinje cell degeneration and ataxia [19].

4. Non coding repeats/ RNA toxicity

This is the likely mechanism of pathogenesis in SCA8, SCA10, SCA31 and SCA36. The putative mechanism of disease includes [20]

1. Transcriptional alterations and the generation of antisense transcripts
2. Sequestration of mRNA-associated protein complexes that lead to aberrant mRNA splicing and processing
3. Alterations in cellular processes, including activation of abnormal signaling cascades and failure of protein quality control pathways

GENOMICS

1. **Anticipation:** The polyglutamine ataxias show the phenomenon of anticipation, where disease onset is seen earlier in successive generations. This occurs due to germ line CAG repeat instability leading to additional repeat expansion. SCA7, for example, has marked anticipation of approximately 20 years/generation [21].
2. **Association with other neurological disorders:** Intermediate-length polyQ expansions (27–33 glutamines) in ATXN2 are significantly associated with amyotrophic lateral sclerosis (ALS) [22]. Ataxin 2 acts as a modifier of TDP-43 toxicity, a protein thought to be critical for ALS pathogenesis, in animal and cellular models. ATXN2 and TDP-43 associate in a complex that depends on RNA.

DISEASE MODELS

The autosomal dominant spinocerebellar ataxias disorders have been studied in cultured cells, animal models, and, most recently, in human inducible pluripotent stem cell derived neurons.

1. **Cultured cells:** Mutations have been studied in both cultured neurons and non-neuronal cell lines.
2. **Animal models:** Various animal models of these disorders exist and include mouse, zebrafish, and fly models of disease that are summarized in Table 2.
3. **Inducible pluripotent stem cell derived neurons:** Patient-derived cells lines have been generated for SCA3 [23].

EVALUATION AND MANAGEMENT

The evaluation and management of a patient with spinocerebellar ataxia involves the rapid identification of any treatable etiologies and, once those are excluded, an efficient and systematic search for a genetic cause, coupled with symptomatic therapies to minimize functional loss.

Clinical Examination and Diagnostic Testing

- A detailed neurological assessment with careful attention to the examination of coordination, sensation (especially proprioception), and vestibular function is essential to the diagnosis of an ataxia (see Box 1) [3, 4].
- Examination must include a careful evaluation of the movements of the eyes for errors in targeting, tracking, dysmetria, or nystagmus.
- Speech may be dysarthric, typically with a scanning quality.

- Ataxia must be defined as either sporadic or familial. Sporadic cases typically favor an acquired process, which should be prioritized for initial testing (see Figure 1) as this has the greatest potential for effective treatment.
- In sporadic cases, once acquired conditions are excluded, genetic and idiopathic disorders represent the next line of investigation.
- A familial history of ataxia necessitates earlier consideration of genetic etiologies, however acquired processes must still be adequately explored (see Figure 1).
- The tempo of disease onset and progression can be very helpful in the prioritization of acquired etiologies for subsequent testing (see Table 3).
- Idiopathic disorders, of which multiple system atrophy is the most likely to present initially with ataxia,[3, 4, 24] remain diagnoses of exclusion and should not be made unless a reasonable exploration of acquired and genetic etiologies has first been pursued.
- For cerebellar ataxia, magnetic resonance imaging of the brain is the initial diagnostic test of choice [3, 4, 25, 26]. Imaging is critical to assess for the presence of cerebellar atrophy (see Figure 2) as well as for the presence of any identifiable evidence of structural or vascular damage (e.g., stroke, tumor, etc.) [27] and/or other lesions or associated neurodegeneration which could be diagnostically useful (e.g., white matter hyperintensities, atrophy of the brainstem or spinal cord, loss of transverse pontine fibers, etc.) [4, 25, 26].
- Subsequent laboratory and diagnostic studies for acquired causes of cerebellar ataxia should be performed in a stepwise fashion and tailored to the presentation of the individual patient (see Figure 1).

Genetic testing

- Careful attention must be paid to clinical phenotype. In general, the autosomal dominant spinocerebellar ataxias (SCAs) show phenotypic heterogeneity,[1, 3, 4] however certain clinical features can aid in the prioritization of disorders for genetic testing (e.g., seizures in SCA10, parkinsonism in SCA3, or dementia in SCA17; see Table 1).
- Ethnicity and geographic origin should also be considered, as several SCAs are more common in specific populations (e.g., SCA3 in Brazil or DRPLA in Japan) [1, 4, 28]. Worldwide, the most common SCA is SCA3, which together with SCA1, SCA2, SCA6, and SCA7 comprise 50% of all dominant ataxias [1, 28, 29]. In late onset cases (onset greater than age 50), SCA6 and Fragile X tremor/ataxia syndrome are most frequent [1, 3, 4].
- Genetic testing should be performed in a stratified fashion based on phenotype (see Figure 3). In sporadic cases, it may be reasonable to screen for the most common autosomal dominant spinocerebellar ataxias, however widespread screening should be avoided as the diagnostic yield is disproportionally low relative to the cost of testing [1, 4, 30].
- Autosomal recessive disorders, particularly late-onset variants of Friedreich ataxia, become a consideration in sporadic patients from small families,[31, 32] complicating diagnostic testing (see Figure 3).
- Newer genome-wide methods of sequencing technology may alleviate a majority of testing problems and become a staple for future testing algorithms (see Box 2, Figure 3)[33, 34].

Box 2

Clinical Exome Sequencing

Recent advances in DNA sequencing technology have made it possible to rapidly and cheaply sequence large amounts of DNA, including whole genomes [38, 39]. Sequencing of the 1–2% of the genome expressed as protein (known as the exome) can examine the approximately 20,000 genes in the human genome simultaneously to localize protein-altering sequence variation, and is expected to dramatically impact the evaluation of neurogenetic disease [33, 34, 39]. Although unable to detect mutations caused by repeat expansion, noncoding variation, or large deletions/duplications [34], with regard to cerebellar ataxia, there are already key examples illustrating the use of this technology in the identification of new ataxia genes, [40, 41] the detection of novel mutations, [42, 43] and the diagnosis of patients with clinically heterogeneous spinocerebellar phenotypes [44]. Questions still remain regarding how best to bioinformatically process these large amounts of sequence information to identify pathogenic variants in individual patients, particularly those involving novel mutations and genes, but there is little doubt that this technology will see widespread clinical use in the immediate future [33, 34].

Current Management and Therapeutic Options

- Many of the acquired causes of cerebellar ataxia (see Figure 1) can be treated or modified, emphasizing the need for prompt recognition to minimize damage to the cerebellum and its associated pathways [4].
- Paraneoplastic and other autoimmune mediated ataxias are particularly important to consider since, if left unchecked, rapid and severe damage to the cerebellum can result and, unfortunately, current treatments are often less than fully effective [4, 35].
- No cures or effective treatments yet exist for genetic or idiopathic ataxias and treatment is therefore wholly symptomatic, however, exercise therapy has been shown to be beneficial in maintaining patient function over time and should be employed for all patients [36, 37].

SUMMARY

The autosomal dominant spinocerebellar ataxias (the SCAs) are late onset progressive degenerative disorders that may be categorized into repeat disorders, disorders of ion-channel dysfunction, and disorders of signal transduction molecules. The identification of additional genes and the development of better cellular and animal model systems of disease pathogenesis continue to advance understanding and suggest new avenues for better diagnosis and potential intervention. Due to the considerable clinical overlap between these disorders and other acquired causes of ataxia, the evaluation of patients with cerebellar ataxia must first include an investigation into potentially treatable causes. If genetic testing is considered, it is best to take a tiered approach, with initial testing including the most common dominant genes, namely SCA1, SCA2, SCA3, SCA6, SCA7 and, in sporadic cases, Friedreich ataxia, the most common recessive cause. Management is mainly supportive, but exercise therapy has been shown to be beneficial in maintaining patient function over time.

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KEY POINTS

- The SCAs or spinocerebellar ataxias are aheterogeneous group of dominantly inherited disorders, the most common of which are SCA1, SCA2, SCA3, SCA6 and SCA7, all of which result from glutamine encoding repeats in the respective genes.
- The polyglutamine ataxias tend to be “ataxia-plus” disorders with extrapyramidal symptoms, long tract signs and cranial nerve dysfunction and have a poorer prognosis. In addition to polyglutamine ataxias, other molecular mechanisms for ataxia include ion-channel dysfunction, disordered signal transduction, and non-coding repeats.
- Advances in DNA sequencing technologies, including whole exome sequencing, are expected to improve the diagnosis of genetic ataxias.
- Animal models of disease recapitulate many of the key features of the human disease and may be good model systems to test therapies.
- Current management for the SCAs is mostly supportive. However, exercise therapy has been shown to be beneficial in maintaining patient function over time
- and should be employed for all patients.

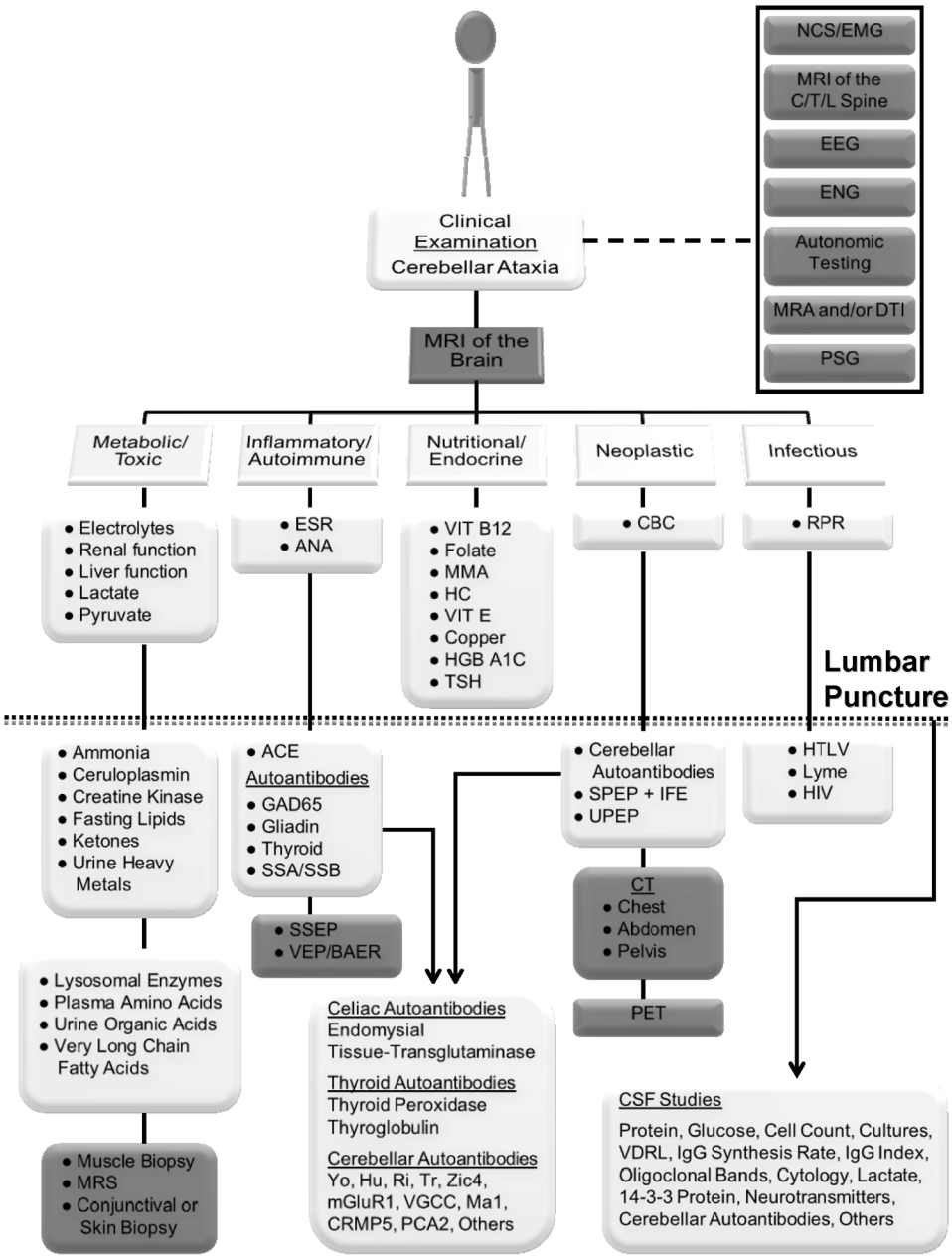

Figure 1. Diagnostic evaluation of an acquired cerebellar ataxia

All patients with clinically identified cerebellar ataxia should have an MRI of the brain performed to assess for masses, vascular lesions/anomalies, traumatic injury, and/or structural problems in addition to evidence of neurodegeneration and/or white matter changes. Additional diagnostic studies (gray boxes) should be performed as warranted based upon the clinical examination (dashed line). If the MRI does not reveal the cause, then laboratory tests (white boxes) should be performed systematically as indicated. Studies are listed under the heading of the class of disorders they most often identify. Note that some tests could identify disorders in more than one class. In a complete evaluation, a patient should receive, at a minimum, all studies listed above the dotted line. Items listed below the dotted line are chosen for more in-depth evaluation of specific etiologies and not all patients may require all studies. The dotted line represents the threshold for performing a lumbar

puncture in a patient undergoing initial workup. Suggested cerebral spinal fluid studies are indicated (arrow). Specific cerebellar (paraneoplastic), celiac, and thyroid autoantibodies are also shown (arrow). Note that there are additional rare acquired causes of cerebellar ataxia which are not listed in this figure.

Abbreviations: ACE = angiotensin converting enzyme, ANA = antinuclear antibodies, BAER = brainstem auditory evoked response, CBC = complete blood count, C/T/L = cervical, thoracic, and/or lumbar, CSF = cerebral spinal fluid, CT = computed tomography, DTI = diffusion tensor imaging, EEG = electroencephalogram, EMG = electromyogram, ENG = electronystagmogram, ESR = erythrocyte sedimentation rate, GAD = glutamic acid decarboxylase, HC = homocysteine, HGB = hemoglobin, HIV = human immunodeficiency virus, HTLV = human T-lymphotropic virus, IFE = immunofixation electrophoresis, MMA = methylmalonic acid, MRI = magnetic resonance imaging, MRA = magnetic resonance angiography, MRS = magnetic resonance spectroscopy, NCS = nerve conduction study, PET = positron emission tomography, PSG = polysomnogram, RPR = rapid plasma reagin, SSA/SSB = Sjögren's syndrome antigen, SPEP = serum protein electrophoresis, SSEP = somatosensory evoked potentials, TSH = thyroid stimulating hormone, UPEP = urine protein electrophoresis, VDRL = venereal disease research laboratory test, VEP = visual evoked potential, VIT = vitamin.

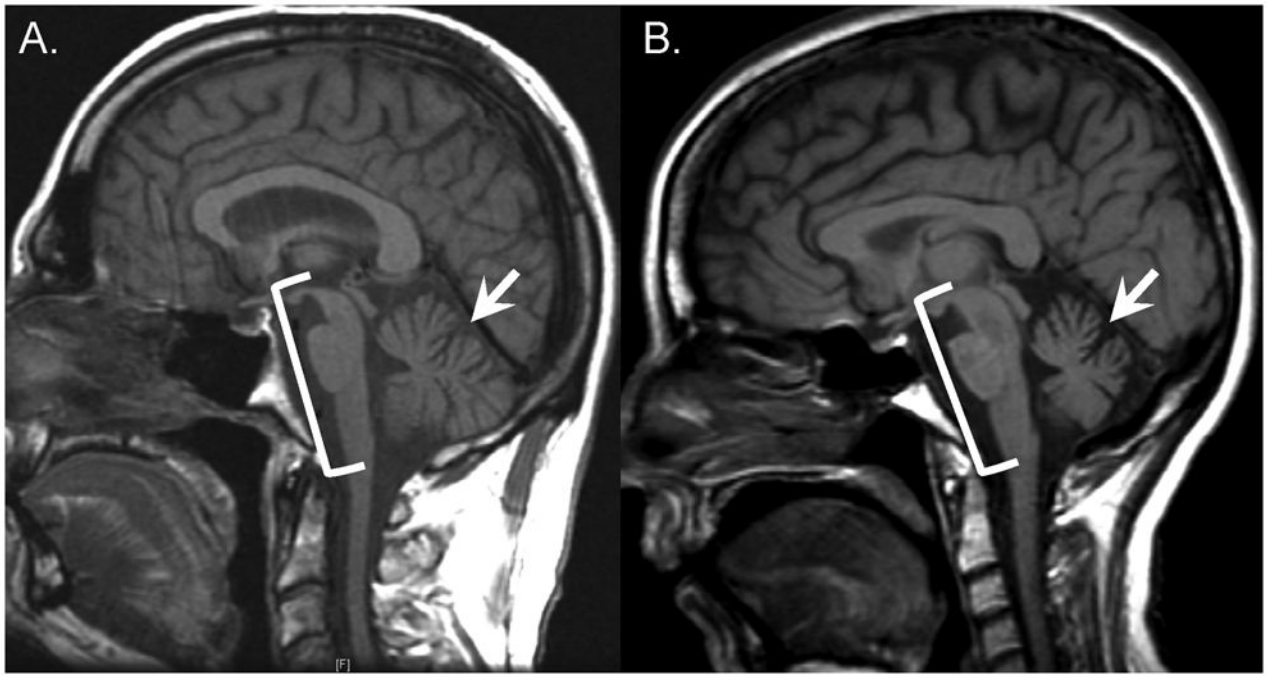

Figure 2. MRI Findings in Spinocerebellar Ataxia

Sagittal T1-weighted magnetic resonance imaging is shown for a patient with A) Spinocerebellar Ataxia Type 3 (SCA3) and B) Multiple System Atrophy (MSA). Cerebellar atrophy (arrow) and brainstem atrophy (bracket) are noted. Note the similarity in imaging characteristics between these patients as this is common among the different ataxia etiologies (i.e., acquired, hereditary, and idiopathic).

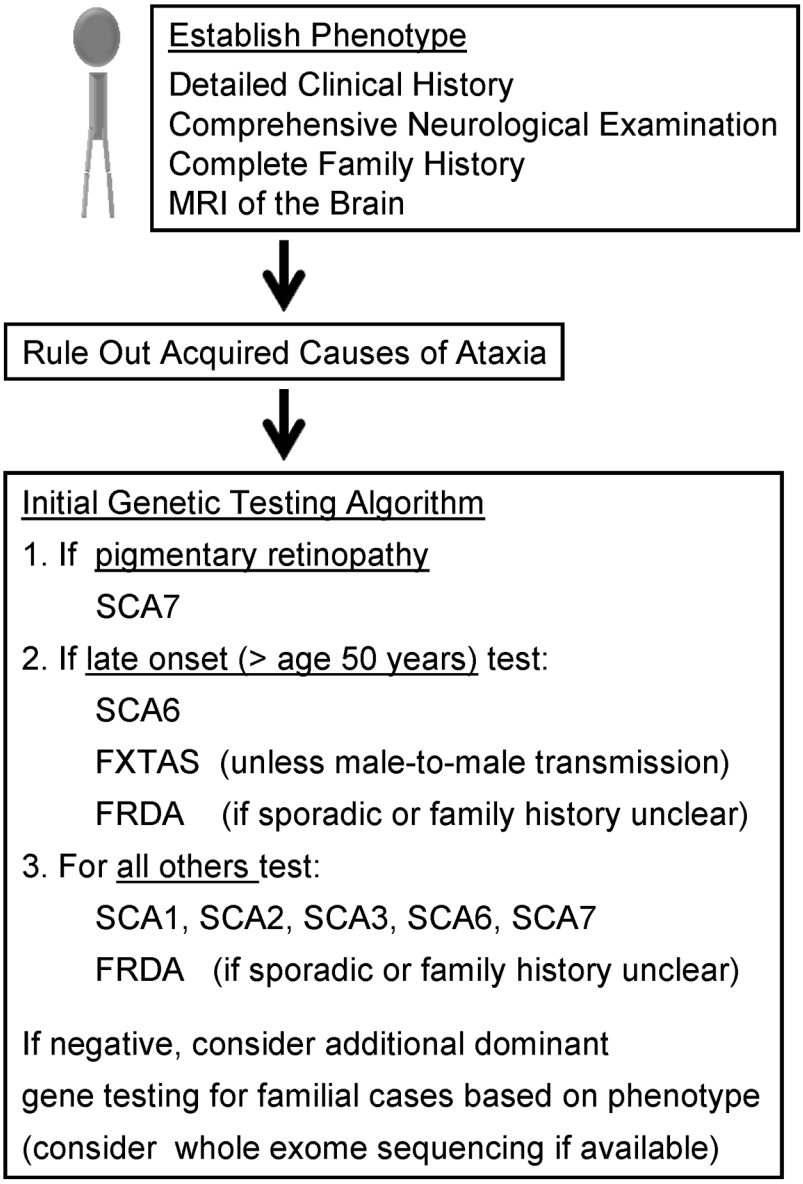

Figure 3. Diagnostic evaluation of a genetic cerebellar ataxia

Abbreviations: FRDA = Friedreich ataxia, FXTAS = Fragile X tremor/ataxia syndrome, SCA = spinocerebellar ataxia.

Table 1

Summary of genes, mutations, and clinical features of autosomal dominant spinocerebellar ataxias.

Name	Locus/ Gene	Protein/Mutation[a]	Normal function[b]	Year[c]	Pathology[d]	Symptoms/ Signs[e]
SCA 1	6p23/ *A TXN 1*	Ataxin 1 CAG repeats 41–81 (normal 25–36)	Gene transcription and RNA splicing	1994	Inferior olivary nuclei Pontine nuclei Purkinje cells	**Pyramidal signs** Amyotrophy Extrapyramidal signs Ophthalmoparesis
SCA 2	12q24/ *A TXN 2*	Ataxin 2 CAG repeats 35–59 (normal 15–24)	RNA processing	1996	Basis pontis Inferior olivary nuclei Purkinje cells	**Slow saccades** Extrapyramidal signs Dementia (rarely) Ophthalmoplegia Peripheral neuropathy Pyramidal signs
SCA 3 (Machado–Joseph Disease/ MJD)	14q24.3-q31/ *ATXN 3*	Ataxin 3 CAG repeats 62–82 (normal 13–36)	Debuiqutinating enzyme involved in protein quality control	1994	Anterior horn cells Clarke's columns Dentate nuclei Dorsal root ganglia Pontine nuclei Purkinje cells Spinocerebellar tracts Substantia nigra Subthalamic nuclei	**Pyramidal signs** Amyotrophy Exophthalmos Extrapyramidal signs Ophthalmoparesis
SCA4	16q22.1/ distinct from SCA31	Unknown	Unknown	--	Unknown	**Sensory axonal neuropathy** Pyramidal signs
SCA5	11q13/ *SPTBN2*	β III Spectrin	Scaffolding protein important for glutamate signaling	2006	Unknown	**Pure cerebellar ataxia** (late onset) Pyramidal signs (early onset)
SCA6	19p13.2/ *CACNA1A*	Cav2.1 CAG repeats 21–30 (normal 6–17)	Calcium channel important for regulating Purkinje neuron excitability	1997	Purkinje cells	**Pure cerebellar ataxia** Late onset, usually >50 years
SCA7	3p21.1-p12	Ataxin 7 CAG repeats 38–130 (normal 7–17)	Gene transcription	1997	Cone-rod dystrophy Dentate nuclei Inferior olivary nuclei Pontine neurons Purkinje cells Retinal ganglion cells	**Pigmentary macular degeneration** Ophthalmoplegia Pyramidal signs
SCA8	13q21.33/ *ATXN8OS ATXN8*	Toxic RNA/ CAG repeats	Unknown	1999	Purkinje cells Substantia nigra	**Pyramidal signs** Diminished vibratory sense Spastic and ataxic dysarthria
SCA9	Unknown	Unknown	Unknown	--	Unknown	Central demyelination (one patient) Extrapyramidal signs Ophthalmoplegia Posterior column loss Pyramidal tract signs

Name	Locus/ Gene	Protein/Mutation[a]	Normal function[b]	Year[c]	Pathology[d]	Symptoms/ Signs[e]
SCA10	22q13.31/ *ATXN10*	Intronic ATTCT repeats	Involved in neuron survival, neuron differentiation, and neuritogenesis	2000	Unknown	**Seizures** Cognitive/neuropsychiatric impairment Polyneuropathy Pyramidal signs
SCA11	15q15.2/ *TTBK2*	Tau tubulin kinase-2	Serine-threonine kinase that putatively phosphorylates tau and tubulin proteins Regulates the genesis of the primary cilium	2007	Unknown	**Pure cerebellar ataxia**
SCA12	5q32/ *PPP2R2B*	Protein phosphatase PP2A CAG repeats in 5'-UTR 51–78 (normal 7–32)	Serine-threonine phosphatase implicated in the negative control of cell growth and division	1999	Unknown	**Upper extremity tremor** Mild or absent gait ataxia Hyperreflexia
SCA13	19q13.3–13.4/ *KCNC3*	Kv3.3	Potassium channel involved in regulating Purkinje neuron excitability	2006	Unknown	**Intellectual disability** (in French pedigree) Pure cerebellar ataxia (in Filipino pedigree)
SCA14	19q13.4/*P RKCG*	Protein Kinase C Gamma	Neuronal serine/threonine protein kinase activated by calcium and diacylglycerol	2003	Unknown	**Pure cerebellar ataxia** Rarely chorea and cognitive deficits
SCA15/SCA16	3p26.1/ *ITPR1*	Inositol 1,4,5-triphosphate receptor	Intracellular calcium channel involved in regulating neuronal excitability	2007	Unknown	**Pure cerebellar ataxia** Rare tremor or cognitive impairment
SCA17/ Huntington disease like 4 (HDL4)	6q27/ *TBP*	TATA box-binding protein CAG repeats 46–63 (normal 25–42)	Gene transcription	2001	Neuronal inclusion bodies in brain Purkinje cells Reduction in brain weight	**Chorea** Dementia Extrapyramidal features Hyperreflexia Psychiatric symptoms
SCA18 Sensorimotor Neuropathy with Ataxia/ SMNA	7q22-q32	Unknown	Unknown	--	Unknown	**Posterior column loss** Amyotrophy Early onset, usually <20 years Hyporeflexia
SCA19/SCA22	1p13.3/ *KCND3*	Kv4.3	Potassium channel involved in regulating neuronal excitability	2012	Unknown	**Pure cerebellar ataxia** Cognitive impairment Myoclonus Postural tremor
SCA20	11p11.2-q13.3/gene duplication	Unknown	Unknown	--	Dentate nucleus calcification	**Spasmodic dysphonia or spasmodic coughing** Palatal tremor
SCA21	7p21.3-p15.1	Unknown	Unknown	--	Unknown	Akinesia Cognitive impairment Dysgraphia Early onset Hyporeflexia Postural tremor

Name	Locus/ Gene	Protein/Mutation[a]	Normal function[b]	Year[c]	Pathology[d]	Symptoms/ Signs[e]
						Resting tremor Rigidity
SCA23	20p13/ *PDYN*	Prodynorphin	Processed to form secreted opioid peptides that serve as ligands for the kappa- type opioid receptor	2010	Cerebellar vermis Cerebellopontine tracts Dentate nuclei Demyelination of posterior and lateral columns (1 patient) Inferior olivary nuclei	**Late onset**, usually >50 years Decreased vibratory sense
SCA25	2p21-p15	Unknown	Unknown	--	Unknown	Areflexia Peripheral sensory neuropathy
SCA26	19p13.3	Unknown	Unknown	--	Unknown	Pure cerebellar ataxia
SCA27	13q34/ *FGF14*	Fibroblast growth factor 14	Interacts with voltage-gated sodium channels and regulates Purkinje neuron excitability	2003	Unknown	**Orofacial dyskinesias** Cognitive impairment Tremor
SCA28	18p11.22-q11.2/ *AFG3L2*	ATPase family gene 3-like 2	Mitochondrial protein synthesis	2010	Unknown	**Early onset**, usually <20 years Hyperreflexia Ophthalmoparesis Ptosis
SCA29	3p26	Unknown	Unknown	--	Unknown	**Congenital** Nonprogressive
SCA30	4q34.3-q35.1	Unknown	Unknown	--	Unknown	Late onset, usually >50 years Pure cerebellar ataxia
SCA31	16q22/ *BEAN1* and *TK2*	Brain expressed, associated with NEDD4 Thymidine Kinase2 TGGAA repeat in intron shared by both genes	Unknown	2009	Purkinje cells	**Pure cerebellar ataxia** Late onset, usually >50 years Sensorineural hearing loss
SCA35	20p13/ *TGM6*	Transglutaminase 6	Post-translational modifications of glutamine residues	2010	Unknown	**Pyramidal signs** Psuedobulbar palsy
SCA36	20p13/ *NOP56*	Nucleolar protein 56 Intronic GGCCTG repeat	Pre-mRNA processing	2011	Dentate nuclei Hypoglossal nucleus Motor neurons Purkinje cells	**Lower motor neuron involvement** Tongue atrophy
DRPLA (Dentato-Rubral Pallidoluysian Atrophy)	12p13.31/ *ATN1*	Atrophin 1 CAG repeats 49–75 (normal 7–23)	Transcriptional co- regulator	1994	Cerebellar white matter Dentate nuclei Globus pallidus Red nucleus Subthalamic nucleus	**Myoclonic epilepsy** Choreoathetosis Dementia

[a] Mutation refer to point mutations in the respective genes, unless otherwise specified.

[b] The normal function of all proteins has not been fully established.

[c] Year refers to initial year of publication of the identified gene.

[d] Pathology refers to loss of neurons in the indicated regions.

[e] Not all patients will have the symptoms/signs that are mentioned. Bold typeface refers to symptoms either characteristic or unique to the particular SCA and thus helpful to diagnosis.

Table 2

Animal models of SCA.

Name	Type of model[a]	Phenotype	Pathology	Selected Therapy Trials
SCA1	Transgenic-(Purkinje neuron specific), 82Q [s1]	Motor incoordination	Shrinkage and marked loss of Purkinje neurons	shRNA [s3]
	Knock-in, 154Q [s2]	Cognitive impairment Kyphosis Motor incoordination Premature death Weight loss	Mild loss of Purkinje neurons	Lithium [s4] Vascular Endothelial Growth Factor (VEGF) [s5]
SCA2	Transgenic 58Q and 127Q (Purkinje neuron specific) [s6]	Motor incoordination	Shrinkage and mild loss of Purkinje neurons	Dantrolene [s7] SK channel activator [s8]
SCA3 (Machado–Joseph Disease/ MJD)	Transgenic (many models including 79Q[s9], 148Q [s10], 71Q [s11], 94Q [s12], 77Q [s13])	Motor incoordination Premature death	Variable shrinkage and mild neuronal loss	Sodium butyrate [s19]
	Yeast Artificial Chromosome Transgenic [s14–16]	Motor incoordination	Mild and late loss of brain stem and cerebellar neurons	Dantrolene [s15]
	Rat model-lentiviral injection and overexpression of mutant ataxin-3 in the striatum or substantia nigra [s17]	Circling behavior following unilateral substantia nigra injection	Fluorojade positive neurons and cell shrinkage	shRNA [s20]
	Fly eye [s18]	Loss of ommatidia		
SCA5	Knock-out [s21]	Motor incoordination	Shrinkage and mild loss of Purkinje neurons	
SCA6	Knock-in 84Q [s22]	Motor incoordination	Very mild Purkinje neuron loss	
SCA7	Transgenic [s23]	Motor incoordination	Mild Purkinje neuron loss	
SCA8	Klh1 deletion [s24]	Motor incoordination	Purkinje neuron shrinkage	
SCA10	Transgenic 500 repeats in 3’ UTR [s25]	Motor incoordination Seizure susceptibility	Loss of CA3 hippocampal neurons	
SCA13	Knockout [s26]	Motor incoordination	No neuronal loss	
	Zebrafish R420H human mutation [s27]		No neuronal loss	
SCA14	Transgenic H501Y [s28]	Abnormal clasping	Altered Purkinje neuron morphology	
SCA15/SCA16	Knockout [s29]	Motor incoordination Seizures	No neuronal loss	
SCA17/ Huntington disease like 4 (HDL4)	Transgenic 109Q [s30]	Motor incoordination	Loss of Purkinje neurons	

Name	Type of model[a]	Phenotype	Pathology	Selected Therapy Trials
SCA27	Knockout [s31]	Cognitive deficits Motor incoordination	No neuronal loss	
DRPLA	Transgenic variable repeat length 76Q- 129Q [s32]	Cognitive deficits Motor incoordination Premature death	Purkinje neuron shrinkage and progressive brain atrophy	

[a] Refers to mouse models unless otherwise specified.

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Table 3

Using the tempo of disease onset and progression to aid diagnosis.

Symptom Onset/Progression	Etiologies to Consider*
Episodic (Minutes to Hours)	Genetic Inflammatory Toxic Vascular
Acute (Hours to Days)	Infection Metabolic Toxic Trauma Vascular
Subacute (Weeks to Months)	Autoimmune Infection Inflammatory Neoplastic Paraneoplastic
Chronic (Months to Years)	Autoimmune Degenerative Genetic Inflammatory Metabolic Neoplastic Paraneoplastic
Static (Years to Decades)	Congenital Cerebellar Injury (any source)

*Not a comprehensive list.