Clinical features and molecular genetics of autosomal recessive cerebellar ataxias

Brent L Fogel, Susan Perlman

Among the hereditary ataxias, autosomal recessive spinocerebellar ataxias comprise a diverse group of neurodegenerative disorders. Clinical phenotypes vary from predominantly cerebellar syndromes to sensorimotor neuropathy, ophthalmological disturbances, involuntary movements, seizures, cognitive dysfunction, skeletal anomalies, and cutaneous disorders, among others. Molecular pathogenesis also ranges from disorders of mitochondrial or cellular metabolism to impairments of DNA repair or RNA processing functions. Diagnosis can be improved by a systematic approach to the categorisation of these disorders, which is used to direct further, more specific, biochemical and genetic investigations. In this Review, we discuss the clinical characteristics and molecular genetics of the more common autosomal recessive ataxias and provide a framework for assessment and differential diagnosis of patients with these disorders.

Department of Neurology, David Geffen School of Medicine at UCLA (B Fogel MD), **and UCLA Ataxia Center** (S Perlman MD)**, University of California at Los Angeles, Los Angeles, USA**

Correspondence to
Dr Susan Perlman, UCLA Ataxia Center, University of California at Los Angeles, 710 Westwood Plaza, Los Angeles, CA 90095, USA
sperlman@mednet.ucla.edu

Clinical features of autosomal recessive ataxias

Insidious loss of balance and coordination can be debilitating for patients and a diagnostic dilemma for clinicians. The phenotype of progressive cerebellar ataxia can result from both acquired and hereditary disorders. For these reasons, a systematic approach to the diagnosis of patients with ataxia is essential. Hereditary ataxias can be divided into autosomal dominant, autosomal recessive, X-linked, and mitochondrial on the basis of mode of inheritance. This Review will focus on the clinical and genetic aspects, as well as the molecular basis for pathogenesis, of the more common autosomal recessive ataxias.

When assessing a patient with ataxia, the clinician may initially be unable to differentiate autosomal recessive ataxia from other forms unless the patient can disclose a characteristic family history of affected relatives. What factors should influence physicians to add this class of ataxic disorders to patients' differential diagnoses?

Most autosomal recessive ataxias are early onset, which traditional classification systems define as before age 20 years.[1] Although useful, such a distinction is not universally applicable, as age at onset can be quite diverse, with typical early-onset, recessively inherited disorders, such as Friedreich's ataxia and Tay-Sachs disease, presenting in adulthood. Phenotype can, therefore, be a more reliable means of identification.

The key feature in all these disorders is spinocerebellar ataxia, involving the cerebellum, brainstem, or spinocerebellar long tracts, typically characterised by poor balance with falls, imprecise hand coordination, postural or kinetic tremor of the extremities or trunk, dysarthria, dysphagia, vertigo, and diplopia.[2] Autosomal dominant spinocerebellar ataxias may also have diverse associated neurological features including retinopathy, optic atrophy, extrapyramidal or pyramidal signs, peripheral neuropathy, cognitive impairment, or epilepsy.[3] Autosomal recessive ataxias, by contrast, are generally associated with peripheral sensorimotor neuropathy, most notably with loss of proprioception and vibration sense as seen in the prototypical disorder,

Friedreich's ataxia.[4,5] The presence or absence of deep tendon reflexes can also be a useful examination finding,[6] as arreflexia is more common in autosomal recessive ataxias. In further contrast to the autosomal dominant ataxias, autosomal recessive ataxias tend to have involvement outside the nervous system.[4,5]

From a diagnostic viewpoint, categorisation of autosomal recessive ataxias as either resembling a Friedreich's ataxia phenotype or as having an early-onset phenotype with cerebellar atrophy is useful (table 1). Due to the heterogeneity among these disorders, further differentiation will generally require detailed assessment of the phenotype, as well as additional diagnostic studies, particularly neuroimaging, because the presence of cerebellar atrophy is a useful distinguishing feature. As many of the autosomal recessive ataxias now have identifiable gene mutations, the goal of this assessment is to provide a focus for genetic testing.

In this Review, we present an overview of the most common autosomal recessive ataxias and discuss strategies for clinical differentiation. Many autosomal recessive disorders, particularly those of metabolic, storage, or mitochondrial function, may include ataxia as an associated or occasional feature; however, only diseases with ataxia as a defining component of the clinical phenotype are covered. Although the molecular genetic causes behind the most common autosomal recessive disorders are known, there are several rare disorders described in single families or a few patients that are not yet understood molecularly and are therefore not mentioned here.

Friedreich's ataxia and phenotypically related disorders

Friedreich's ataxia is an important consideration in all assessments of autosomal recessive ataxic syndromes. However, several other ataxic disorders strongly mimic this phenotype. Therefore, the initial characterisation of a patient as having Friedreich's ataxia phenotype is a useful first step in differentiation. Despite their clinical similarity, these disorders are easily differentiated by

	Gene/Protein	Gene	Locus	Protein function
Friedreich's ataxia-like				
Friedreich's ataxia	Frataxin	FRDA	9q13	Mitochondrial iron metabolism
Ataxia with vitamin E deficiency	α-tocopherol transfer protein	TTPA	8q13.1–13.3	Vitamin E homoeostasis
Abetalipoproteinaemia	Microsomal triglyceride transfer protein	MTP	4q22–24	Lipoprotein metabolism
Refsum's disease	Phytanoyl-CoA hydroxylase	PHYH	10pter–11.2	Fatty-acid oxidation
	Peroxin 7	PEX7	6q21–22.2	Peroxisomal protein importation
Friedreich's ataxia-like with cerebellar atrophy				
Late-onset Tay-Sachs disease	β-hexosaminidase A	HEXA	15q23–24	Glycosphingolipid metabolism
Cerebrotendinous xanthomatosis	Sterol 27-hydroxylase	CYP27	2q33–ter	Bile-acid synthesis
DNA polymerase γ disorders (mitochondrial recessive ataxia syndrome)	DNA polymerase γ	POLG	15q22–26	Mitochondrial DNA repair and replication
Spinocerebellar ataxia with axonal neuropathy	Tyrosyl-DNA phosphodiesterase 1	TDP1	14q31–32	DNA repair
Early-onset ataxia with cerebellar atrophy				
Ataxia telangiectasia	Ataxia telangiectasia-mutated	ATM	11q22–23	DNA damage response
Ataxia telangiectasia-like disorder	Meiotic recombination 11	MRE11	11q21	DNA damage response
Ataxia with oculomotor apraxia, type 1	Aprataxin	APTX	9p13	DNA repair, possibly RNA processing
Ataxia with oculomotor apraxia, type 2	Senataxin	SETX	9q34	Possibly DNA repair, DNA transcription, or RNA processing
Autosomal recessive ataxia of Charlevoix-Saguenay	Sacsin	SACS	13q11	Possibly protein folding
Infantile-onset spinocerebellar ataxia	Twinkle, twinky	C10orf2	10q24	DNA replication
Cayman ataxia	Caytaxin	ATCAY	19p13.3	Possibly neurotransmitter metabolism
Marinesco-Sjögren's syndrome	BiP-associated protein	SIL1	5q31	Possibly protein folding

Table 1: Molecular characterisation of the autosomal recessive ataxias

laboratory testing and, ultimately, through genetic analysis.

Friedreich's ataxia

Friedreich's ataxia is the most common of the autosomal recessive ataxias and the most common hereditary ataxia overall with a prevalence of approximately one person in 30 000 to one in 50 000 in most populations and a carrier frequency of approximately one in 85 in white people.[7–10] Age at onset is typically age 5–25 years. Clinically, Friedreich's ataxia is characterised by early-onset progressive gait and limb ataxia, dysarthria, loss of vibration and proprioceptive sense, areflexia, abnormal eye movements (such as fixation instability), and pyramidal weakness of the feet with upgoing toes.[11–13] Cardiomyopathy, diabetes, scoliosis, and pes cavus are other common systemic complications.[11–13] Large sensory neurons in the dorsal root ganglia are lost initially, with subsequent deterioration of the spinocerebellar tract, pyramidal tract, and dorsal columns.[14] Neuroimaging does not show progressive cerebellar degeneration (figure 1),[11] unlike the autosomal-dominant hereditary ataxias.[3] Although the phenotype is well-described and detailed, there are various atypical phenotypes,[10,11,15] including late-onset presentations after age 25 years, which are commonly associated with lower limb spasticity, retained reflexes, and mild cerebellar vermian atrophy.[16] Friedreich's ataxia should be considered in all patients with sporadic or recessive ataxia, with the exception of those with severe olivopontocerebellar atrophy on neuroimaging.[10]

In about 98% of patients, the disease is caused by a triplet GAA expansion within the first intron of the frataxin gene found on chromosome 9q13.[17] The increased number of GAA repeats may allow the formation of a "sticky" triplex DNA structure that impedes transcription of the gene and limits protein production.[18–21] The inverse correlation of age at onset, severity of the disease, and associated systemic symptoms with the size of the repeat expansions, which can range from 70–90 repeats (normal less than 40) to over 1000, is likely caused by residual protein expression from the alleles with smaller GAA expansions.[7,8,10,22,23] Point mutations, although rare (about 2–4% of patients), can cause the disorder[7,8,10,23] and must be considered when assessing a new patient with ataxia, as routine testing may only screen for repeat expansions and may misidentify a compound heterozygote. Some point mutations result in a more severe phenotype and others in a milder phenotype.[7,8,23] Tissue mosaicism may also contribute to the observed phenotype seeming disparate relative to the GAA repeat lengths.[24,25]

Frataxin is a mitochondrial protein.[26] Current evidence suggests that loss of frataxin impairs mitochondrial iron handling and respiratory chain function and contributes to increased oxidative stress and cellular damage.[27–29] Studies of mutants in the yeast homologue Yfh1p have shown inhibition of oxidative phosphorylation and accumulation of iron[30] as well as an inability to detoxify
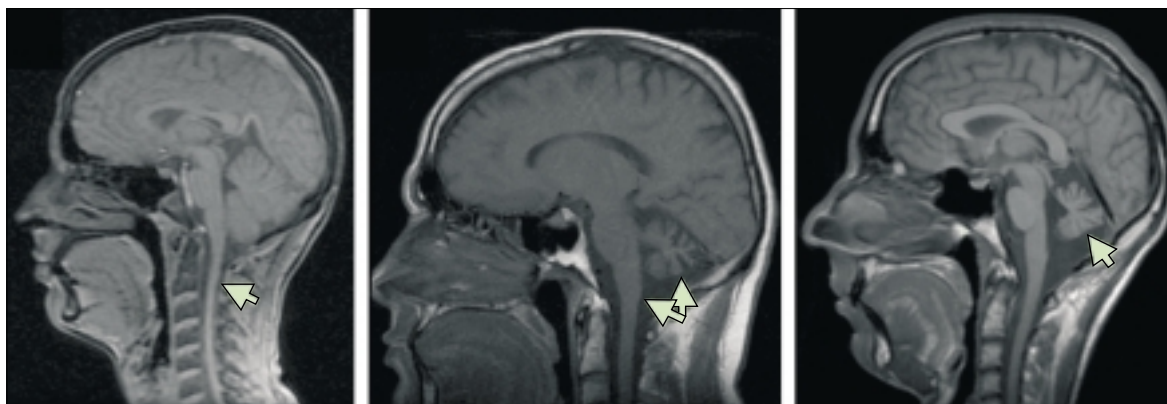
Figure 1: Neuroimaging features of selected autosomal recessive ataxias
T1-weighted sagittal MRI images are shown for a 14-year-old boy with Friedreich's ataxia (left) showing mild atrophy of the cervical spinal cord (arrow) and a normal cerebellum; a 35-year-old man with ataxia telangiectasia (middle) demonstrating moderate cerebellar atrophy and mild volume loss in the brainstem (arrows); and a 21-year-old man with ataxia with oculomotor apraxia type 2 (right) and marked atrophy of the cerebellar vermis (arrow).

iron, resulting in hypersensitivity to oxidative stress.[31] This phenotype can be rescued by the human frataxin protein,[32] demonstrating a functional similarity. A murine knockout model of frataxin is lethal during embryogenesis,[33] and this too can be rescued by the human protein.[34] Neuron-specific and striated-muscle-specific knockout mice demonstrate a phenotype of ataxia and proprioceptive loss as well as cardiac hypertrophy and a deficiency in respiratory-chain complexes,[35] suggesting the usefulness of this system as a model for studying Friedreich's ataxia. On the basis of these studies, oxidative damage within the mitochondria seems to have a key role in the disease phenotype.[36,37]

Given the current knowledge of the pathogenesis of Friedreich's ataxia, treatment options have been directed at antioxidant protection. A recent uncontrolled, open-label, 4 year pilot study of ten patients on a combination of coenzyme Q_{10} and vitamin E reported improvement in cardiac function and suggested possible stabilisation or reduced decline in certain neurological symptoms.[38] Studies of low-dose idebenone, a synthetic analogue of coenzyme Q_{10}, seem to show reduction of cardiac hypertrophy but no improvement in neurological symptoms.[39–42] Consistent with these clinical studies, idebenone also seems to be cardioprotective in the *FRDA* mouse model.[43] No drugs have led to any improvement in ataxia or other associated neurological features in patients, and treatment for this disease remains symptomatic.[2]

Ataxia with vitamin E deficiency
This disorder presents with a clinically similar phenotype to Friedreich's ataxia,[44,45] but serum concentrations of vitamin E are low.[45] Most patients are from north Africa where its incidence may be as common as that of Friedreich's ataxia,[44] but many have been reported elsewhere including Europe, North America, and Japan.[45] Like Friedreich's ataxia, age at onset is before 20 years

but, by contrast, decreased visual acuity or retinitis pigmentosa may be an early finding.[44,46] Cardiomyopathy is the most common systemic finding but seems to be less common than in Friedreich's ataxia.[45,46] Patients also tend to have more head titubation[44,45] as well as less neuropathy and a slower disease course.[44] The disease is caused by mutation of the α-tocopherol transfer protein on chromosome 8q13.[47,48] The α-tocopherol transfer protein mediates the incorporation of vitamin E into circulating lipoproteins, and the mutations presumably reduce delivery to the CNS.[49] Mutations are varied, including missense, nonsense, frameshift, and splice-site mutations, and may affect the severity of the disease,[45] presumably via residual protein activity with certain mutations. Supplementation with vitamin E seems to stop progression of the disease,[46,50] and can mildly improve cerebellar ataxia.[50] A mouse model has been developed that shows late-onset head tremor, ataxia, and retinal degeneration, the neurological aspects of which resolve with supplementation of vitamin E.[51] As is suspected for Friedreich's ataxia, the mechanism underlying this pathogenesis seems to be increased oxidative stress.[49,51]

Abetalipoproteinaemia
This disease is caused by mutations in the gene for the large subunit of microsomal triglyceride transfer protein, located on chromosome 4q22–24,[52,53] which functions in the assembly of apolipoprotein-B containing very low-density lipoproteins and chylomicrons.[54] The neurological phenotype presents before age 20 years and is similar to Friedreich's ataxia, but is generally also associated with lipid malabsorption, hypocholesterolaemia, acantho-cytosis, and retinitis pigmentosa.[53,54] Patients become deficient in the lipid-soluble vitamins, especially vitamin E, the loss of which likely has neurological and ophthalmological complications.[54] Treatment involves dietary modification and vitamin replacement, which

may prevent neurological complications if begun early.[54] *MTP* knockout mice have an embryonic lethal phenotype; however, conditional knockouts have abnormalities in plasma lipoproteins.[55]

Refsum's disease

Refsum's disease is clinically characterised by cerebellar ataxia, peripheral polyneuropathy, sensorineural deafness, retinitis pigmentosa, and anosmia, with skeletal abnormalities, ichthyosis, renal failure, and cardiac myopathy or arrhythmias as additional associated features.[56–58] The disease is primarily caused by mutation of the gene for the peroxisomal enzyme phytanoyl-CoA hydroxylase, *PHYH*, on chromosome 10pter–11.2.[56–58] Less commonly, mutation of *PEX7* on chromosome 6q21–22.2, which encodes the peroxin 7 receptor protein needed for peroxisomal importation of proteins containing a type 2 peroxisomal targeting signal, can produce an identical phenotype due to impaired importation of proteins into the peroxisome, including phytanoyl-CoA hydroxylase.[56,59]

PEX7 mutations can also cause the more complex syndrome of rhizomelic chondrodysplasia punctata type 1,[56,59] and other disorders of peroxisome biogenesis can cause the severe phenotypes of neonatal adreno-leukodystrophy and Zellweger's syndrome.[56] Therefore, clinical diagnosis of disorders involving ataxia, poly-neuropathy, and retinitis pigmentosa may need a full screen of peroxisomal function, a search for mitochondrial disorders, or consideration of a glycosylation defect.[59–61]

Onset of Refsum's disease is typically before age 20 years but can be much later.[56,57] Because of impaired branched-chain fatty acid α-oxidation, phytanic acid, found primarily in dairy products, meat, and fish, accumulates to high levels in body fat.[56–58] This accumulation within myelinated neurons is likely pathogenic, although the precise mechanism remains unclear.[56–58] Stressful conditions, such as rapid weight loss or illness, can result in mobilisation of phytanic acid from fat stores, which can cause sudden worsening of symptoms or even an acute presentation similar to Guillain-Barré syndrome.[56–58] Dietary restriction halts disease progression,[56–58] so early identification of this disorder is essential so that treatment may be started. Plasmapheresis could be considered in patients presenting in an acutely ill state to rapidly reduce plasma concentrations of phytanic acid.[58]

Friedreich's ataxia phenotype with cerebellar atrophy

As with the disorders described above, the following disorders can mimic the Friedreich's ataxia phenotype; however, they can be readily distinguished by the presence of cerebellar atrophy or other findings on neuroimaging. Furthermore, the presence of clinical neurological findings not typically seen in Friedreich's ataxia, such as epilepsy or cognitive or psychiatric

symptoms, should also alert physicians to consider these disorders in the differential diagnosis.

Late-onset Tay-Sachs disease

Tay-Sachs disease is a G_{M2}-gangliosidosis caused by a deficiency of the enzyme β-hexosaminidase A, the gene for which, *HEXA*, is on chromosome 15q23–24.[62,63] This is typically a severe infantile disorder associated with developmental delay, hypotonia, mental retardation, seizures, and blindness with the presence of a cherry-red spot on fundoscopy, resulting in death by age 3 years.[63] In contrast, the late-onset phenotype presents as either a childhood-onset or adult-onset disease characterised by cerebellar dysfunction, areflexia, proximal muscle weakness with subsequent muscle atrophy and fasciculations, and psychiatric or behavioural problems.[64] The juvenile-onset form can also include spasticity, seizures, and dementia.[64] These differences in phenotype seem to arise because of genotypic variations, with the severe infantile form resulting from two inactive alleles, whereas the later onset forms retain at least one allele with a less severe mutation resulting in residual enzyme activity.[63,64] It is important to consider this cause in the differential diagnosis of autosomal recessive ataxia, as the later onset form can present as a Friedreich's ataxia phenotype. An important distinction is the presence of notable cerebellar atrophy on MRI.[64] The disease is typically seen in Ashkenazi Jewish populations, but has also been reported in non-Jewish people.[63,64]

Knockout mouse models seem to most closely mimic the late-onset phenotype, primarily due to murine metabolic differences that prevent early ganglioside accumulation.[62,65,66] Progressive CNS inflammation has been suggested as a potential mediator of disease pathogenesis.[67] Although the available mouse models offer insight into the biology of this disease, there are no effective treatment options.[62] Substrate reduction therapy[68] and gene therapy[69] are being explored for this and other gangliosidoses.

Cerebrotendinous xanthomatosis

This disorder is caused by mutation of *CYP27* on chromosome 2, which encodes the mitochondrial enzyme sterol 27-hydroxylase, part of the hepatic bile-acid-synthesis pathway, resulting in increases of serum cholestanol and bile alcohols.[70–72] Deposition of these metabolites in CNS tissues probably causes the clinical phenotype.[71,72] Although generally thought of as a rare disorder, it may be seen in diverse ethnic populations,[72] and recent studies have suggested prevalence may be as high as one per 50 000 white people for certain mutations.[70] Neurological symptoms generally start around age 20 years and can include ataxia with pyramidal or extrapyramidal signs, sensorimotor peripheral neuropathy, seizures, psychiatric problems, and dementia; although the phenotype can be quite diverse.[70–72] Associated features include juvenile cataracts,

tendon xanthomas, early atherosclerosis, osteoporosis, and chronic diarrhoea.[70–72] Signs on neuroimaging include generalised cerebral and cerebellar atrophy as well as diffuse white-matter hyperintense lesions on MRI.[70,72] Early diagnosis is important because the disease is treatable by bile-acid replacement therapy with chenodeoxycholic acid.[71,72]

DNA polymerase γ disorders including mitochondrial recessive ataxia syndrome

Several neurodegenerative disorders are associated with mutation of *POLG*, the catalytic subunit of mitochondrial DNA polymerase γ, including progressive external ophthalmoplegia[73,74] and the severe hepatocerebral disturbances seen in Alpers' syndrome.[73,74] Additionally, several *POLG* mutations produce ataxic syndromes in an autosomal recessive manner.[75–80] Several of these patients present with ataxia due to sensory neuropathy,[75] including SANDO syndrome (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis),[76] and therefore will not be considered here. Six Norwegian patients from at least three different families have a syndrome consisting of cerebellar ataxia, ophthalmoplegia, sensorimotor neuropathy with prominent dorsal column involvement and areflexia, myoclonus, impaired cognition, epilepsy, and migraine headaches with onset before age 23 years.[77] MRI in these patients showed hyperintensities in the thalamus, occipital lobes, brainstem, and cerebellum, as well as cerebellar atrophy in one patient.[77] Four of the patients were homozygous for the same missense mutation, Ala467Thr.[77] A similar phenotype has been reported in three members of a Finnish family with onset around age 30 years,[78] who have mutations within *POLG*.[75] Further genetic analysis of a large group of Finnish patients with ataxia identified several additional patients with these mutations; 27 patients from 15 different families were identified, all of whom were homozygous for two missense mutations (Trp748Ser and a known polymorphism Glu1143Gly) in *cis*.[79] These patients had a variable age at onset, from childhood to adulthood with a median at 28 years.[79] Clinically they demonstrated progressive cerebellar ataxia, sensorimotor peripheral neuropathy with involvement of the dorsal columns and leg areflexia, and about half of all patients had various combinations of mild cognitive impairment, psychiatric features, epilepsy, or myoclonus or other involuntary movements.[79] MRI showed bilateral white-matter hyperintensities in the cerebellum and mild vermian atrophy, with occasional signal changes in the thalamus.[79] Carrier prevalence was estimated as one per 125 making this disorder, which the authors called mitochondrial recessive ataxia syndrome (MIRAS), the most prevalent late-onset ataxia in Finland.[79] A more recent study of primarily Norwegian patients with either homozygous Ala467Thr, homozygous Trp748Ser (Glu1143Gly), or heterozygous Ala467Thr/Trp748Ser(Glu1143Gly) showed the syndromes to be clinically identical with a mean age

at onset of 14·5 years.[80] The results of this study also suggest that liver failure is a commonly associated feature.[80] Epilepsy was common and was the presenting symptom in many cases,[80] thus clinically distinguishing this disorder from other Friedreich's ataxia phenotypes.

POLG is located on chromosome 15q22–26,[73] and the product is the only DNA polymerase found in mitochondria, and therefore functions in both the replication and repair of the mitochondrial genome.[73] Disruption of the enzyme's proofreading function or a catalytic polymerase defect with a resultant increase in mitochondrial mutations may be responsible for the disease phenotypes;[73] however, how these specific mutations affect POLG function and contribute to the precise pathogenesis of this ataxic syndrome is unknown.

Spinocerebellar ataxia with axonal neuropathy

This childhood-onset disorder, found in Saudi Arabia, is characterised by cerebellar ataxia with atrophy, peripheral axonal sensorimotor neuropathy, distal amyotrophy, and pes cavus.[81] The gene, *TDP1*, is found on chromosome 14q31–32 and encodes tyrosyl-DNA phosphodiesterase 1, which is likely involved in repair of DNA-topoisomerase I complexes during transcription and replication in dividing cells[81] and topoisomerase I-related single-stand break repair in postmitotic neurons.[82,83] Oxidative stress and transcription may lead to single-strand breaks in the nervous system DNA, which become persistent in patients with spinocerebellar ataxia with axonal neuropathy, resulting in the neurodegenerative phenotype.[82,83]

Early-onset ataxia with cerebellar atrophy

This final class of disorders differs from those previous in that the age at onset is typically much younger than seen in Friedreich's ataxia and phenotypically similar disorders. Cerebellar atrophy is also a prominent feature. Ataxia telangiectasia is the prototypical disorder in this group. Although they may present in the teenage years, ataxia with oculomotor apraxia types 1 and 2 are also included in this category due to their notable similarities to ataxia telangiectasia. This category is defined solely by the clinical phenotype of the included disorders and is therefore distinct from the early-onset cerebellar ataxia classification originally defined by Harding for disorders of unknown cause.[1,84]

Ataxia telangiectasia

In patients with ataxia telangiectasia, onset of cerebellar dysfunction begins by age 2–3 years and is severely progressive.[85–88] Assessment of eye movement will commonly show oculomotor apraxia.[88] There is notable clinical variability, however, and symptoms can present much later in life.[88] Cerebellar atrophy is typically seen on MRI (figure 1), but may not be present early.[85,88] Associated

features include oculocutaneous telangiectasias, variable degrees of immunodeficiency, and an increased risk for various cancers, especially leukaemia or lymphoma.[85–87] Prevalence is variable but is estimated to be as high as one per 40 000 in the USA.[5,85,88] High concentrations of serum α fetoprotein is a typical laboratory finding and patients are also radiosensitive.[85,86,88]

Ataxia telangiectasia results from mutation of the AT-mutated gene, *ATM*, on chromosome 11q22–23.[85–87,89] The protein is a serine/threonine protein kinase involved in the DNA damage response pathway.[85–87] ATM is initially involved in the signal transduction cascade triggered by DNA damage, particularly double-stranded DNA breaks.[87,90,91] Loss of protein function seems to disrupt pathways leading to either cell-cycle checkpoint regulation or apoptosis, resulting in a syndrome of cellular genomic instability,[87,90,91] which likely gives rise to the clinical features of the disease. Phenotype can vary in severity depending on whether or not there is a complete absence of ATM protein.[85,86,88]

There are several other disorders with clinical and biochemical similarities to ataxia telangiectasia, including ataxia telangiectasia-like disorder (ATLD) and Nijmegen breakage syndrome (NBS).[85,86] Clinically, ATLD is very similar to ataxia telangiectasia but has later onset with slower progression; patients lack telangiectasias and do not have raised concentrations of serum α fetoprotein.[85,86,92] NBS, in contrast, differs from ataxia telangiectasia in that patients have microcephaly and growth retardation with decreased intelligence and they lack telangiectasias, elevated α fetoprotein, and ataxia.[86,88,92] ATLD is caused by mutation in the meiotic recombination 11 gene, *MRE11*, whereas NBS is caused by mutation of the nibrin gene, *NBS1*.[85,86] Both of these proteins are components of the meiotic recombination complex that is rapidly recruited to sites of DNA damage and participates in the initiation of the DNA damage response pathway, including the activation of ATM.[90,91] Although *ATM* knockout mice are viable,[93–95] both *NBS1* and *MRE11* knockouts die during embryogenesis.[85,93] Although ATM-deficient mice show phenotypic similarities to ataxia telangiectasia, they do not seem to have gross histological changes in the cerebellum or overt ataxia.[93–95] Recently developed *NBS1* hypomorphic (gene function partly reduced) mice have phenotypes similar to both human ataxia telangiectasia and NBS including cerebellar degeneration and ataxia[93] and may be useful to elucidate further the pathogenesis and role of these proteins in the CNS. In human beings, NBS and ataxia telangiectasia do not overlap clinically—except perhaps in the Fresno phenotype of the latter, which clinically seems to be a combination of both disorders, but only shows mutations in ATM genetically.[88] In the case of ataxia telangiectasia and ATLD, the availability of genetic testing is the quickest means of providing a definitive diagnosis. Treatment for all these disorders is primarily symptomatic.

Ataxia with oculomotor apraxia

Another ataxic syndrome, very similar to ataxia telangiectasia, has been recently determined to be two distinct disorders. Ataxia with oculomotor apraxia type 1, reported in patients from Europe, Japan, and north Africa,[96–99] presents later than ataxia telangiectasia, at about age 7 years[99–101] and sometimes even much older.[98] Patients have cerebellar gait and limb ataxia; sensorimotor neuropathy with notable dorsal column involvement and areflexia; eye movement abnormalities including nystagmus, fixation instability, and variable oculomotor apraxia; extrapyramidal signs; and mild cognitive impairment.[98–101] MRI shows cerebellar atrophy, especially of the vermis.[98–101] Laboratory studies show hypo-albuminaemia, hypercholesterolaemia, and normal serum α fetoprotein.[98–101] The disease is caused by mutation of the aprataxin gene, *APTX*, on chromosome 9p13.[96,97,102] The protein likely plays a part in DNA repair, particularly single-strand DNA breaks,[103,104] although other additional roles are possible, such as in RNA processing.[103] How the protein affects pathogenesis and contributes to the phenotypic distinctions from other DNA repair disorders is unknown.

Ataxia with oculomotor apraxia type 2 presents with a similar phenotype as type 1, but age at onset is in the early teens and there is perhaps a lesser degree of certain features, such as oculomotor apraxia, extrapyramidal signs, or cognitive changes in some populations.[105–108] In further contrast to type 1, laboratory studies show normal albumin and high serum α fetoprotein concentrations, although MRI again shows cerebellar, particularly vermian, atrophy (figure 1).[105–108] Ataxia with oculomotor apraxia type 2 could be the second most common autosomal recessive ataxia after Friedreich's ataxia in the European population.[105] Type 2 is caused by mutation in the gene for senataxin, *SETX*, on chromosome 9q34.[105–107] The senataxin protein contains a DNA/RNA helicase domain[106] and, in cultured cells, is localised to the cytoplasm and the nucleolus, possibly in a cell-cycle-dependent manner.[109] Although the functional role of human senataxin is unknown, its yeast orthologue, *Sen1p*,[106] is implicated in DNA transcription, DNA repair, and the processing of non-coding RNAs.[110] Interestingly, specific missense mutations in the senataxin gene, similar but distinct from those found in ataxia with oculomotor apraxia type 2, cause an autosomal dominant form of juvenile amyotrophic lateral sclerosis (ALS4), a disorder not seen in heterozygous carriers of type 2 mutations.[109,111] One possible explanation for this dichotomy is that the amyotrophic lateral sclerosis mutations produce a specific gain-of-function phenotype whereas the ataxia mutations produce a diffuse loss-of-function phenotype;[109,111] however, further study of senataxin will be necessary to determine precisely which functions are affected and how they contribute to pathogenesis.

Autosomal-recessive spastic ataxia of Charlevoix-Saguenay

Characterised primarily by progressive cerebellar dysfunction, pyramidal signs such as spasticity with hyperreflexia, and peripheral sensorimotor neuropathy with amyotrophy,[112–115] autosomal recessive spastic ataxia of Charlevoix-Saguenay was first identified in northeast Canada.[112,116] More recently, the disorder has been described in Europe, Eurasia, north Africa, and Japan.[113–115,117–121] Hypermyelinated retinal fibres seen on fundoscopy have been described in many patients, predominantly those from Canada,[112,115,120] but is not typical of cases seen elsewhere.[113,114,117–119,121] Onset is typically between age 1–5 years,[112,113,115] but has been reported in the teens in some families.[114] MRI shows cerebellar vermian atrophy.[112] The gene implicated in this disorder, *SACS*, is on chromosome 13q11.[112,116] This gene contains one of the largest known exons in the human genome, at about 13 kb in size.[116] The protein, known as sacsin, is predicted to have a chaperone role in protein-folding.[116] The cellular role of sacsin and the mechanism by which loss of sacsin function contributes to the pathogenesis of autosomal recessive spastic ataxia of Charlevoix-Saguenay remains unknown.

Infantile-onset spinocerebellar ataxia

This disorder, seen in Finland, is a severe ataxic syndrome with onset before age 2 years.[122,123] Infants present with a progressive course that includes cerebellar ataxia, hypotonia, sensory neuropathy with areflexia, optic atrophy, ophthalmoplegia, hearing loss, involuntary movements, and epilepsy.[122,123] Female hypogonadism is an associated feature.[122,123] MRI shows atrophy of the cerebellum, brainstem, and spinal cord[122] with corresponding atrophic changes seen on pathology.[123] The gene *C10orf2* on chromosome 10q24 is implicated in this disorder; it encodes the proteins twinkle, a mitochondrial helicase involved in DNA replication, and twinky whose current function is unknown.[122] Similar to POLG, twinkle mutations also cause progressive external ophthalmo-

	FRDA	AVED	ABL	RD	LOTS	CTX	MIRAS	SCAN1	AT	ATLD	AOA1	AOA2	ARSACS	IOSCA	CA	MSS
Age at onset (years)	<25	<20	<20	<20	<20	<20	2–45	<20	<3	<20	<20	<20	<20	<2	<20	<20
Adult-onset variants	+	+	–	+	+	+	+	–	+	–	+	+	+	–	–	–
Gait/limb ataxia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nystagmus	+	–	+	–	+	–	+	–	+	+	+	+	+	–	+	+
Sensory neuropathy	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Motor weakness	+	–	–	–	+	+	+	+	+	+	+	+	+	+	–	+
Amyotrophy	+	–	+	+	+	+	+	+	+	–	+	+	+	+	–	+
Pes cavus	+	+	+	+	–	+	+	+	–	–	+	+	+	+	–	–
Oculomotor apraxia	–	–	–	–	–	–	–	–	+*	+*	+*	+*	–	–	–	–
Ophthalmoplegia	–	–	–	–	–	–	+*	–	–	–	+*	–	–	+*	–	–
Saccadic ocular pursuit	–	–	–	–	+*	–	+*	–	–	–	–	+*	+*	–	–	–
Gaze fixation instability	+*	–	–	–	–	–	–	–	–	–	+*	–	–	–	–	–
Strabismus	–	–	–	–	–	–	–	–	–	–	–	+*	–	–	–	+*
Spasticity	–	–	–	–	+*	+*	–	–	–	–	–	–	+*	–	–	–
Hypotonia	–	–	–	–	+*	–	–	–	–	–	+*	–	–	+*	+*	+*
Extensor plantar sign	+*	+*	–	–	–	–	+*	–	+*	–	–	+*	+*	–	–	–
Deep tendon reflexes	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↑*	↓	–	↓
Tremor	–	+*	–	–	+*	–	+*	–	+*	–	+*	+*	–	–	+*	+*
Head titubation	–	+*	–	–	–	–	+*	–	–	–	–	+*	–	–	–	–
Myoclonus	–	–	–	–	+*	+*	+*	–	+*	–	–	+*	–	–	–	–
Dystonia	–	–	–	–	+*	+*	–	–	+*	+*	+*	+*	–	–	–	–
Chorea/choreoathetosis	–	–	–	–	+*	–	+*	–	+*	+*	+*	+*	–	+*	–	–
Parkinsonism	–	–	–	–	–	+*	–	–	–	–	–	–	–	–	–	–
Psychomotor retardation	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+*	+*
Cognitive impairment	–	–	–	–	+*	+*	+*	–	–	–	+*	+*	+*	+*	–	+*
Psychiatric problems	–	–	–	–	+*	+*	+*	–	–	–	–	–	–	–	–	–

The typical or most common clinical features of the various autosomal recessive ataxic disorders are shown. Due to profound variability in clinical presentation, not all patients will present with all the features listed and, in some cases, notable deviations may also be observed. +=feature may be present. –=feature not present, uncommon, or not reported. ↓=reduced or absent. ↑=increased. *Clinical features useful for differential diagnosis. FRDA=Friedreich's ataxia. AVED=ataxia with vitamin E deficiency. ABL=abetalipoproteinaemia. RD=Refsum's disease. LOTS=late-onset Tay-Sachs disease. CTX=cerebrotendinous xanthomatosis. MIRAS=mitochondrial recessive ataxia syndrome. SCAN1=spinocerebellar ataxia with axonal neuropathy. AT=ataxia telangiectasia. ATLD=ataxia telangiectasia-like disorder. AOA1=ataxia with oculomotor apraxia, type 1. AOA2=ataxia with oculomotor apraxia, type 2. ARSACS=autosomal recessive ataxia of Charlevoix-Saguenay. IOSCA=infantile-onset spinocerebellar ataxia. CA=Cayman ataxia. MSS=Marinesco-Sjögren syndrome.

Table 2: Clinical characterisation of the autosomal recessive ataxias

plegia.[73,122] This suggests that similar pathogenetic mechanisms may cause both infantile-onset spinocerebellar ataxia and the POLG related ataxic disorders, although why the former is much more severe is unknown.

Cayman ataxia

This rare childhood-onset disorder is found in an isolated inbred population from Grand Cayman Island in the Caribbean and is characterised by cerebellar ataxia with atrophy of the cerebellum on neuroimaging, hypotonia, and psychomotor retardation.[124] The gene, *ATCAY*, is located on chromosome 19p13.3 and encodes the protein caytaxin.[124,125] Caytaxin contains a binding domain similar to that of the α-tocopherol transfer protein, which is mutated in ataxia with vitamin E deficiency, but likely binds a different

	FRDA	AVED	ABL	RD	LOTS	CTX	MIRAS	SCAN1	AT	ATLD	AOA1	AOA2	ARSACS	IOSCA	CA	MSS
Retinitis pigmentosa	–	+*	+*	+*	–	–	–	–	–	–	–	–	–	–	–	–
Epilepsy	–	–	–	–	+*	+*	+*	–	–	–	–	–	–	+*	–	–
Hearing loss	+*	–	–	+*	–	–	+*	–	–	–	–	–	–	+*	–	–
Cardiomyopathy	+*	+*	+*	+*	–	–	–	–	–	–	–	–	–	–	–	–
Diabetes	+*	–	–	–	–	–	–	–	+*	–	–	–	–	–	–	–
Scoliosis	+*	–	–	–	–	–	–	–	–	–	+*	+*	–	–	–	+*
Skeletal deformities	–	–	–	+*	–	–	–	–	–	–	–	–	–	–	–	+*
Cataracts	–	–	–	–	–	+*	–	–	–	–	–	–	–	–	–	+*
Optic atrophy	–	–	–	–	–	–	–	–	–	–	+*	–	–	+*	–	–
Hypogonadism	–	–	–	–	–	–	–	–	–	–	–	+*	–	–	–	+*
Oculocutaneous telangiectasias	–	–	–	–	–	–	–	–	+*	–	–	–	–	–	–	–
Tendon xanthomas	–	–	–	–	–	+*	–	–	–	–	–	–	–	–	–	–
Hypermyelinated retinal fibers	–	–	–	–	–	–	–	–	–	–	–	–	+*	–	–	–
Lymphoid cancer	–	–	–	–	–	–	–	–	+*	–	–	–	–	–	–	–
Radiosensitivity	–	–	–	–	–	–	–	–	+*	+*	–	–	–	–	–	–
Immunodeficiency	–	–	–	–	–	–	–	–	+*	+*	–	–	–	–	–	–
Lipid malabsorption	–	–	+*	–	–	–	–	–	–	–	–	–	–	–	–	–
Migraine-like headaches	–	–	–	–	–	–	+*	–	–	–	–	–	–	–	–	–
Liver failure	–	–	–	–	–	–	+*	–	–	–	–	–	–	–	–	–
Renal failure	–	–	–	+*	–	–	–	–	–	–	–	–	–	–	–	–
Post-viral rhabdomyolysis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+*
Other associated features	–	–	–	an,ic	bl,f,isr	cd,op,pa	–	–	–	–	–	–	–	–	–	ss
Low vitamin E	–	+*	+*	–	–	–	–	–	–	–	–	–	–	–	–	–
Low fat soluble vitamins	–	–	+*	–	–	–	–	–	–	–	–	–	–	–	–	–
Low albumin	–	–	–	–	–	–	–	+*	–	–	+*	–	–	–	–	–
Low lipoproteins	–	–	+*	–	–	–	–	–	–	–	–	–	–	–	–	–
Low immunological factors	–	–	–	–	–	–	–	–	+*	+*	–	–	–	–	–	–
High phytanic acid	–	–	–	+*	–	–	–	–	–	–	–	–	–	–	–	–
High cholestanol	–	–	–	–	–	+*	–	–	–	–	–	–	–	–	–	–
High bile alcohols	–	–	–	–	–	+*	–	–	–	–	–	–	–	–	–	–
High α-fetoprotein	–	–	–	–	–	–	–	–	+*	–	–	+*	–	–	–	–
High cholesterol	–	–	–	–	–	–	–	+*	–	–	+*	+*	–	–	–	–
Acanthocytosis	–	–	+*	–	–	–	–	–	–	–	–	–	–	–	–	–
High CSF protein	–	–	–	+*	–	–	–	–	–	–	–	–	–	–	–	–
Nerve conduction studies	AS	AS	AS	DSM*	ASM	ASM	ASM	ASM	ASM	ASM	ASM	ASM	ASM	AS	–	DSM*
MRI spinal-cord atrophy	+*	–	–	–	–	–	–	–	–	–	–	–	+*	+*	–	–
MRI white-matter changes	–	–	–	–	–	+*	+*	–	–	–	–	–	–	–	–	–
MRI cerebellar atrophy	–	–	–	–	+*	+*	+*	+*	+*	+*	+*	+*	+*	+*	+*	+*

Clinical findings associated with the various autosomal recessive ataxias are shown along with key laboratory and other diagnostic test results. +=feature may be present. –=feature not present, uncommon, or not reported. *Features useful for differential diagnosis. an=anosmia. bl=blindness. cd=chronic diarrhoea. f=fasciculations. ic=ichthyosis. isr=increased startle response. op=osteoporosis. pa=premature atherosclerosis. ss=short stature. AS=axonal sensory neuropathy. ASM=axonal sensorimotor neuropathy. DSM=demyelinating sensorimotor neuropathy. FRDA=Friedreich's ataxia. AVED=ataxia with vitamin E deficiency. ABL=abetalipoproteinaemia. RD=Refsum's disease. LOTS=late-onset Tay-Sachs disease. CTX=cerebrotendinous xanthomatosis. MIRAS=mitochondrial recessive ataxia syndrome. SCAN1=spinocerebellar ataxia with axonal neuropathy. AT=ataxia telangiectasia. ATLD=ataxia telangiectasia-like disorder. AOA1=ataxia with oculomotor apraxia, type 1. AOA2=ataxia with oculomotor apraxia, type 2. ARSACS=autosomal recessive ataxia of Charlevoix-Saguenay. IOSCA=infantile onset spinocerebellar ataxia. CA=Cayman ataxia. MSS=Marinesco-Sjögren syndrome.

Table 3: **Phenotypic and diagnostic characterisation of the autosomal recessive ataxias**

unknown ligand.[125] In rodents, the protein seems to interact with kidney-type glutaminase and mutations are speculated to affect glutamate synthesis at synapses, potentially causing abnormal neuron growth or neurotoxicity.[126]

Marinesco-Sjögren syndrome

This rare infantile-onset or childhood-onset syndrome is characterised by cerebellar ataxia, cataracts, mental retardation, and short stature associated with hypogonadotropic hypogonadism, and skeletal deformities.[127–129] Patients may also present with variable degrees of myopathy involving hypotonia, muscle weakness, and atrophy, as well as peripheral neuropathy or epilepsy.[127–129] MRI may show cerebellar atrophy.[127] The causative gene, *SIL1*, is located on chromosome 5q31 and encodes a nucleotide exchange factor for heat-shock protein 70 family member HSPA5, which functions as a molecular chaperone during nascent protein folding and transport.[128,129] Because *SIL1* is ubiquitously expressed,[128] it is unclear why its impairment causes the specific features seen in the Marinesco-Sjögren phenotype.

Conclusion

Among the hereditary ataxias, those with autosomal recessive inheritance form a heterogeneous population. The major disorders can be effectively grouped into three categories. The first two of these are best represented clinically by Friedreich's ataxia, while the last category is exemplified by ataxia telangiectasia. Although additional clinical assessment can aid in further differentiation within these categories (table 2), ancillary testing with simple laboratory studies and neuroimaging can be quite helpful in many cases, particularly for disorders that resemble Friedreich's ataxia (table 3). Armed with this information, directed genetic testing can then be done to definitively establish the diagnosis (figure 2). Because of its prevalence and variability of presentation, almost all patients should be screened initially for Friedreich's ataxia. Subsequently, clinical phenotype can direct further diagnostic biochemical testing, if available, and suggest relevant genetic testing when appropriate for management or when a molecular diagnosis is desired. Genetic testing can be expensive, currently ranging, on average, from US$300 for repeat expansion or specific mutation screening to US$1000 or more for sequencing of an entire gene and therefore focused testing is recommended when a genetic diagnosis is clinically warranted.

Although many advances have occurred in our understanding of the molecular and cellular pathogenesis underlying many of these disorders, particularly Friedreich's ataxia, further study is needed to better understand the biology of these disorders. Why global metabolic changes involving the mitochondria, lipid biochemistry, or other fundamental cellular processes
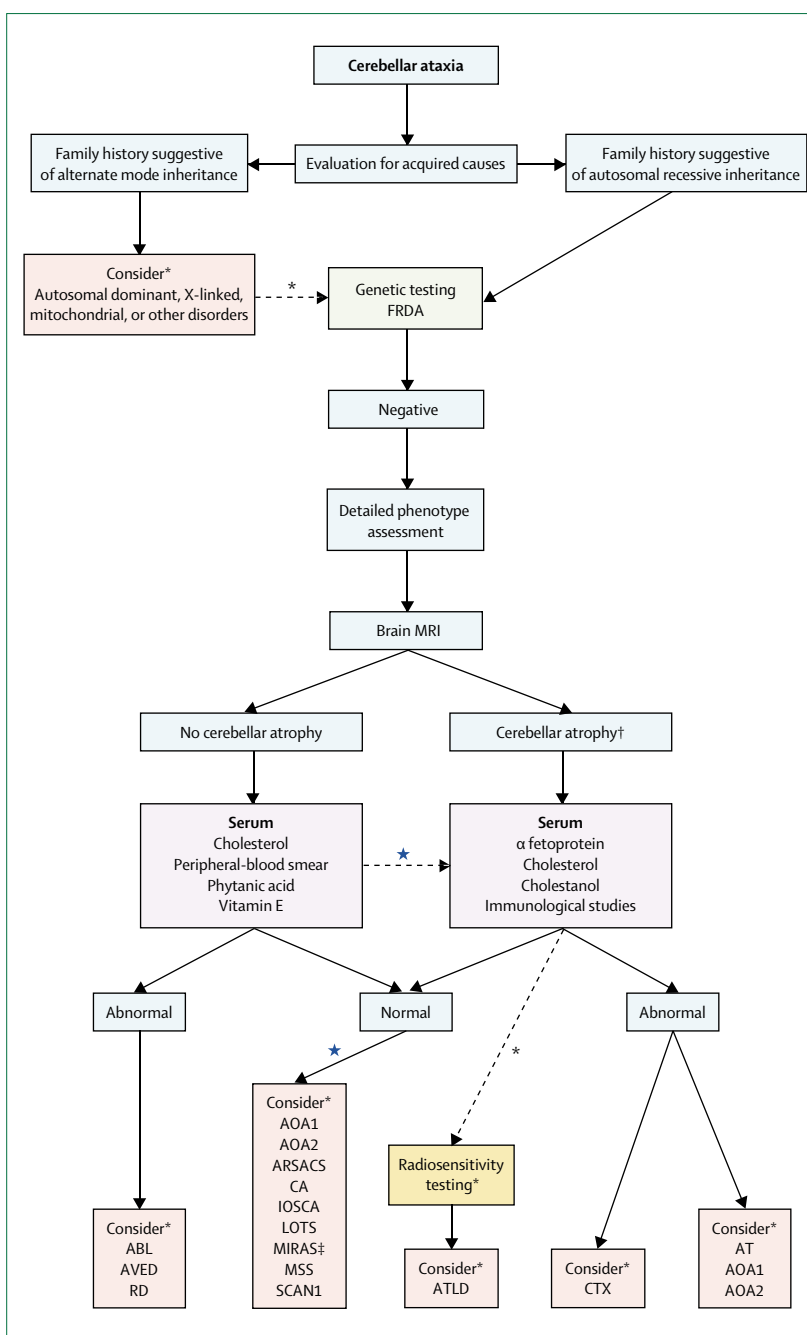
Figure 2: **Diagnostic assessment of a patient with a suspected autosomal recessive hereditary ataxia**
Blue boxes represent clinical or diagnostic considerations; red boxes indicate points requiring further clinical or diagnostic assessment; points for establishing a definitive diagnosis are indicated on the basis of type of test as green (genetic), purple (serum), or yellow (radiosensitivity) boxes. Note that ataxic disorders characterised by cerebellar atrophy may present with normal neuroimaging early in their course; therefore these conditions should also be investigated in patients with normal imaging if clinically warranted (blue star). Further considerations may include focused genetic testing if a molecular diagnosis is desired. *=if clinically indicated. †=or white-matter changes. ‡=or other POLG cerebellar ataxic disorder. FRDA=Friedreich's ataxia. AVED=ataxia with vitamin E deficiency. ABL=abetalipoproteinaemia. RD=Refsum's disease. LOTS=late-onset Tay-Sachs disease. CTX=cerebrotendinous xanthomatosis. MIRAS=mitochondrial recessive ataxia syndrome. SCAN1=spinocerebellar ataxia with axonal neuropathy. AT=ataxia telangiectasia. AOA1=ataxia with oculomotor apraxia, type 1. AOA2=ataxia with oculomotor apraxia, type 2. ARSACS=autosomal recessive ataxia of Charlevoix-Saguenay. IOSCA=infantile-onset spinocerebellar ataxia. CA=Cayman ataxia. MSS=Marinesco-Sjögren syndrome.
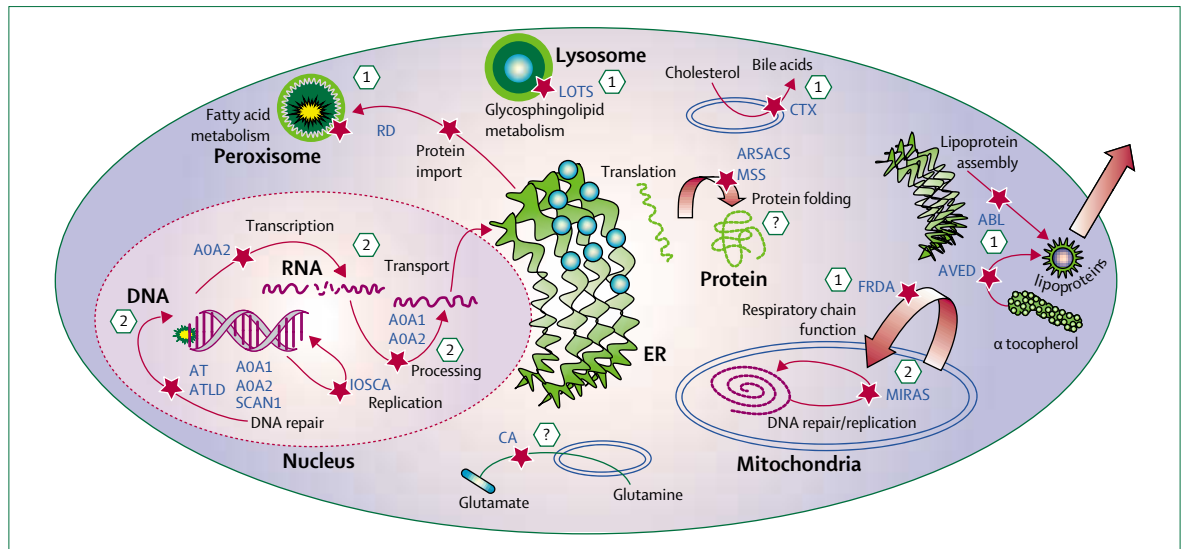
***Figure 3*: Molecular pathogenesis of the autosomal recessive ataxias**
A generic human cell is depicted, with major organelles labelled. The pathways or sites affected by the various underlying mutations causing the different autosomal recessive ataxias are indicated by a red star. Not all of these processes occur in the same cell types; please see text for more details. Although the precise mechanisms of pathogenesis are not known in all cases (?), suspected causes include increased oxidative stress and other metabolic anomalies leading to premature cell death (1), and genetic instability (2). Processes occurring within or in association with a specific subcellular structure are depicted near the respective organelle. ER=endoplasmic reticulum. FRDA=Friedreich's ataxia. AVED=ataxia with vitamin E deficiency. ABL=abetalipoproteinaemia. RD=Refsum's disease. LOTS=late-onset Tay-Sachs disease. CTX=cerebrotendinous xanthomatosis. MIRAS=mitochondrial recessive ataxia syndrome. SCAN1=spinocerebellar ataxia with axonal neuropathy. AT=ataxia telangiectasia. AOA1=ataxia with oculomotor apraxia, type 1. AOA2=ataxia with oculomotor apraxia, type 2. ARSACS=autosomal recessive ataxia of Charlevoix-Saguenay. IOSCA=infantile-onset spinocerebellar ataxia. CA=Cayman ataxia. MSS=Marinesco-Sjögren syndrome.

such as DNA repair, protein folding, or RNA processing so profoundly and specifically affect the cerebellum and spinocerebellar pathways is an important area for further investigation (figure 3). The effects of oxidative stress, metabolic complications leading to premature cell death, and genetic instability appear to be key underlying mechanisms in several of these disorders and may ultimately aid in the development of effective treatment strategies. Current treatments are unfortunately limited primarily to symptomatic management but, with continued research, hopefully physicians will be able to provide more options to their recessive ataxia patients in the future.

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1966 until June 2006 with the terms "cerebellar ataxia", "recessive cerebellar ataxia", "Friedreich ataxia", "AVED", "abetalipoproteinemia", "Refsum disease", "late onset Tay-Sachs", "cerebrotendinous xanthomatosis", "POLG ataxia", "SCAN1", "ataxia telangiectasia", "AOA1", "AOA2", "ARSACS", "IOSCA", "Cayman ataxia", and "Marinesco-Sjogren". Due to space limitations, emphasis was placed on comprehensive reviews and primary articles published after 1996. Articles were also identified through searches of the authors' own files and references from relevant articles. Only papers published in English were reviewed.

References
1   Harding AE. Classification of the hereditary ataxias and paraplegias. *Lancet* 1983; **1:** 1151–55.
2   Perlman S. Symptomatic and disease-modifying therapy for the progressive ataxias. *Neurologist* 2004; **10:** 275–89.
3   Schols L, Bauer P, Schmidt T, Schulte T, Riess O. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. *Lancet Neurol* 2004; **3:** 291–304.
4   Di Donato S, Gellera C, Mariotti C. The complex clinical and genetic classification of inherited ataxias—II: autosomal recessive ataxias. *Neurol Sci* 2001; **22:** 219–28.
5   van de Warrenburg BPC, Sinke RJ, Kremer B. Recent advances in hereditary spinocerebellar ataxias. *J Neuropathol Exp Neurol* 2005; **64:** 171–80.
6   Harding AE. Early onset cerebellar ataxia with retained tendon reflexes: a clinical and genetic study of a disorder distinct from Friedreich's ataxia. *J Neurol Neurosurg Psychiatry* 1981; **44:** 503–08.
7   Pandolfo M. Molecular pathogenesis of Friedreich ataxia. *Arch Neurol* 1999; **56:** 1201–08.
8   Pandolfo M. Molecular basis of Friedreich ataxia. *Mov Disord* 2001; **16:** 815–21.
9   Cossee M, Schmitt M, Campuzano V, et al. Evolution of the Friedreich's ataxia trinucleotide repeat expansion: Founder effect and premutations. *Proc Natl Acad Sci USA* 1997; **94:** 7452–57.
10   Schols L, Amoiridis G, Przuntek H, Frank G, Epplen JT, Epplen C. Friedreich's ataxia. *Brain* 1997; **120:** 2131–40.
11   Alper G, Narayanan V. Friedreich's ataxia. *Pediatr Neurol* 2003; **28:** 335–41.

12   Harding AE. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain* 1981; **104:** 589–620.

13   Delatycki MB, Williamson R, Forrest SM. Friedreich ataxia: an overview. *J Med Genet* 2000; **37:** 1–8.

14   Voncken M, Ioannou P, Delatycki MB. Friedreich ataxia—update on pathogenesis and possible therapies. *Neurogenetics* 2004; **5:** 1–8.

15   Lynch DR, Farmer JM, Balcer LJ, Wilson RB. Friedreich ataxia: effects of genetic understanding on clinical evaluation and therapy. *Arch Neurol* 2002; **59:** 743–47.

16   Bhidayasiri R, Perlman S, Pulst SM, Geschwind DH. Late-onset Friedreich ataxia. 2005; **62:** 1865–69.

17   Campuzano V, Montermini L, Molto MD, Pianese L, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* 1996; **271:** 1423–27.

18   Bidichandani SI, Ashizawa T, Patel PI. The GAA triplet-repeat expansion in Friedreich ataxia interferes with transcription and may be associated with an unusual DNA structure. *Am J Hum Genet* 1998; **62:** 111–21.

19   Grabczyk E, Usdin K. The GAA*TTC triplet repeat expanded in Friedreich's ataxia impedes transcription elongation by T7 RNA polymerase in a length and supercoil dependent manner. *Nucleic Acids Res* 2000; **28:** 2815–22.

20   Patel PI, Isaya G. Friedreich ataxia: from GAA triplet-repeat expansion to frataxin deficiency. *Am J Hum Genet* 2001; **69:** 15–24.

21   Sakamoto N, Chastain PD, Parniewski P, et al. Sticky DNA: Self-association properties of long GAA*TTC repeats in R*R*Y triplex structures from Friedreich's ataxia. *Mol Cell* 1999; **3:** 465–75.

22   Mateo I, Llorca J, Volpini V, Corral J, Berciano J, Combarros O. GAA expansion size and age at onset of Friedreich's ataxia. *Neurology* 2003; **61:** 274–75.

23   Puccio H, Koenig M. Recent advances in the molecular pathogenesis of Friedreich ataxia. *Hum Mol Genet* 2000; **9:** 887–92.

24   Montermini L, Richter A, Morgan K, et al. Phenotypic variability in Friedreich ataxia: role of the associated GAA triplet repeat expansion. *Ann Neurol* 1997; **41:** 675–82.

25   Hellenbroich Y, Schwinger E, Zuhlke C. Limited somatic mosaicism for Friedreich's ataxia GAA triplet repeat expansions identified by small pool PCR in blood leukocytes. *Acta Neurol Scand* 2001; **103:** 188–92.

26   Campuzano V, Montermini L, Lutz Y, et al. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Hum Mol Genet* 1997; **6:** 1771–80.

27   Bradley JL, Blake JC, Chamberlain S, Thomas PK, Cooper JM, Schapira AHV. Clinical, biochemical and molecular genetic correlations in Friedreich's ataxia. *Hum Mol Genet* 2000; **9:** 275–82.

28   Cavadini P, O'Neill HA, Benada O, Isaya G. Assembly and iron-binding properties of human frataxin, the protein deficient in Friedreich ataxia. *Hum Mol Genet* 2002; **11:** 217–27.

29   Lodi R, Copper JM, Bradley JL, et al. Deficit of *in vivo* mitochondrial ATP production in patients with Friedreich ataxia. *Proc Natl Acad Sci USA* 1999; **96:** 11492–95.

30   Babcock M, de Silva D, Oaks R, et al. Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin. *Science* 1997; **276:** 1709–12.

31   Gakh O, Park S, Liu G, et al. Mitochondrial iron detoxification is a primary function of frataxin that limits oxidative damage and preserves cell longevity. *Hum Mol Genet* 2006; **15:** 467–79.

32   Cavadini P, Gellera C, Patel P, Isaya G. Human frataxin maintains mitochondrial iron homeostasis in *Saccharomyces cerevisiae*. *Hum Mol Genet* 2000; **9:** 2523–30.

33   Cossee M, Puccio H, Gansmuller A, et al. Inactivation of the Friedreich ataxia mouse gene leads to early embryonic lethality without iron accumulation. *Hum Mol Genet* 2000; **9:** 1219–26.

34   Pook MA, Al-Mahdawi S, Carroll CJ, et al. Rescue of the Friedreich's ataxia knockout mouse by human YAC transgenesis. *Neurogenetics* 2001; **3:** 185–93.

35   Puccio H, Simon D, Cossee M, et al. Mouse models for Friedreich ataxia exhibit cardiomyopathy, sensory nerve defect and Fe-S enzyme deficiency followed by intramitochondrial iron deposits. *Nat Genet* 2001; **27:** 181–86.

36   Wilson, RB. Frataxin and frataxin deficiency in Friedreich's ataxia. *J Neurol Sci* 2003; **207:** 103–05.

37   Durr A. Friedreich's ataxia: treatment within reach. *Lancet Neurol* 2002; **1:** 370–74.

38   Hart PE, Lodi R, Rajagopalan B, et al. Antioxidant treatment of patients with Friedreich ataxia. *Arch Neurol* 2005; **62:** 621–26.

39   Buyse G, Mertens L, Di Salvo G, et al. Idebenone treatment in Friedreich's ataxia: neurological, cardiac, and biochemical monitoring. *Neurology* 2003; **60:** 1679–81.

40   Hausse AO, Aggoun Y, Bonnet D, et al. Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. *Heart* 2002; **87:** 346–49.

41   Mariotti C, Solari A, Torta D, Marano L, Fiorentini C, Di Donato S. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2003; **60:** 1676–79.

42   Rustin P, von Kleist-Retzow JC, Chantrel-Groussard K, Sidi D, Munnich A, Rotig A. Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study. *Lancet* 1999; **354:** 477–79.

43   Seznec H, Simon D, Monassier L, et al. Idebenone delays the onset of cardiac functional alteration without correction of Fe-S enzymes deficit in a mouse model for Friedreich ataxia. *Hum Mol Genet* 2004; **13:** 1017–24.

44   Benomar A, Yahyaoui M, Meggouh F, et al. Clinical comparison between AVED patients with 744 del A mutation and Friedreich ataxia with GAA expansion in 15 Moroccan families. *J Neurol Sci* 2002; **198:** 25–29.

45   Cavalier L, Ouahchi K, Katden HJ, et al. Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families. *Am J Hum Genet* 1998; **62:** 301–10.

46   Marzouki N, Benomar A, Yahyaoui M, et al. Vitamin E deficiency ataxia with (744 del A) mutation on α-TTP gene: genetic and clinical peculiarities in Moroccan patients. *Eur J Med Genet* 2005; **48:** 21–28.

47   Ben Hamida C, Doerflinger N, Belal S, et al. Localization of Friedreich ataxia phenotype with selective vitamin E deficiency to chromosome 8q by homozygosity mapping. *Nat Genet* 1996; **5:** 195–200.

48   Ouahchi K, Arita M, Kayden H, et al. Ataxia with isolated vitamin E deficiency is caused by mutations in the α-tocopherol transfer protein. *Nat Genet* 1995; **9:** 141–45.

49   Copp RP, Wisniewski T, Hentati F, Larnaout A, Ben Hamida M, Kayden HJ. Localization of α-tocopherol transfer protein in the brains of patients with ataxia with vitamin E deficiency and other oxidative stress related neurodegenerative disorders. *Brain Res* 1999; **822:** 80–87.

50   Gabsi S, Gouider-Khouja N, Belal S, et al. Effect of vitamin E supplementation in patients with ataxia with vitamin E deficiency. *Eur J Neurol* 2001; **8:** 477–81.

51   Yokota T, Igarashi K, Uchihara T, et al. Delayed-onset ataxia in mice lacking alpha-tocopherol transfer protein: model for neuronal degeneration caused by chronic oxidative stress. *Proc Natl Acad Sci USA* 2001; **98:** 15185–90.

52   Narcisi TM, Shoulders CC, Chester SA, et al. Mutations of the microsomal triglyceride-transfer-protein in abetalipoproteinemia. *Am J Hum Genet* 1995; **57:** 1298–310.

53   Wang J, Hegele RA. Microsomal triglyceride transfer protein (MTP) gene mutations in canadian subjects with abetalipoproteinemia. *Hum Mutat* 2000; **15:** 294–95.

54   Berriot-Varoqueaux N, Aggerbeck LP, Samson-Bouma M-E, Wetterau JR. The role of the microsomal triglyceride transfer protein in abetalipoproteinemia. *Annu Rev Nutr* 2000; **20:** 663–97.

55   Chang BHJ, Liao W, Li L, Nakamuta M, Mack D, Chan L. Liver-specific inactivation of the abetalipoproteinemia gene completely abrogates very low density lipoprotein/low density lipoprotein production in a viable conditional knockout mouse. *J Biol Chem* 1999; **274:** 6051–55.

56   Jansen GA, Waterham HR, Wanders RJA. Molecular basis of Refsum disease: sequence variations in phytanoyl-CoA hydroxylase (PHYH) and the PTS2 receptor (PEX7). *Hum Mutat* 2004; **23:** 209–18.

57   Wills AJ, Manning NJ, Reilly MM. Refsum's disease. *Q J Med* 2001; **94:** 403–06.

58   Weinstein R. Phytanic acid storage disease (Refsum's disease): clinical characteristics, pathophysiology and the role of therapeutic apheresis in its management. *J Clin Apher* 1999; **14:** 181–84.

59 van den Brink DM, Brites P, Haasjes J, et al. Identification of PEX7 as the second gene involved in Refsum disease. *Am J Hum Genet* 2003; **72:** 471–77.

60 Schon EA, Santra S, Pallotti F, Girvin ME. Pathogenesis of primary defects in mitochondrial ATP synthesis. *Semin Cell Dev Biol* 2001; **12:** 441–48.

61 Eklund EA, Freeze HH. The congenital disorders of glycosylation: a multifaceted group of syndromes. *NeuroRx* 2006; **3:** 254–63.

62 Jeyakumar M, Butters TD, Dwek RA, Platt FM. Glycosphingolipid lysosomal storage diseases: therapy and pathogenesis. *Neuropathol Appl Neurobio* 2002; **28:** 343–57.

63 Montalvo ALE, Filocamo M, Vlahovicek K, et al. Molecular analysis of the HEXA gene in Italian patients with infantile and late onset Tay-Sachs disease: detection of fourteen novel alleles. *Hum Mutat* 2005; **26:** 2–8.

64 Neudorfer O, Pastores GM, Zeng BJ, Gianutsos J, Zarodd CM, Kolodny EH. Late-onset Tay-Sachs disease: phenotypic characterization and genotypic correlations in 21 affected patients. *Genet Med* 2005; **7:** 119–23.

65 Miklyaeva EI, Dong W, Bureau A, et al. Late onset Tay-Sachs disease in mice with targeted disruption of the Hexa gene: behavioral changes and pathology of the central nervous system. *Brain Res* 2004; **1001:** 37–50.

66 Jeyakumar M, Smith D, Eliot-Smith E, et al. An inducible mouse model of late onset Tay-Sachs disease. *Neurobiol Dis* 2002; **10:** 201–10.

67 Jeyakumar M, Thomas R, Elliot-Smith E, et al. Central nervous system inflammation is a hallmark of pathogenesis in mouse models of GM1 and GM2 gangliosidosis. *Brain* 2003; **126:** 974–87.

68 Aerts JMFG, Hollak CEM, Boot RG, Groener JEM, Maas M. Substrate reduction therapy of glycosphingolipid storage disorders. *J Inherit Metab Dis* 2006; **29:** 449–56.

69 Cachon-Gonzalez MB, Wang SZ, Lynch A, Ziegler R, Cheng SH, Cox TM. Effective gene therapy in an authentic model of Tay-Sachs-related diseases. *Proc Natl Acad Sci USA* 2006; **103:** 10373–78.

70 Lorincz MT, Rainier S, Thomas D, Fink JK. Cerebrotendinous xanthomatosis. possible higher prevalence than previously recognized. *Arch Neurol* 2005; **62:** 1459–63.

71 Moghadasian MH, Salen G, Frohlich JJ, Scudamore CH. Cerebrotendinous xanthomatosis. a rare disease with diverse manifestations. *Arch Neurol* 2002; **59:** 527–29.

72 Verrips A, Hoefsloot LH, Steenbergen GCH, et al. Clinical and molecular genetic characteristics of patients with cerebrotendinous xanthomatosis. *Brain* 2000; **123:** 908–19.

73 Longley MJ, Graziewica MA, Bienstock RJ, Copeland WC. Consequences of mutations in human DNA polymerase γ. *Gene* 2005; **354:** 125–31.

74 Horvath R, Hudson G, Ferrari G, et al. Phenotypic spectrum associated with mutations of the mitochondrial polymerase γ gene. *Brain* 2006; **129:** 1674–84.

75 Van Goethem G, Luoma P, Rantamaki M, et al. POLG mutations in neurodegenerative disorders with ataxia but no muscle involvement. *Neurology* 2004; **63:** 1251–57.

76 Van Goethem G, Martin JJ, Dermaut B, et al. Recessive POLG mutations presenting with sensory and ataxic neuropathy in compound heterozygote patients with progressive external ophthalmoplegia. *Neuromuscul Disord* 2003; **13:** 133–42.

77 Winterthun S, Ferrari G, He L, et al. Autosomal recessive mitochondrial ataxic syndrome due to mitochondrial polymerase γ mutations. *Neurology* 2005; **64:** 1204–08.

78 Rantamaki M, Krahe R, Paetau A, Cormand B, Mononen I, Udd B. Adult-onset autosomal recessive ataxia with thalamic lesions in a Finnish family. *Neurology* 2001; **57:** 1043–49.

79 Hakonen AH, Heiskanen S, Juvonen V, et al. Mitochondrial DNA polymerase W748S mutation: a common cause of autosomal recessive ataxia with ancient European origin. *Am J Hum Genet* 2005; **77:** 430–41.

80 Tzoulis C, Engelsen BA, Telstad W, et al. The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. *Brain* 2006; **129:** 1685–92.

81 Takashima H, Boerkoel CF, John J, et al. Mutation of TDP1, encoding a topoisomerase I-dependant DNA damage repair enzyme, in spinocerebellar ataxia with axonal neuropathy. *Nat Genet* 2002; **32:** 267–72.

82 El-Khamisy SF, Saifi GM, Weinfeld M, et al. Defective DNA single-strand break repair in spinocerebellar ataxia with axonal neuropathy-1. *Nature* 2005; **434:** 108–13.

83 El-Khamisy SF, Caldecott KW. TDP1-dependant DNA single-strand break repair and neurodegeneration. *Mutagenesis* 2006; **21:** 219–24.

84 Filla A, De Michele G, Cavalcanti F, et al. Clinical and genetic heterogeneity in early onset cerebellar ataxia with retained tendon reflexes. *J Neurol Neurosurg Psychiatry* 1990; **53:** 667–70.

85 Ball LG, Xiao W. Molecular basis of ataxia telangiectasia and related diseases. *Acta Pharmacologica Sinica* 2005; **26:** 897–907.

86 Taylor AMR, Byrd PJ. Molecular pathology of ataxia telangiectasia. *J Clin Pathol* 2005; **58:** 1009–15.

87 McKinnon PJ. ATM and ataxia telangiectasia. *EMBO Rep* 2004; **5:** 772–76.

88 Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. *DNA Repair (Amst)* 2004; **3:** 1187–96.

89 Savitsky K, Bar-Shira A, Gilad S, et al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995; **268:** 1749–53.

90 Shiloh Y. The ATM-mediated DNA-damage response: taking shape. *Trends Biochem Sci* 2006; **31:** 402–10.

91 Lee JH, Lim DS. Dual role of Nbs1 in the ataxia telangiectasia mutated-dependent DNA damage response. *FEBS J* 2006; **273:** 1630–36.

92 Taylor AMR, Groom A, Byrd PJ. Ataxia-telangiectasia-like disorder (ATLD) – its clinical presentation and molecular basis. *DNA Repair (Amst)* 2004; **3:** 1219–25.

93 Frappart PO, Tong WM, Demuth I, et al. An essential function for NBS1 in the prevention of ataxia and cerebellar defects. *Nat Med* 2005; **11:** 484–90.

94 Barlow C, Hirotsune S, Paylor R, et al. Atm-deficient mice: a paradigm of ataxia telangiectasia. *Cell* 1996; **86:** 159–71.

95 Xu Y, Ashley T, Brainerd EE, Bronson RT, Meyn MS, Baltimore D. Targeted disruption of ATM leads to growth retardation, chromosomal fragmentation during meiosis, immune defects, and thymic lymphoma. *Genes Dev* 1996; **10:** 2411–22.

96 Moreira MC, Barbot C, Tachi N, et al. The gene mutated in ataxia-ocular apraxia 1 encodes the HIT/Zn-finger protein aprataxin. *Nat Genet* 2001; **29:** 189–93.

97 Date H, Onodera O, Tanaka H, et al. Early-onset ataxia with ocular motor apraxia and hypoalbuminemia is caused by mutations in a new HIT superfamily gene. *Nat Genet* 2001; **29:** 184–88.

98 Criscuolo C, Mancini P, Sacca F, et al. Ataxia with oculomotor apraxia type 1 in southern Italy: late onset and variable phenotype. *Neurology* 2004; **63:** 2173–75.

99 Amouri R, Moreira MC, Zouari M, et al. Aprataxin gene mutations in Tunisian families. *Neurology* 2004; **63:** 928–29.

100 Le Ber I, Moreira MC, Rivaud-Pechoux S, et al. Cerebellar ataxia with oculomotor apraxia type 1: clinical and genetic studies. *Brain* 2003; **126:** 2761–72.

101 Shimazaki H, Takiyama Y, Sakoe K, et al. Early-onset ataxia with oculomotor apraxia and hypoalbuminemia: the aprataxin gene mutations. *Neurology* 2002; **59:** 590–95.

102 Moreira MC, Barbot C, Tachi N, et al. Homozygosity mapping of Portuguese and Japanese forms of ataxia-oculomotor apraxia to 9p13, and evidence for genetic heterogeneity. *Am J Hum Genet* 2001; **68:** 501–08.

103 Kijas AW, Harris JL, Harris JM, Lavin MF. Aprataxin forms a discrete branch in the HIT (histidine triad) superfamily of proteins with both DNA/RNA bindings and nucleotide hydrolase activities. *J Biol Chem* 2006; **281:** 13939–48.

104 Mosesso P, Piane M, Palitti F, Pepe G, Penna S, Chessa L. The novel human gene aprataxin is directly involved in DNA single-strand-break repair. *Cell Mol Life Sci* 2005; **62:** 485–91.

105 Le Ber I, Bouslam N, Rivaud-Pechoux S, et al. Frequency and phenotypic spectrum of ataxia with oculomotor apraxia 2: a clinical and genetic study in 18 patients. *Brain* 2004; **127:** 759–67.

106 Moreira MC, Klur S, Watanabe M, et al. Senataxin, the ortholog of a yeast RNA helicase, is mutant in ataxia-ocular apraxia 2. *Nat Genet* 2004; **36:** 225–27.

107 Duquette A, Roddier K, McNabb-Baltar J, et al. Mutations in senataxin responsible for Quebec cluster of ataxia with neuropathy. *Ann Neurol* 2005; **57:** 408–14.

108 Criscuolo C, Chessa L, Di Giandomenico S, et al. Ataxia with oculomotor apraxia type 2: a clinical, pathologic, and genetic study. *Neurology* 2006; **66:** 1207–10.

109 Chen YZ, Hashemi SH, Anderson SK, et al. Senataxin, the yeast Sen1p orthologue: characterization of a unique protein in which recessive mutations cause ataxia and dominant mutations cause motor neuron disease. *Neurobiol Dis* 2006; **23:** 97–108.

110 Ursic D, Chinchilla K, Finkel JS, Culbertson MR. Multiple protein/protein and protein/RNA interactions suggest roles for yeast DNA/RNA helicase Sen1p in transcription, transcription-coupled DNA repair, and RNA processing. *Nucleic Acids Res* 2004; **32:** 2441–52.

111 Chen YZ, Bennett CL, Huynh HM, et al. DNA/RNA helicase gene mutations in a form of juvenile amyotrophic lateral sclerosis (ALS4). *Am J Hum Genet* 2004; **74:** 1128–35.

112 Bouchard JP, Richter A, Mathieu J, et al. Autosomal recessive spastic ataxia of Charlevoix-Saguenay. *Neuromuscl Disord* 1998; **8:** 474–79.

113 El Euch-Fayache G, Lalani I, Amouri R, et al. Phenotypic features and genetic findings in sacsin-related autosomal recessive ataxia in Tunisia. *Arch Neurol* 2003; **60:** 982–88.

114 Mrissa N, Belal S, Ben Hamida C, et al. Linkage to chromosome 13q11-12 of an autosomal recessive cerebellar ataxia in a Tunisian family. *Neurology* 2000; **54:** 1408–14.

115 Richter AM, Ozgul RK, Poisson VC, Topaloglu H. Private SACS mutations in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) families from Turkey. *Neurogenetics* 2004; **5:** 165–70.

116 Engert JC, Berube P, Mercier J, et al. ARSACS, a spastic ataxia common in northeastern Quebec, is caused by mutations in a new gene encoding an 11.5-kb ORF. *Nat Genet* 2000; **24:** 120–25.

117 Criscuolo C, Banfi S, Orio M, et al. A novel mutation in SACS gene in a family from southern Italy. *Neurology* 2004; **62:** 100–02.

118 Criscuolo C, Sacca F, De Michele G, et al. Novel Mutation of SACS gene in a Spanish family with autosomal recessive spastic ataxia. *Mov Disord* 2005; **20:** 1358–61.

119 Grieco GS, Malandrini A, Comanducci G, et al. Novel SACS mutations in autosomal recessive spastic ataxia of Charlevoix-Saguenay type. *Neurology* 2004; **62:** 103–06.

120 Ogawa T, Takiyama Y, Sakoe K, et al. Identification of a SACS gene missense mutation in ARSACS. *Neurology* 2004; **62:** 107–09.

121 Hara K, Onodera O, Endo M, et al. Sacsin-related autosomal recessive ataxia without prominent retinal myelinated fibers in Japan. *Mov Disord* 2005; **20:** 380–82.

122 Nikali K, Suomalainen A, Saharinen J, et al. Infantile onset spinocerebellar ataxia is caused by recessive mutations in mitochondrial proteins twinkle and twinky. *Hum Mol Genet* 2005; **14:** 2981–90.

123 Lonnqvist T, Paetau A, Nikali K, von Boguslawski K, Pihko H. Infantile onset spinocerebellar ataxia with sensory neuropathy (IOSCA): neuropathological features. *J Neurol Sci* 1998; **161:** 57–65.

124 Nystuen A, Benke PJ, Merren J, Stone EM, Sheffield VC. A cerebellar ataxia locus identified by DNA pooling to search for linkage disequilibrium in an isolated population from the Cayman Islands. *Hum Mol Genet* 1996; **5:** 525–31.

125 Bomar JM, Benke PJ, Slattery EL, et al. Mutations in a novel gene encoding a CRAL-TRIO domain cause human Cayman ataxia and ataxia/dystonia in the jittery mouse. *Nat Genet* 2003; **35:** 264–69.

126 Buschdorf JP, Chew LL, Zhang B, et al. Brain-specific BNIP-2-homology protein Caytaxin relocalizes glutaminase to neurite terminals and reduces glutamate levels. *J Cell Sci* 2006; **119:** 3337–50.

127 Slavotinek A, Goldman J, Weisiger K, et al. Marinesco-Sjogren syndrome in a male with mild dysmorphism. *Am J Med Genet A* 2005; **133:** 197–201.

128 Anttonen AK, Mahjneh I, Hamalainen RH, et al. The gene disrupted in Marinesco-Sjogren syndrome encodes SIL1, an HSPA5 cochaperone. *Nat Genet* 2005; **37:** 1309–11.

129 Senderek J, Krieger M, Stendel C, et al. Mutations in SIL1 cause Marinesco-Sjogren syndrome, a cerebellar ataxia with cataract and myopathy. *Nat Genet* 2005; **37:** 1312–14.