Adult-Onset Cerebellar Ataxias

Adult-onset cerebellar ataxias have overlapping phenotypes and diverse causes; tiered testing is a useful diagnostic framework.

By Pravin Khemani, MD

The objective of this review is to provide clinical neurologists with practical tips for the evaluation and treatment of adult-onset cerebellar ataxias. These conditions can be challenging to diagnose, owing to overlapping phenotypes from diverse etiologies. The overarching physical finding of "ataxia," derived from the Greek "lack of order," is universally seen in this group of diseases, yet is more a descriptive term unifying a constellation of findings than a specific diagnosis. After gaining familiarity with common and uncommon ataxia presentations, the diagnostic process can be assisted by the medical history and clinical features, as with any neurologic condition. A comprehensive and detailed review of all cerebellar ataxias, a topic that can fill textbooks, is not within scope of this review; however, the information provided generates a framework for evaluating ataxias to make diagnosis less daunting.

Cerebellar Anatomy and Physiology

Although it comprises just 10% of brain volume, the cerebellum accounts for 80% of brain surface area and close to 50% of the brain's neurons—truly a marvel of anatomic packaging.[1] Complex microanatomy and interconnectedness of the cerebellum with all areas of the brain integrate sensory input for accurate motor and nonmotor planning to produce precise actions. In addition, the cerebellum modulates cognition and emotion.[2] On brain MRI, there are 3 functional somatotopic cerebellar regions easily identified; these are often affected in cerebellar ataxias (Figure). Cerebellar lesions lead to a mismatch between intended and executed movement, producing common signs of ataxias.

Symptoms and Signs of Ataxias

Individuals with cerebellar disorders report difficulty with walking and balance, falls, dizziness, blurred or double vision, slurred speech, clumsiness, poor penmanship, knocking objects over when reaching for them, and tremors. Cerebellar signs include impaired cancellation of the vestibuloocular reflex (VOR), nystagmus, dysarthria, limb tremor, axial tremor (titubation), dysmetria, and limb and gait ataxia. Dyssynergia and hypotonia are not common but are identifiable in certain cerebellar diseases. Pathologic processes that disrupt cerebellar connections to the cortex underlie cerebellar cognitive affective syndrome (CCAS or Schmahmann syndrome), which

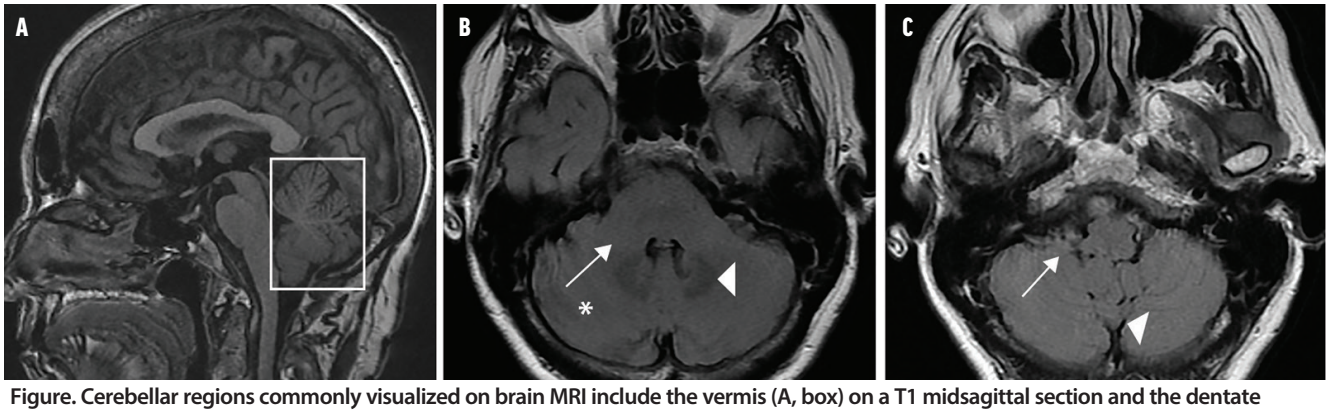

Figure. Cerebellar regions commonly visualized on brain MRI include the vermis (A, box) on a T1 midsagittal section and the dentate nucleus (B, arrowhead), middle cerebellar peduncle (B, arrow), lateral hemisphere (B, *), flocculus (C, arrow), and nodulus (C, arrowhead) on axial fluid-attenuated inversion recovery (FLAIR) sequences. Lesions of the vermis cause head, trunk, and stance ataxia. Lesions in the lateral hemispheres and cerebellar nuclei cause limb or apendicular ataxia, dysarthria, and cerebellar cognitive affective syndrome (CCAS). Flocculonodular lobe lesions cause oculomotor and vestibular signs (eg, nystagmus and Romberg sign).

manifests as impaired executive functioning, visuospatial difficulties, expressive language errors, blunted affect, and disinhibited behavior.[2] The frequency and presence of ataxic signs is variable. In severe or advanced stages, individuals with cerebellar ataxia may become anarthric and dysphagic, and require the use of a wheelchair for mobility.

Acute cerebellar lesions (eg, strokes) may be precisely localized and identified by neuroimaging, owing to functional disruption in specific vascular territories compared with neurodegenerative ataxias that cause more widespread and progressive cellular damage. Because cerebellar symptomatology overlaps despite dissimilar etiology, the importance of a detailed history and thorough neurologic examination, including use of a standardized rating instrument (eg, the Scale for Assessment and Rating of Ataxia [SARA]) cannot be overstated.[3]

Ataxia Classification

Cerebellar ataxias may be broadly classified as acquired, genetic, or sporadic based on the underlying pathologic process (Table 1). Although most genetic ataxias are chronic and progressive, the episodic ataxias (EA), which are genetic, may present as specifically triggered discrete events interspersed with symptom-free intervals.

Sporadic ataxias include multiple system atrophy (MSA), which is subdivided into a cerebellar subtype (MSA-C) and a parkinsonism subtype (MSA-P)), and idiopathic late-onset cerebellar ataxia (ILOCA). MSA-C is a neurodegenerative α-synucleinopathy characterized by dysautonomia and cerebellar deficits.[4] As either subtype of MSA progresses, both parkinsonian and cerebellar signs are present (See also *Atypical Parkinsonian Syndromes* in this issue).

TABLE 1. TYPES OF ATAXIAS

Type (presentation)	Mechanisms
Acquired (acute or subacute)	Vascular and structural lesions
	Infectious, parainfectious (eg, acute cerebellitis, inflammatory, or immune-mediated
	Substrate deficiency (vitamin B_1, B_{12}, E or A)
	Toxin or drug induced
Genetic (hereditary; chronic, slowly progressive)	Autosomal dominant spinocerebellar ataxia (SCA) 1-49
	Autosomal recessive cerebellar ataxia (ARCA)
	Episodic ataxia
	Mitochondrial ataxia
	X-linked ataxia
Sporadic (subacute or chronic)	Idiopathic late-onset cerebellar ataxia
	Multiple system atrophy

ILOCA is somewhat of a "waste-basket" diagnostic category, capturing all ataxias without a discernible etiology despite a thorough evaluation. With periodic genetic testing and clinical follow-up, people diagnosed with ILOCA may eventually be diagnosed with a hereditary ataxia or MSA-C.[5]

Diagnostic Approach

The rate of ataxia progression, from onset of symptoms to maximal deficit, is a clue to whether the ataxia is acquired, genetic, or sporadic (Table 2). Acquired ataxias typically present acutely and progress rapidly from vascular, immune-mediated, infectious, and toxic causes. Substrate deficiencies (eg, vitamin B_1, B_{12}, E or A) and iatrogenic insults, except acute drug overdoses, present subacutely. Unless there is a known family history, adult-onset genetic ataxias may not present to the neurologist until later in the disease course because of their insidious onset and slow progression. MSA-C progresses much more rapidly than ILOCA and genetic ataxia and causes significant disability in a short time, with death occurring 6 to 10 years after symptom onset. MSA is diagnosed as clinically probable, clinically established, or neuropathologically established in order of increasing specificity by clinical criteria guidelines.[5]

Table 2 shows a rational diagnostic approach to ataxias based on clinical presentation and potential etiology. Although tests are labeled as first-, second-, and third-line options based on acuity, the order of testing must match the clinical scenario. Additionally, not all tests from each tier need to be done for every person with cerebellar ataxia. Brain, and sometimes spinal cord, MRI is recommended for all ataxias considering the high diagnostic value of MRI for diverse types of ataxias.

Acute and Subacute Ataxias

Acute and subacute ataxias can typically be identified with neuroimaging, serum and cerebrospinal fluid (CSF) markers, and common ancillary tests. Prompt recognition of acquired ataxias (Table 1) is important because specific treatments are available and delaying treatment may cause irreversible neurologic damage.

Inflammatory and Immune-Mediated Ataxias. Paraneoplastic-, gluten-, glutamic acide decarboxylase (GAD65)-ataxias and steroid-responsive encephalopathy and ataxia (SREAT) are antibody-associated.[6] Ataxias may also be secondary to connective tissue diseases (eg, systemic lupus erythematosus [SLE], Sjogren syndrome, and sarcoidosis) and multiple sclerosis (MS) owing to the centrality of the immune system in pathogenesis.

Diagnosing gluten ataxia requires a high degree of suspicion because diagnostic tests are known to be unreliable, and presentations can be atypical.[7] Serum levels of antiGAD65 are not specific for the neurologic syndrome, and CSF levels must be obtained. Although not all paraneoplastic antibodies result in ataxia, a comprehensive panel may be cheaper than individual antibody tests. Because new antibodies are

TABLE 2. DIAGNOSTIC TESTING FOR ATAXIA

Clinical presentations of ataxia	Acute (sudden onset, rapid progression)	Subacute (indidious onset, progression days to months)[a]	Chronic (gradual onset, progression months to years)[a]
Diagnostic tests	**Type of ataxia**		
	Acquired		**Sporadic[b] or genetic**
MRI studies: Brain (with contrast if high suspicion for infectious, inflammatory, or neoplastic etiology) then head/neck MR angiography if brain MRI warrants, or cervical and spine MRI if myelopathic or pyramidal signs not explained by MRI findings (for all 3 presentations)			
First-line diagnostic studies			
Blood chemistry and blood cell count with differential; vitamins B_1, B_{12}, E, and folate; methylmalonic acid, thyroid stimulating hormone (TSH); rapid plasma reagin (RPR); HIV; heavy metal, prescription drug, and, if acute setting, alcohol levels; antiGQ1, reverse transcriptase polymerase chain reaction (rtPCR) for SARS-CoV-2; viral encephalitis panel	High yield in metabolic, infectious, inflammatory, immune mediated ataxia		Low yield in chronic ataxia unless high suspicion based on clinical course and neuroimaging
Urine toxicology			
Cerebrospinal fluid (CSF) protein, cell count with differential, angiotensin converting enzyme (ACE), IgG synthesis, index, and rate; viral encephalitis panel			
12-lead ECG and echocardiography, chest x-ray or CT			
Second-line diagnostic studies			
Serum antibodies: antinuclear antigens (ANA), paraneoplastic, gluten, glutamic acid decarboxylase 65 (GAD65), thyroid peroxidase (TPO), human T-lymphotropic virus type (HTLV) 1 & 2, *T. whipplei*, *Listeria*; test for prions with real-time quaking-induced conversion (RT-QUIC)	Informed by clinical course, neuroimaging, and first-line tests		Low yield in chronic ataxia unless high suspicion based on clinical course and neuroimaging
Chest, abdomen, and pelvis CT			
Third-line diagnostic studies			
Fasting blood levels of very long chain fatty acids (VLCFA), cholestanol, cholesterol panel, alpha-fetoprotein (AFP), immunoglobulins, amino acids, phytanic acid, lactate, pyruvate, albumin, lipoproteins, oxysterols, bile acids, and sphingolipids	Low diagnostic yield in the setting of acute ataxia unless clinical course or neuroimaging indicate otherwise	Consider in subacute and chronic ataxias when first- and second-line diagnostic tests are inconclusive or nondiagnostic	
Urine levels of organic acids			
Peripheral blood smear (PBS)			
Dopamine transporter (DaT) scan			
Autonomic and vestibular testing			
Ophthalmologic examination			
Polysomnography			
Electrodiagnostic studies			
Skin biopsy for abnormally phosphorylated α synuclein deposition			
Muscle biopsy (if genetic tests for mitochondrial disorders inconclusive)			
Genetic studies	Low diagnostic yield unless a clear family history of ataxia is present		High-yield

[a]Subacute vs chronic depends on symptom evolution timeline and when patient sought neurologic consultation; if history is lacking or incorrect, the diagnostic investigation needs to be broad and stratified. [b]Sporadic neurodegenerative ataxias are both diagnoses of inclusion and exclusion; evaluation for acquired treatable and genetic mimics is warranted before diagnosing other rare conditions (eg, clinically probable multiple system atrophy [MSA] or idiopathic late-onset cerebellar ataxia [ILOCA]) confidently. Recommendations for test order are based on putative ataxia mechanisms to minimize unnecessary testing but should not be followed rigidly (eg, if suspicion for genetic ataxia is high or family members have a known causative variant, it is reasonable to perform genetic testing first).

periodically discovered and implicated in cerebellar ataxia, using a standardized laboratory (eg, Mayo Clinic Labs) where a sample can be reflexed for additional testing is suggested. SREAT is a debatable diagnosis that is confirmed if neurologic symptoms resolve after solumedrol infusions in the setting of elevated thyroperoxidaase (TPO) antibodies. Screening for malignancy in high-risk individuals (eg, people who smoke or have family or prior history of neoplasm) by body CT scans is standard of care for unexplained subacute ataxias.

Infectious and Parainfectious Ataxias. Several pathogens, including those with specific antimicrobial treatment, are implicated in cerebellar ataxia and should be tested depending on the patient's risk factors (Table 2).

Toxin- and Drug-Induced Ataxias. Alcohol, recreational drugs of all kinds, certain heavy metals (eg, mercury) organic solvents (eg, toluene), and prescription medications including lithium, phenytoin, metronidazole, and chemotherapeutic agents are all associated with direct or indirect cerebellar damage. Serum and urine assays and, in certain instances, specific toxicology tests can confirm exposure. Early elimination of these agents can mitigate progressive damage.

Sporadic Ataxias

MSA is established by clinical criteria supported by ancillary tests, whereas ILOCA is more a diagnosis of exclusion.[4,5] CoQ10 deficiency has been implicated in a Japanese cohort but is not a ubiquitous cause of MSA.[9] A dopamine transporter (DaT) scan that can detect presynaptic nigrostriatal denervation has limited utility in MSA-C, especially if denervation is primarily in postsynaptic striatal neurons.[10,11] [^{123}I]metaiodobenzylguanidine myocardial scintigraphy (cardiac-MIBG) or fluorodeoxyglucose positron emission tomography (FDG-PET) are supportive tests for MSA but are not as readily available in the US as a DaT scan.[4] The Syn-one test, a skin biopsy assay for phosphorylated α-synuclein in cutaneous nerve fibers, can potentially distinguish MSA from genetic ataxia mimics.[12] Because rapid eye movement sleep behavior disorder (RBD) and central sleep apnea are common in MSA, polysomnography should be done whenever MSA is suspected. Progressive supranuclear palsy (PSP) is another sporadic neurodegenerative disorder that can mimic a chronic cerebellar ataxia in initial disease stages.[13]

Additional ancillary tests listed in the online-only Table e1 have diagnostic utility for ataxia,[14,15] including serum markers of genetic ataxias that can be used to narrow the potential causative genes for more targeted testing.

Genetic Ataxias

When there is a clear family history with a known genetic variant, multiple lines of investigation can be avoided; however, this is a rarity in clinical practice. Often, the evaluation of chronic cerebellar ataxias is expensive, extensive, and exhausting for the patient and their family members, which is why a tiered cost-effective evaluation is recommended.

Definitive diagnosis of a genetic ataxia is a pathogenic mutation correlating with the phenotype. In the appropriate clinical context, neuroimaging clues, selected ancillary tests, and certain serum markers (Table 2 and online-only Table e1) can facilitate targeted gene testing.[15-17]

Establishing the proband's pedigree by taking a detailed family history is the first step to ascertaining an inheritance pattern with the understanding that absence of family history does not exclude genetic ataxia. Pretest genetic counseling discussing the risks and benefits of genetic testing is critical. When genetic counseling is not readily available, consider referral to the nearest institution with a genetics department or contracting with a Healthcare Information and Portability Accountability Act (HIPAA)-compliant commercial entity that offers genetic counseling at affordable rates. Posttest genetic counseling for results interpretation should also be standard of care.

The number of genetic ataxias has expanded significantly with next-generation sequencing (NGS), which includes whole exome sequencing (WES) and whole genome sequencing (WGS), to the point that there are too many to memorize. Just as knowledge of diagnostic markers can refine genetic testing, there is value in knowing unique extracerebellar features of certain ataxias (online-only Table e2) to improve the accuracy of genetic testing, especially when NGS is inaccessible. A pragmatic approach to genetic testing in various clinical scenarios is shown in the online-only Figure e1. Periodic testing with updated genetic platforms is suggested if initial test results are negative before ILOCA is diagnosed.

Autosomal Dominant Ataxias. Spinocerebellar ataxia 3 (SCA3) is the most common autosomal dominant ataxia followed by SCAs 1, 2, 6, 7, 8, 10, and 12 in no specific order because prevalence varies by regional and ethnic differences.[18] SCAs are numbered in order of discovery and genetic confirmation, with SCA49 being the most recently reported.[19] Conventionally, dentatorubral-pallidoluysian atrophy (DRPLA) is included in the list of SCAs, but EAs are not, although they are inherited in a dominant manner.

Autosomal Recessive Ataxias. Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) and Friedreich ataxia (FA) are among the most common autosomal recessive ataxias, with CANVAS primarily reported after age 45.[14] Although typically associated with biallelic intronic polynucleotide expansions in the *RFC1* gene, compound heterozygotes with CANVAS have been recently reported.[20] Based on clinical features, autosomal recessive ataxias have been classified into primary ataxic or multisystemic disorders.[21]

X-Linked Ataxias. Fragile X-associated tremor/ataxia syndrome (FXTAS) is the most common X-linked ataxia in adults with a preponderance in XY heterozygotes. FXTAS is caused by a premutation in the *FMR1* gene that also causes fragile X syndrome in children when the mutation is fully expanded.

Mitochondrial Ataxias. Pathogenic variants in nuclear or mitochondrial DNA cause mitochondrial ataxias, which follow a maternal or Mendelian inheritance.[22] Expression and severity of mitochondrial ataxias varies within and in between generations owing to heteroplasmy. Common mitochondrial ataxias in adults include DNA polymerase γ (POLG1) syndromes, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and myoclonic epilepsy with ragged red fibers (MERRF).

Pitfalls of Genetic Testing. Polynucleotide expansion repeat ataxias are most commonly caused by pathogenic polyglutamine expansions. These ataxias are typically associated with anticipation recognized by earlier and more severe disease expression in subsequent generations, with a few exceptions. Polynucleotide expansions are not readily identified on all NGS platforms, especially if expansions are very large; therefore, individual gene or selective expansion panel testing may be needed. FA, CANVAS, and SCAs 10, 31, 36, 37, and 39 are caused by pathogenic variants in introns; as such, exome sequencing platforms may fail to detect them. Currently, the only lab that offers CANVAS testing in the US is the University of Chicago Genetic Laboratory Services (https://dnatesting.uchicago.edu/tests/single-gene-repeat-expansion-analysis). Hereditary spastic paraplegia (HSP) can present as a spastic ataxia and Huntington disease (HD) as a choreiform ataxia.[13,23] Testing for these disorders should be considered in the appropriate clinical context if genetic testing for cerebellar ataxia is nondiagnostic.

Ataxia Treatment

A full discussion of ataxia treatment is out of scope for this review. Table 3 lists acquired and genetic ataxias with specific pharmacologic treatments designed to curtail disease progression.[14,15] All ataxias warrant timely and effective management to improve quality of life. Multidisciplinary symptomatic treatment (online-only Table e3) from education and support, to neurorehabilitation, prompt pharmacologic intervention, palliative care, and hospice for end-of-life care is especially relevant in neurodegenerative ataxias.[24,25]

The National Ataxia Foundation (NAF; https://www.ataxia.org) is an excellent resource for patients, caregivers, and healthcare providers treating ataxia. As yet, there is no disease-modifying treatment for sporadic and genetic ataxias, but there is significant scientific progress regarding pathogenesis of cerebellar disorders, and multiple ataxia trials are ongoing. Omaveloxolone is under review by the Food and Drug Administration (FDA) for potential treatment of FA. Targeted genetic technologies using antisense oligonucleotides and RNA silencing show promise and research studies of these agents are (or are soon to be) underway in polyglutamine ataxias, including SCA3.[18,26] Neuromodulation is being investigated as well.[27]

TABLE 3. ATAXIA-SPECIFIC TREATMENTS

Signs	Ataxias
Acute ataxias	
Strokes, multiple sclerosis, metabolic, infectious, parainfectious, immune-mediated, iatrogenic, and toxin associated	These ataxias have etiology-specific treatment, therefore, prompt diagnosis is important
Subacute and chronic ataxias	
Gluten ataxia or celiac disease	Gluten-free diet failing which immunotherapy is an option
AntiGAD65^{+} syndrome	Intravenous (IV) solumedrol followed by IVIG or PLEX acutely; IV or oral immunomodulator maintenance therapy
Paraneoplastic ataxia	Treat underlying malignancy; immunotherapy as per guidelines
Steroid-responsive encephalopathy with associated thyroiditis (SREAT) ataxia	Consult endocrinology; IV solumedrol
Ataxia with vitamin E deficiency (AVED)	Consult nutritionist; supplement oral vitamin E
Abetalipoproteinemia (ABL)	Consult nutritionist, low-fat diet, supplement oral vitamin E
CoQ10 deficiency ataxia	High-dose CoQ10 supplement
Cerebrotendinous xanthomatosis (CTX)	Consult nutritionist; oral chenodeoxycholic acid
Refsum disease	Restrict dietary phytanic acid; PLEX for acute deterioration
GLUT 1 deficiency	Ketogenic diet
Episodic ataxia type 2	Acetazolamide, 4-aminopyridine
Niemann–Pick disease type C	Miglustat

Abbreviations: GAD65, glutamic acid decarboxylase 65; GLUT1, glucose transporter 1; IVIG, IV immunoglobulin; PLEX, plasma exchange.

Moving Forward

Knowledge about ataxia needs to be urgently disseminated if we are to prepare the next generation of specialists to move the field forward. With this objective in mind, NAF has launched the annual Ataxia Clinical Training (ACT) program, which is a didactic conference designed for neurology fellows who are particularly interested in the field. More information about applying for ACT can be obtained by visiting the NAF site at https://www.ataxia.org/ataxia-clinical-training/. ■

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Disclosures
PK has disclosures at practical neurology.com

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Online Supplemental Materials By Pravin Khemani, MD

TABLE e1. PHENOTYPE-DIAGNOSTIC TEST-GENOTYPE CORRELATIONS FOR ATAXIA

Clinical course (in addition to ataxia)	Neuroimaging and other diagnostic biomarkers	Gene: Disease
Pyramidal signs, amyotrophy, hypermetric saccades	Global cerebellar and brainstem atrophy, 'hot cross bun' sign	*ATXN1*: SCA1
Hyporeflexia, hypometric saccades, amyotrophy, autonomic dysfunction, parkinsonism, dystonia; may mimic MSA or ALS	Global cerebellar and brainstem atrophy 'olivopontocerebellar' pattern; 'hot cross bun' sign	*ATXN2*: SCA2
Pyramidal signs, 'bulging eyes,' amyotrophy, neuropathy, parkinsonism, RBD symptoms, autonomic dysfunction; may mimic atypical parkinsonism, MSA, ALS	Global cerebellar atrophy	*ATXN*: SCA3
Neuropathy, areflexia, Babinski signs, scoliosis, pes cavus, cardiomyopathy, diabetes	Spinal cord atrophy, mild or no cerebellar atrophy; elevated cholesterol, serum glucose, and hemoglobin A1c	*FXN*: FA
Neuropathy, areflexia, vestibulopathy, chronic cough, autonomic dysfunction	Cerebellar vermian atrophy; abnormal vestibular tests, diminished VOR, gain on HIT on vestibular testing	*RFC1*: CANVAS
XY heterozygote with tremor, ataxia, neuropathy, parkinsonism	T2 hyperintensities in the MCP, mild cerebellar atrophy	*FMR1*: FXTAS
Spasticity, peripheral neuropathy, hearing loss, autonomic dysfunction, seizures; predominantly French-Canadian ancestry	Superior vermian and spinal cord atrophy T2 linear hypointensities in mid pons near pyramidal tracts, thinning of corpus callosum	*SACS*: ARSACS
Sensory myeloneuropathy, visual impairment, areflexia: FA-like picture without musculoskeletal abnormalities	Cerebellar and/or spinal cord atrophy; low serum vitamin E	*TTP*: AVED;
	Cerebellar and/or spinal cord atrophy; low serum vitamin E, abnormal lipoprotein profile, PBS shows acanthocytes	*MTTP*: ABL
Oculomotor apraxia, +/- telangiectasias, polyneuropathy, chorea, dystonia, sensitivity to ionizing radiation, chorea, infections, immune deficiency	Cerebellar atrophy, hemosiderin deposits and telangiectasias seen in GRE sequences; elevated AFP, low IgA levels	*ATM*: AT
Oculomotor apraxia, polyneuropathy	Cerebellar atrophy; elevated AFP	*SETX*: AOA2
	Cerebellar atrophy, low albumin, elevated cholesterol	*APTX*: AOA1
Sensory neuropathy, ophthalmoplegia, myopathy, myoclonus, seizures, visual impairment, liver dysfunction	Cerebellar vermian atrophy, T2 hyperintensities of inferior olivary nucleus (ION); abnormal liver function tests, elevated lactate and pyruvate, abnormal muscle biopsy	*POLG1*:POLG Ataxia
Diverse central and peripheral nervous system involvement, visual, cardiac, hepatic symptoms, including acute stroke-like symptoms, neuropathy, myoclonus and myopathy	T2 hyperintensities resembling strokes; elevated lactate, pyruvate, abnormal muscle biopsy, EEG may show epileptiform activity	MELAS, MERRF, other mitochondrial disorders
Ataxia, early cataracts, cognitive impairment, seizures	T2 peridentate hyperintensities and gliotic lesions; elevated cholestanol	*P450 CYP27A1*: CTX
XY heterozygote with pyramidal signs, neuropathy, adrenal insufficiency, visual impairment, impotence, cognitive impairment	Abnormal T2 MRI signal in posterior cerebral hemispheres, cerebellum, and spinal cord; elevated fasting very long-chain fatty acids (VLCFAs)	*ABCD1*: ALD

Abbreviations: *ABCD1, ATP-binding cassette, sub-family D member 1*; AFP, alfafetoprotein; ALD, adrenoleukodystrophy; ALS, amyotrophic lateral sclerosis; *APTX, aprataxin*; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; AOA, ataxia with oculomotor apraxia; AT, ataxia-telangectasia; *ATM, AT mutated*; *ATXN, ataxin*; AVED, ataxia with vitamin E deficiency; CANVAS, cerebellar ataxia with neuropathy and vestibular areflexia syndrome; CTX, cerebrotendinous xanthomatosis; DRPLA, dentatorubral-pallidoluysian atrophy; FA, Friedreich ataxia; *FXN, frataxin*; *FMR1, fragile X messenger ribonucleoprotein 1*; FXTAS, fragile X–associated tremor/ataxia syndrome; Hbg, hemoglobin; HD, Huntington disease; HIT, head-impulse test; HSP, hereditary spastic paraplegia; MCP, middle cerebellar peduncles; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; MSA, multiple system atrophy; *MTTP, microsomal triglyceride transfer protein*; PBS, peripheral blood smear; *POLG, DNA polymerase* γ; RBD, rapid eye movement sleep behavior disorder; *RFC1, replication factor C subunit 1*; *SACS, sacsin*; SCA, spinocerebellar ataxia; *SETX, senataxin*; SPG, spastic paraplegia; *TTP, tocopherol transfer protein*; VOR, vestibular-ocular reflex.

Adult-Onset Cerebellar Ataxias

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TABLE e2. EXTRACEREBELLAR CLUES TO GENETIC ATAXIAS	
Signs	**Ataxias**
Pyramidal signs (spasticity and hyperreflexia)	Common in autosomal dominant ataxias (eg, autosomal recessive spastic ataxia of Charlevoix-Saguenay [ARSACS], hereditary spastic paraplegia [HSP]); uncommon in autosomal recessive ataxias (eg, Friedreich ataxia [FA], cerebellar ataxia with neuropathy and vestibular areflexia syndrome [CANVAS], ataxia-telangectasia AT)
Severe neuropathy or areflexia	Primarily autosomal recessive ataxias
Motor neuronopathy	Spinocerebellar ataxias (SCAs) 2, 3, 36
Myopathy, strokes, visual impairment, cardiac disease, seizures, cognitive impairment, liver disease	Mitochondria-associated (eg, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged red fibers [MERRF], neuropathy ataxia and retinitis pigmentosa [NARP], DNA polymerase γ [POLG]-associated disorders
Parkinsonism, dystonia, tremor, myoclonus	Common in multiple system atrophy (MSA); variable in inherited ataxias
Chorea	Huntington disease [HD], HD-like, SCA17, dentatorubral-pallidoluysian atrophy [DRPLA]
Autonomic dysfunction, rapid eye movement [REM] sleep behavior disorder [RBD]	Most common in multiple system atrophy [MSA]; also seen in SCAs 1, 2, 3, and CANVAS
Seizures	Most common in SCA10
Neuropathy and retinitis pigmentosa	NARP, a mitochondrial ataxia
Visual impairment or blindness	Most common in SCA7; also in FA, spastic paraplegia [SPG] 7, ataxia with vitamin E deficiency [AVED], POLG-related ataxia
Downbeat nystagmus	SCAs 5, 6
Oculomotor apraxia	ataxia with oculomotor apraxia [AOA] 1, 2, 4 and AT
Tendon xanthoma, early cataracts, seizures, cognitive impairment	Cerebrotendinous xanthomatosis (CTX)
Severe cognitive impairment/dementia	SCAs 1, 2, 3, 6, 8, 10, 12, 17, 19, 21, 42, DRPLA, HD, HD-like, CTX
Intellectual disability	SCAs 13, 27
Hyperkeratotic skin lesions, retinitis pigmentosa	SCA34
Chronic cough	CANVAS

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TABLE e3. SYMPTOMATIC TREATMENTS FOR ATAXIAS

Symptom	Referrals/diagnostic testing	Treatment/Intervention
Ataxia literacy	National Ataxia Foundation (https://www.ataxia.org)	Patient education and support
Impaired balance, coordination, balance; speech, musculoskeletal/ orthopedic issues	Physiatrist, physical therapist, occupational therapist, and speech therapist who are knowledgeable about ataxia	Eliminate/minimize drugs and toxins that can worsen ataxia,[a] treat secondary causes of ataxia including nutritional deficiencies, amantadine, riluzole, 4-aminopyridine or varenicline
Cognitive impairment	Neuropsychologic testing	Acetylcholinesterase inhibitors
Neuropsychiatric issues	Psychiatrist or neuropsychiatrist; cognitive behavioral insomnia therapy (CIBT)	Judicious use of medications for mood, anxiety, and psychosis
Oscillopsia, visual impairment, and double vision	Ophthalmologist, neuro-ophthalmologist	Gabapentin, clonazepam, memantine, and chlorzoxazone for oscillopsia; prisms for double vision
Dysphagia	Speech-language pathologist	Speech exercises and dysphagia precautions
Drooling	Speech-language pathologist	Glycopyrrolate, chemodenervation
Parkinsonism, chorea, dystonia, myoclonus, restless leg syndrome, tremor	Movement disorder specialist	Judicious use of medications for bothersome movements[b]
Spasticity	Physiatrist; neurorehabilitative specialist	Antispasticity agents (oral and intrathecal) with caution,[c] chemodenervation
Neurogenic orthostatic hypotension (nOH)	Cardiologist, if other cardiovascular comorbidities are present	Address drugs or disorders that worsen OH symptoms, nonpharmacologic treatment of OH, vigilence for supine hypertension, droxidopa, midodrine, fludrocortisone for disabling OH symptoms
Neuropathy	Screen for common causes of peripheral neuropathy	Treat underlying cause, use gabapentin, pregabalin, tricyclic antidepressants (TCAs) as needed for pain/discomfort
Urologic symptoms caused by neurogenic bladder	Urologist	Solifenacin, mirabegron (minimize anticholinergics)
Cardiac, oncologic, endocrinologic, dermatologic, urologic, and gynecologic issues	Referral to appropriate subspecialists	Regular follow-up care; preimplantation genetic counseling for those with ataxia who are planning a family
Caregiver burden	Social work	Encourage seeking assistance for coping strategies; support groups

[a]Alcohol, antiseizure medications, anticholinergics, amiodarone, chemotherapeutic agents; [b]commonly used drugs for abnormal movements include levodopa for parkinsonism; tetrabenazine for bothersome chorea; anticholinergics and chemodenervation for dystonia; levetiracetam, valproate, benzodiazepines, zonegran and lamotrigine for myoclonus; dopaminergic agonists, gabapentin, pregabalin, gabapentin enacrbil for restless leg syndrome; trial of essential tremor medications like propranolol, primidone, gabapentin, topiramate for tremor; [c]excessive use of antispasticity agents can cause hypotonia and weakness.

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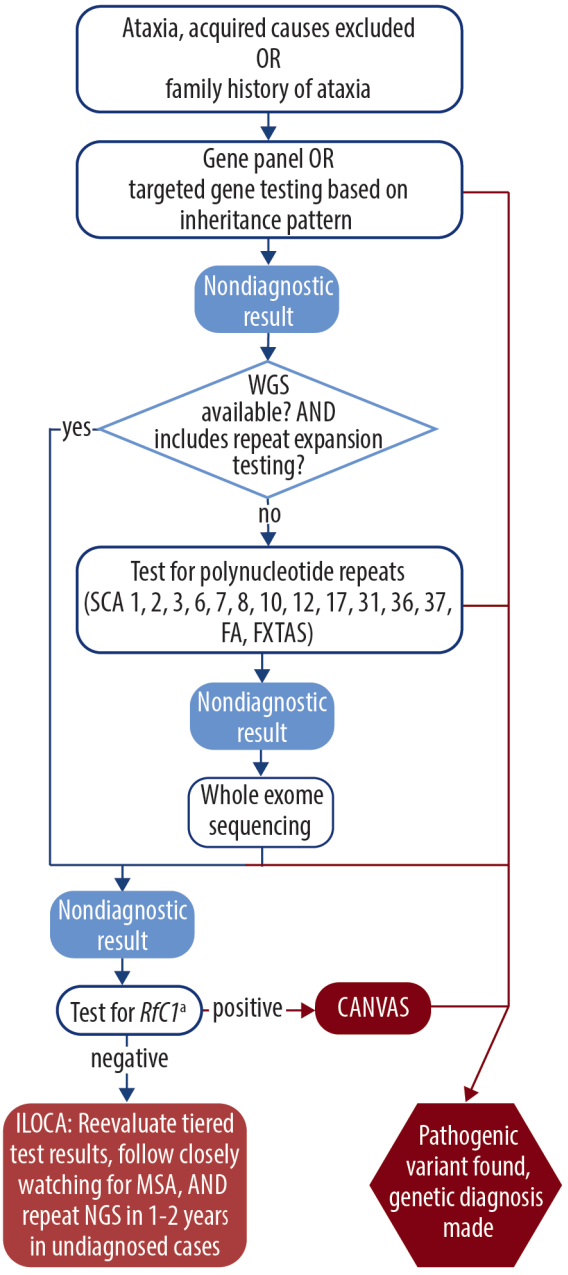

Figure e1. Family history and clinical course guide the approach to genetic testing for ataxias. a*RfC1* testing may precede NGS in people over age 45 with classic phenotypes. Abbreviations: CANVAS, cerebellar ataxia with neuropathy and vestibular areflexia syndrome; FA, Friedrich ataxia; FXTAS, fragile X–associated tremor/ataxia syndrome; NGS, next-generation sequencing; *RfC1, replication factor C subunit 1*; ILOCA, idiopathic late onset cerebellar ataxia; MSA, multiple system atrophy; SCA, spinocerebellar ataxia; WGS, whole genome sequencing.