OVERVIEW OF AFFERENT AND CEREBELLAR ATAXIAS

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Introduction

Ataxia

The term ataxia comes from the Greek and means “lack of order”. Ataxia designates the jerky or irregular character of movement or posture. Cerebellar ataxia results from a genuine cerebellar disorder or from a combined involvement of cerebellar and extra-cerebellar structures, especially the brainstem. Afferent ataxia is attributed to a loss of proprioceptive sensory feedback during movement and stance, probably due to loss of function of muscle spindles [1]. Pathology in afferent ataxia may be found in peripheral nerves, dorsal root ganglia, and spinal cord.

Cerebellar ataxia

Cerebellar patients are typically clumsy, the cerebellum being involved in limb coordination and control of balance. Cerebellum is functionally asymmetrical, not only for motor, but also for cognitive operations. It is currently considered that cerebellar signs fall into one of the following six categories:
(1) Oculomotor disturbances
(2) Speech deficits
(3) Disturbances in limb movements
(4) Deficits of posture and gait
(5) Deficits of cognitive operations
(6) Subtle autonomic signs.

Afferent ataxia

Clinically, afferent ataxia is often distinguished from a genuine cerebellar ataxia by (1) the heavy dependence on visual guidance, (2) the minor degree of oculomotor deficits, and (3) the absence of dysarthria. In most cases, afferent ataxia is associated with impaired tendon reflexes and sensory deficits. [2]

Presentations and etiologies

Presentation may be acute, subacute or slowly progressive, both in children and in adults. In addition, there are congenital and episodic ataxias. Etiologies include hereditary and acquired conditions.

Sporadic ataxias

Sporadic cerebellar ataxias

The main causes of acute cerebellar ataxia in adults are vascular lesions, cranial traumatisms, infections, intoxications, immune ataxias, vestibular disorders, and psychogenic causes.

Paraneoplastic cerebellar degeneration often presents as a subacute cerebellar syndrome and may occur before the identification of an underlying cancer, usually a small-cell lung cancer, a breast or ovarian cancer, or a lymphoma. A profound cerebellar atrophy of rapid progression characterizes most of these syndromes.

Alcohol is the most common cerebellotoxic agent. Chronic consumption causes cerebellar atrophy predominating in the anterior vermis [3]. In these patients, ataxia of gait is more severe than limb ataxia.

Wernicke encephalopathy combines a mental confusional state, oculomotor deficits (most often nystagmus and various degrees of paralysis of external rectus muscles) and gait ataxia. The main conditions associated with Wernicke encephalopathy are alcoholism, hyperemesis gravidarum, gastroplasty/intestinal surgery, prolonged parenteral nutrition, long stay in critical care units, dialysis, chemotherapy or immunosuppressive drugs, thyrotoxicosis and food refusal (psychogenic) [4].

In addition to multiple sclerosis, whose lesions commonly affect the cerebellum and its afferent and efferent connections, several immune ataxias have been recognized [5,6]. Antibodies to glutamic acid decarboxylase (GAD) are found in the serum of most patients with type 1 diabetes, but also in immune-mediated syndromes affecting the central nervous system, including stiff-person syndrome and a few patients with cerebellar ataxia [7], mostly women also affected with diabetes. Gluten ataxia is a type of autoimmune ataxia described to occur in genetically susceptible patients (the HLA class II type DQ2 is overrepresented) who produce circulating antigliadin antibodies following exposure to gliadin in food [8]. Ataxia may develop in the absence of enteropathy and may have an insidious course. Neurophysiological investigations show evidence of a sensorimotor axonal neuropathy in half of the patients. However, this entity remains controversial, as antigliadin antibodies are found in asymptomatic individuals and have been reported in subjects with other forms of degenerative ataxia, including hereditary diseases [9]. Ataxia can occur in the context of Hashimoto encephalopathy, but, rarely, subacute or chronic progressive ataxia has been reported to be the main neurological symptom in individuals with anti-thyroid antibodies, in most of whom cerebellar atrophy was shown on MRI [10,11]. Case reports of improvement with intravenous immunoglobulins suggest a role of autoimmunity in these patients. Ataxia may also occur in the context of a systemic autoimmune disease, as systemic lupus erythematosus and Sjögren's syndrome. In these conditions, a role for autoantibodies directed against cellular components of the nervous system has been postulated, but pathogenic mechanisms have not yet been fully elucidated. In the case of Sjögren's syndrome, an autoimmune sensory neuronopathy may cause afferent ataxia [2].

Multiple system atrophy (MSA) combines at various degrees symptoms of dysautonomia, parkinsonism, and cerebellar ataxia and corticospinal signs [12]. Pathologically, glial cytoplasmic alpha-synuclein inclusions are the hallmark of the disease. Predominant parkinsonian features that respond poorly to levodopa treatment characterize the parkinsonian variant of MSA (MSA-P), whereas the group of MSA-C refers to patients who exhibit predominant cerebellar deficits Symptoms of autonomic impairment may appear before motor symptoms. They consist of urinary tract dysfunction (incontinence, urinary urgency or retention), orthostatic hypotension, digestive tract dysfunction (constipation or diarrhea), erectile dysfunction, and dyshydrosis. Sleep disorders such as rapid eye movement sleep behavior disorder, central sleep apnea, and stridor may also predate the onset of motor symptoms [12]. MSA represents the most common non-hereditary degenerative ataxia. The disorder typically starts around the age of 55 years. MSA is a progressive, eventually fatal disease with a median survival of around 10 years after symptom onset [12]. MRI shows progressive cerebellar and pontine atrophy. Atrophy of pontocerebellar fibers gives a characteristic appearance on axial T2-weighted images of the pons, called the "cross bun sign"

Acquired afferent ataxias

Acquired afferent ataxias may be immune-mediated (including Sjögren syndrome and paraneoplastic), toxic (including iatrogenic), vitamin-related (e.g. vit B12), or of unknown cause [2]

References

1. Macefield, V. G., Norcliffe-Kaufmann, L., Gutiérrez, J., Axelrod, F. B. & Kaufmann, H. Can loss of muscle spindle afferents explain the ataxic gait in Riley-Day syndrome? *Brain* **134,** 3198–3208 (2011).
2. Sghirlanzoni, A., Pareyson, D. & Lauria, G. Sensory neuron diseases. *The Lancet Neurology* **4,** 349–361 (2005).
3. Manto, M. Toxic agents causing cerebellar ataxias. *Handb Clin Neurol* **103,** 201–213 (2012).
4. Laureno, R. Nutritional cerebellar degeneration, with comments on its relationship to Wernicke disease and alcoholism. *Handb Clin Neurol* **103,** 175–187 (2012).
5. Iwasaki, Y. *et al.* Subacute cerebellar ataxia and atrophy developed in a young woman with systemic lupus erythematosus whose cerebrospinal fluid was positive for antineuronal cell antibody. *Lupus* **21,** 324–328 (2012).
6. Hadjivassiliou, M. *et al.* Cerebellar ataxia as a possible organ-specific autoimmune disease. *Mov. Disord.* **23,** 1370–1377 (2008).
7. Honnorat, J. *et al.* Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. *Arch. Neurol.* **58,** 225–230 (2001).
8. Hadjivassiliou, M., Sanders, D. S., Woodroofe, N., Williamson, C. & Grünewald, R. A. Gluten ataxia. *Cerebellum* **7,** 494–498 (2008).
9. Abele, M., Schöls, L., Schwartz, S. & Klockgether, T. Prevalence of antigliadin antibodies in ataxia patients. *Neurology* **60,** 1674–1675 (2003).

10. Selim, M. & Drachman, D. A. Ataxia associated with Hashimoto's disease: progressive non-familial adult onset cerebellar degeneration with autoimmune thyroiditis. *J. Neurol. Neurosurg. Psychiatr.* **71,** 81–87 (2001).
11. Ferracci, F., Bertiato, G. & Moretto, G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. *J. Neurol. Sci.* **217,** 165–168 (2004).
12. Wenning, G. K. *et al.* The natural history of multiple system atrophy: a prospective European cohort study. *Lancet Neurol* (2013). doi:10.1016/S1474-4422(12)70327-7

RECESSIVE ATAXIAS

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Degenerative recessive ataxias are progressive, severe disabling diseases of complex etiology that affect both the central and peripheral nervous systems. Degenerative ataxias are caused by progressive alterations of either the cerebellum, the spinocerebellar tracts or the sensory tracts (posterior columns) of the spinal cord. Different combinations of these pathological sites are also often observed, as well as other neurological and extra-neurological alterations (peripheral nerves, pyramidal and extra-pyramidal systems, cortical, ocular, auditory, visceral dysfunction…).

Recessive ataxias affect about 1 person out of 20 000, one third of which is accounted for by Friedreich's ataxia (FRDA), which represent the most common form of recessive ataxia in the European/Caucasian populations. Another 20 % of cases are accounted for by a growing list of molecular defects, most of which represent less than a percent of the total number of cases, while nearly 50 % of the cases remain without a diagnosis[1].

Only a few forms were known well prior to gene identification (FRDA, ataxia-telangiectasia, Refsum disease, abetalipoproteinemia, ataxia with isolated vitamin E deficiency, spastic ataxia of the Charlevoix-Saguenay). On the contrary, many forms of recessive ataxia were identified or well delineated only recently and following gene localization or identification. The reasons why these forms of ataxia were only recently identified are the paucity of selective criteria, the broad overlap of clinical presentations, the high variability of disease onset and severity, the rarity of the particular forms. These diagnostic difficulties also explain the difficulties to identify the remaining forms of recessive ataxia and the high proportion of cases without a diagnosis.

A list of the major recessive degenerative ataxias and a summary of their main clinical and biochemical features can be found in **Table 1**.

Pathogenesis
The most common recessive ataxia in individuals of European ancestry, FRDA, is due to a GAA repeat expansion, which, the disease being recessive, is present in homozygosis in affected individuals[2]. The FRDA GAA expansion mutation occurs in an intron of the gene encoding frataxin, a small mitochondrial protein participating in the biogenesis of iron-sulfur (Fe-S) clusters, important co-factors for many proteins with different function (energy production, iron, amino-acid and purine metabolism, DNA repair) and cellular localization[3]. The expanded GAA repeat induces a condensed chromatin conformation that is not permissive for gene transcription, so frataxin is not produced in sufficient amounts[4]. Rare FRDA patients are compound heterozygotes for the GAA repeat expansion, including a loss-of-function point mutation or deletion in frataxin.

In Japan, the most common recessive ataxia is ataxia with oculomotor apraxia type 1 (AOA1), which is characterized by early onset ataxia with cerebellar atrophy, sensorimotor neuropathy, and by the characteristic biochemical findings of hypoalbuminemia and progressive hypercholesterolemia. AOA1 is due to mutations affecting a protein (aprataxin) involved in repair of single strand DNA breaks[5].

Along with FRDA, other recessive ataxias have mitochondrial dysfunction as a major pathogenic mechanism, including ataxia with vitamin E deficiency (AVED), and possibly ARSACS. DNA repair defects are found, in addition to AOA1, also in ataxia telangiectasia (AT), AT-like disease, and AOA2. Altered protein quality control semmes to be another common mechanism, primarily involved in the pathogenesis of Marinesco-Sjögren syndrome, ARSACS, and ataxia due to mutations in the *STUB1* gene. However, as new causative genes are discovered it is clear that other cellular functions may be altered, such as lipid metabolism, cannabinoid metabolism, and ion channels. Oxidative stress may have a causative role in many of these disorders, particularly when mitochondria are primarily altered or DNA lesions, which in neurons are mostly due to oxidative damage, cannot be properly repaired[6].

A proportion of recessive ataxias appear to be mild variants of metabolic diseases, including variants of Tay-Sachs disease, Sandhoff disease, Krabbe disease, cerebro-tendinous xanthomatosis, carbohydrate glycoprotein deficiency type 1a and Niemann-Pick disease type C. The atypical presentation of these patients, often associated with mild metabolic alterations, often makes early diagnosis difficult.

Hereditary afferent ataxias
Several recessive ataxias have an afferent component in addition to cerebellar involvement. FRDA is the main example, as it is characterized by proprioceptive loss and prominent pathology in the dorsal root ganglia and dorsal columns. Other conditions with an afferent contribution to ataxia include AVED, ataxia telangiectasia, AOA1 and 2, abetalipoproteinemia.

Hereditary neuropathies may cause afferent ataxia, some are dominantly inherited like Charcot-Marie-Tooth (CMT) disease type 2B, an axonal form with mutations in the *RAB7* gene; other are recessive, as Dejerine-Sottas disease (due to mutations in *PMP22* [CMT1E] or periaxin genes [CMT4F]); and the hereditary sensory and autonomic neuropathies (HSAN I-V)[7].

Rare recessive afferent ataxia disorders include posterior column ataxia and retinitis pigmentosa (PCARP, due to *FLVCR* mutations) as well as SANDO (Sensory ataxia, neuropathy, dysarthria and ophthalmoparesis, due to *POLG1* mutations). Whereas PCARP presents with afferent ataxia, night blindness, and areflexia in infancy, with further progression in the second decade, SANDO is of late onset. MIRAS (mitochondrial recessive ataxia syndrome) is a recessive ataxia due to a specific *POLG1* mutation that differs from SANDO because of juvenile onset, cerebellar involvement, mild cognitive impairment, involuntary movements, psychiatric symptoms, and epilepsy[7].

Congenital ataxias:
This group of disorders includes cerebellar malformations that cause impaired motor development with usually nonprogressive ataxia. Other malformations affecting the central nervous system and/or other organs may co-exist. MRI is a very useful tool to orient diagnosis. Joubert syndrome and related disorders are the most common genetic congenital ataxias. These recessive conditions are characterized by vermis hypoplasia and large, horizontal superior cerebellar peduncles, which, in axial MRI images, generate the pathognomonic “molar tooth sign”. Clinically, nonprogressive ataxia is accompanied by hypotonia, oculomotor apraxia, episodes of apnea/hyperpnea in infancy, and variable intellectual disability. Eyes, liver and kidneys may be variably affected in a group of diseases related to Joubert syndrome, collectively called ciliopathies. These diseases are all due to mutations in genes encoding proteins of the primary cilium, a microtubule-containing extension of the cell membrane essential for the development of many tissues[7].

Diagnosis
Most degenerative recessive ataxias have symptom onset in childhood or adolescence, but variability is considerable. In the case of FRDA, the instability of the causative repeat expansion mutation explains part of the variability in onset and severity, with larger expansions associated with earlier onset and more severe disease. However, diseases due to “classical” mutations may also show substantial clinical variability, including in age of symptom onset, often without any clear genotype-phenotype correlation.

The first symptom of most recessive ataxias is usually gait imbalance, followed by limb ataxia and dysarthria. The type of ataxia, afferent, cerebellar or mixed, and the additional, including extra-ataxic and systemic clinical features, if present, may orient the diagnosis, although confirmation by genetic or biochemical testing is necessary.

A useful distinction is between cases with marked cerebellar atrophy and those with mild or absent cerebellar atrophy. In the latter case, a genetic test for FRDA is indicated even if onset has been unusually late and the clinical picture is atypical. In addition to late onset, up to the seventh decade, atypical FRDA cases may present with retained reflexes, spasticity, mild or absent limb ataxia, lack of dysarthria, and no cardiomyopathy. Conversely, FRDA is virtually excluded in the presence of prominent cerebellar atrophy.

While most metabolic ataxias can be diagnosed by metabolic screens, definite diagnosis of the degenerative recessive ataxias is only achieved by the identification of the causing mutations, which is a tedious and costly process and is not provided for the rarest forms of ataxia. Having a definitive diagnosis is mandatory for precise genetic counseling and appropriate therapeutic interventions.

When family history supports recessive inheritance, i.e. when multiple sibs are affected and parents are unaffected, patients should be first tested for FRDA, except when cerebellar atrophy is prominent. Further testing should be guided by clinical and biochemical findings, such as cholestanol, vitamin E, cholesterol, albumin, CK, and α-fetoprotein, whose alteration indicate or suggest the diagnosis of cerebrotendinous xanthomatosis (cholestanolosis), ataxia with vitamin E deficiency (AVED), AOA1, and AT or AOA2, respectively. As a further step, referral to a specialized center for next -generation sequencing (NGS) based genetic analysis is recommended.

It has to be kept in mind that sporadic cases may represent instances of recessive disorders with only one affected sib. Considering the variability of clinical presentation and age of onset of recessive ataxias, there is an emerging consensus that a genetic recessive etiology should be considered for sporadic cases of degenerative ataxia with no identifiable acquired cause even when onset is after age 40. In addition to atypical cases of diseases usually presenting earlier in life, in some recently discovered recessive ataxias, like the form due to mutations in *ANO10*, symptoms usually begin after the age of 40.

The progressive introduction of NGS in the diagnostic arena has greatly improved our ability to diagnose recessive ataxias. While whole-genome sequencing still remains a research tool, many laboratories are now using whole exome sequencing (WES), clinical exome sequencing, or targeted NGS approaches to sequence all known ataxia genes. The benefits of such increased diagnostic power may be great if accompanied by careful clinical assessment. However, NGS generates a huge amount of data, including variants of unknown significance (VUS) that may be difficult and time-consuming to correctly interpret and relate to observed phenotypes. While nothing can replace adherence to criteria to evaluate pathogenicity and clinical judgement when evaluating VUS, a supporting tool may be very helpful in many circumstances. With this purpose group of ataxia experts has recently developed and validated an algorithm to assist the interpretation of NGS data for recessive ataxia diagnosis, which may become generally available in the near future[8].

Treatment

Although they are all characterized by ataxia as early and prominent feature, the genetic, clinical, pathophysiological, pathogenetic and neuropathological characteristics of these diseases are quite diverse, so therapeutic approaches have to be adapted to each specific condition. In addition, there is currently no effective symptomatic treatment for ataxia that could be applicable to all these different clinical situations.

Intensive coordinative training may improve functional performance in various cerebellar and afferent ataxias and remains, along with other rehabilitative approaches, the main therapeutic option that we can currently offer these patients.

Potential disease-modifying therapeutics can be divided into two main categories: 1) those that modulate gene expression, and 2) those that target specific pathogenic mechanisms triggered by the genetic defect.

Therapies that modulate gene expression may target the pathogenic process in inherited ataxias at its roots. As an example, increasing gene expression in FRDA represent a potentially valuable therapeutic approach, for which there is already proof-of-principle. Furthermore, recessive ataxias, being due to loss-of-function mutations, may in principle benefit from gene or protein replacement therapies.

As mentioned above, specific treatments are available for some of the metabolic ataxias. Various neuroprotective and antioxidant treatment have been attempted in other recessive ataxias, in particular FRDA, but so far randomized clinical trials have been negative, indicating a need to improve these approaches. Better understanding of pathogenic mechanisms and development of appropriate animal and cellular models are necessary steps before novel therapeutics may be developed and tested.

New findings in the past year

Discovery of new ataxia genes has continued, particularly thanks to next generation sequencing (NGS) approaches. NGS is rapidly becoming the preferred approach for genetic diagnosis of many inherited ataxias, after screening for the most common etiologies, in particular repeat expansion disorders like FRDA and the most common SCAs.

There is continuing progress in the study of pathogenesis of inherited ataxias, opening the way to potential therapeutic approaches. As the pipeline of potential therapies expands, recent publications also reflect increased efforts to define endpoints for clinical trials [9]. Progress includes studies on natural history and biomarkers, focusing in particular on FRDA[10].

Differential diagnosis of the major non-Friedreich recessive ataxias

Condition	Onset age	DD/ID	PN	Other movt dsd	Opthalmolgic abnormalities	Other clinical features	Early cerebellar atrophy	Other MRI features	Diagnostic tests
AVED	Late childhood, adolescence	-	+	+/-	↓ acuity, retinitis pigmentosa	Prominent post column loss. Pyramidal signs. Cardiomyopathy	-	-	↓vitamin E, *TTPA* genetic testing
AT	Early childhood	-	+/-	+	Oculomotor apraxia	Telangiectasia, immunodeficiency	-	-	↑ AFP, low Igs, *ATM* genetic testing
AOA1	Childhood	+/-	+	+	Oculomotor apraxia	Hypoalbuminaemia, hypercholesterolemia	+	-	*APTX* genetic testing
AOA2	Late childhood to early adulthood	-	+	+	Oculomotor apraxia	Moderately elevated AFP. Raised CK in some	+	-	*SETX* genetic testing
ARSACS	Childhood	-	+	-	-	Marked spasticity. Hypermyelinated retinal fibres	+	Linear pontine hypointensities	*SACS* genetic testing
CTX	Childhood- adulthood	+	+	+/-	Cataracts	Tendon xanthomas, chronic diarrhea, seizures	+	Cerebral atrophy, WM abnormalities	↑ cholestanol. *CYP27A1* genetic testing
Marinesco-Sjogren syndrome	Childhood	+	-	-	Cataracts	Myopathy, hypogonadism, short stature, skeletal anomalies	+	Cerebellar cortical T2 abnormalities	Electron dense structures on muscle biopsy. *SIL1* genetic testing
SCAN1	Adolescence	-	+	-	-	Hypoalbuminaemia, hypercholesterolaemia	+	-	*TDP1* genetic testing
SCAs	Often adulthood, but also childhood	-	+/-	+/-	+/-	Phenotypic variability	+	Spinal cord	Specific genetic testing
GAN	Early to mid childhood	+	+	-	-	Kinky hair, pyramidal signs	-	WM signal abnormalities	Giant axons on nerve biopsy. *GAN* genetic testing
CMT	Childhood to adulthood	-	+	-	-		-	-	Specific genetic testing
Mitochondrial disorders	Wide range	+/-	+/-	+/-	+/-	Variable	+/-	Variable brainstem, basal ganglia and WM abnormalities	Lactate/pyruvate abnormalities, muscle respiratory chain analysis, genetic testing of mtDNA/ nuclear DNA
CoQ10 deficiency	Childhood to adulthood	+	+	-	+/-	Seizures, myopathy, pyramidal signs	+	-	CoQ10 deficiency in muscle/fibroblasts, genetic testing (various genes)
Late-onset GM2 gangliosidosis	Childhood to adulthood	-	-	+	Optic atrophy, retinitis pigmentosa	Seizures, cognitive regression, psychiatric disturbance	+	-	Beta-hexosaminidase A enzymatic testing, *HEXA* genetic testing
Condition	**Onset age**	**DD/ID**	**PN**	**Other movt dsd**	**Opthalmolgic abnormalities**	**Other clinical features**	**Early cerebellar atrophy**	**Other MRI features**	**Diagnostic tests**
Abetaliproteinemia	Infancy and childhood	-	+	-	Retinitis pigmentosa	Diarrhea, fat malabsorption (including Vitamin E deficiency), red cell acanthocytosis	-	-	Extremely low cholesterol levels, abnormal lipoprotein profile. *MTP* genetic testing
Refsum disease	Childhood to young adulthood	-	+	-	Retinitis pigmentosa	Deafness, anosmia, ichthyosis	-	-	↑ Phytanic acid, deficiency of PhyH enzyme activity. Genetic testing of *PHYH*, *PEX7*.
CDG1a	Infancy to adulthood	+/-	+	+	+/-	Seizures, hypogonadism, skeletal abnormalities	+	White matter abnormalities	Abnormal transferrin isoform pattern. Deficient phosphomannomutase activity, *PMM2* genetic testing
Wilson disease	Childhood to adulthood	-	-	+	Kayser-Fleischer rings	Liver disease, psychiatric disturbance	-	Basal ganglia, thalamic and brainstem abnormalities	↓serum copper and caeruloplasmin ↑ urinary copper excretion, *ATP7B* genetic testing

NB The Leuko screen offers combined determination of Arylsulfatase A, Hexosaminidase A+B and Galactocerebrosidase in leukocytes.

Abbreviations:
AFP = alpha-fetoprotein; AOA1/2 = Ataxia Oculomotor apraxia ½; AR = autosomal recessive; ARSACS Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; AT = Ataxia telangiectasia; AVED = Ataxia with vitamin E deficiency; CDG1a = Congenital disorder of glycosylation 1a; CK = creatine kinase; CMT = Charcot-Marie-Tooth disease; CTX = Cerebrotendinous xanthomatosis; DD/ID = significant developmental delay/ intellectual disability; GAN = Giant axonal neuropathy; PhyH = phytanoyl-CoA hydroxylase; PN = peripheral neuropathy; SCAs = Spinocerebellar ataxias; SCAN = Spinocerebellar Ataxia with Axonal Neuropathy; WM = White matter.

References

1. Anheim, M., Tranchant, C. & Koenig, M. The autosomal recessive cerebellar ataxias. *N. Engl. J. Med.* **366,** 636–646 (2012).
2. Campuzano, V. *et al.* Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* **271,** 1423–1427 (1996).
3. Pastore, A. & Puccio, H. Frataxin: a protein in search for a function. *J. Neurochem.* **126 Suppl 1,** 43–52 (2013).
4. Yandim, C., Natisvili, T. & Festenstein, R. Gene regulation and epigenetics in Friedreich's ataxia. *J. Neurochem.* **126 Suppl 1,** 21–42 (2013).
5. Tumbale, P., Williams, J. S., Schellenberg, M. J., Kunkel, T. A. & Williams, R. S. Aprataxin resolves adenylated RNA-DNA junctions to maintain genome integrity. *Nature* **506,** 111–115 (2014).
6. Pandolfo, M. Drug Insight: antioxidant therapy in inherited ataxias. *Nat Clin Pract Neurol* **4,** 86–96 (2008).
7. Pandolfo, M. & Manto, M. Cerebellar and Afferent Ataxias. *Continuum (Minneap Minn)* **19,** 1312–1343 (2013).
8. Renaud, M., submitted.
9. Paap, B. K. *et al.* Standardized Assessment of Hereditary Ataxia Patients in Clinical Studies. **3,** 230–240 (2016).
10. Reetz, K. *et al.* Progression characteristics of the European Friedreich’s Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study. *The Lancet Neurology* **15,** 1346–1354 (2016).