

Milestones in Ataxia

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ABSTRACT: The past 25 years have seen enormous progress in the deciphering of the genetic and molecular basis of ataxias, resulting in improved understanding of their pathogenesis. The most significant milestones during this period were the cloning of the genes associated with the common spinocerebellar ataxias, ataxia telangiectasia, and Friedreich ataxia. To date, the causative mutations of more than 30 spinocerebellar ataxias and 20 recessive ataxias have been identified. In addition, there are numerous acquired ataxias with defined molecular causes, so that the entire number of distinct ataxia disorders exceeds 50 and possibly approaches 100. Despite this enormous heterogeneity, a few recurrent pathophysiological themes stand out. These

include protein aggregation, failure of protein homeostasis, perturbations in ion channel function, defects in DNA repair, and mitochondrial dysfunction. The clinical phenotypes of the most common ataxia disorders have been firmly established, and their natural history is being studied in ongoing large observational trials. Effective therapies for ataxias are still lacking. However, novel drug targets are under investigation, and it is expected that there will be an increasing number of therapeutic trials in ataxia. ©2011 *Movement Disorder Society*

Key Words: ataxia; clinical scale; DNA repair; ion channel dysfunction; mitochondrial dysfunction; polyglutamine disorders

Ataxia literally means absence of order and denotes a clinical syndrome of incoordination caused by lesions of the cerebellum and its afferent or efferent connections. The term *ataxia* is also used to designate specific diseases of the nervous system in which progressive ataxia is the prominent clinical manifestation. The practice to use ataxia to designate a disease goes back to the middle of the 19th century, when Duchenne coined the term *locomotor ataxia* for tabes dorsalis. In the 20th century, a neuropathological

approach to the ataxias inspired by the seminal work of Holmes and Greenfield prevailed, and classifications based on neuropathological categories, such as olivopontocerebellar atrophy, cerebellar cortical atrophy, or spinocerebellar degeneration, were in common use.^{1,2} However, a consensus on the proper classification of cerebellar degenerations was never reached. The situation changed with the work of Harding in the early 1980s. Harding clearly recognized the inconsistencies of the neuropathological classifications, in particular that hereditary diseases manifesting in a single family often had to be assigned to different neuropathological categories, whereas, on the other hand, disorders that were clinically and genetically distinct were put into the same category. Consequently, Harding proposed a new classification that was based mainly on clinical and genetic criteria.³ The new classification was not only widely accepted but paved the way for a renewed interest of clinical neurologists in ataxias. Intensive clinical research at that time coincided with the advent of novel molecular genetic methods that allowed the successful linking of chromosomal loci to ataxia disorders in large multigeneration families, an approach that finally led to identification of the first ataxia genes in the 1990s (Table 1).

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TABLE 1. Classification of ataxias

1. Hereditary ataxias
1.1. Autosomal recessive ataxias
1.1.1. Friedreich ataxia (FRDA)
1.1.2. Ataxia telangiectasia (AT)
1.1.3. Autosomal recessive ataxia with oculomotor apraxia type 1 (AOA1)
1.1.4. Autosomal recessive ataxia with oculomotor apraxia type 2 (AOA2)
1.1.5. Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)
1.1.6. Ataxia with isolated vitamin E deficiency (AVED)
1.1.7. Marinesco-Sjögren syndrome (MSS)
1.1.8. Autosomal recessive ataxias due to POLG mutations (MIRAS, SANDO)
1.1.9. Cerebrotendinous xanthomatosis (CTX)
1.1.10. Refsum disease
1.1.11. Abetalipoproteinemia
1.1.12. Other autosomal recessive ataxias
1.2. Autosomal dominant ataxias
1.2.1. Spinocerebellar ataxias (SCA)
1.2.2. Episodic ataxias (EAs)
1.3. X-linked ataxias
1.3.1. Fragile X-associated tremor/ataxia syndrome (FXTAS)
1.3.2. Other X-linked ataxias
1.4. Ataxias due to mitochondrial mutations
2. Nonhereditary degenerative ataxias
2.1 Multiple system atrophy, cerebellar type (MSA-C)
2.2 Sporadic adult-onset ataxia of unknown origin (SAOA)
3. Acquired ataxias
3.1. Alcoholic cerebellar degeneration (ACD)
3.2. Ataxia due to other toxic reasons
3.3. Ataxia due to acquired vitamin deficiency
3.4. Paraneoplastic cerebellar degeneration
3.5. Other immune-mediated ataxias
3.6. Ataxia in chronic CNS infection
3.7. Superficial siderosis

Advances in the Past 25 Years

Genetic

Among all disciplines, genetics has had the strongest impact on the development of the ataxia field in the past 25 years. During this period, linkage of numerous ataxia disorders to chromosomal loci was demonstrated, and in most cases, the mutations causing these disorders were subsequently found. The identification of mutations causing dominantly inherited spinocerebellar ataxias (SCAs) started in 1993 with the discovery that an unstable expansion of a translated CAG repeat underlies SCA1.⁴ This finding placed SCA1 in the group of polyglutamine disorders that at that time included spinobulbar muscular atrophy (SBMA) and Huntington's disease (HD). Subsequently, translated CAG repeat mutation were also found to cause SCA2, MJD/SCA3, SCA6, SCA7, and SCA17. A common feature of all CAG repeat disorders is the inverse relation between age of onset and age at disease onset. In SCA8, SCA10, SCA12, and SCA31, untranslated repeat expansions in noncoding regions of the respective genes were identified. More recently, nonrepeat mutations were increasingly found to cause dominantly inherited

ataxias. The affected genes include beta-III spectrin (*SPTBN2*) in SCA5, tau tubulin kinase 2 (*TTBK2*) in SCA11, a potassium channel in SCA13, protein kinase C γ , PKC γ in SCA14, inositol 1,4,5-triphosphate receptor type 1 (*ITPR1*) in SCA15/16, fibroblast growth factor 14 (*FGF14*) in SCA27, and ATPase family gene 3-like 2 (*AFG3L2*) in SCA28 (Table 2).^{5,6}

A similar degree of heterogeneity is present in recessive ataxia. In a number of recessive ataxias, such as Refsum's disease, abetalipoproteinemia, cerebrotendinous xanthomatosis (CTX), and ataxia with vitamin E deficiency (AVED), the biochemical defects were known before the new positional cloning techniques in the 1990s allowed a breakthrough in the genetic elucidation of ataxias. The most important discoveries in the genetics of recessive ataxia were the cloning of the ataxia-telangiectasia mutated (*ATM*) gene in 1995⁷ and the discovery of an intronic GAA repeat mutation causing Friedreich ataxia (FRDA) in 1996.⁸ Subsequently, more than 20 genes for recessive ataxias were identified, many of them by the use of homozygosity mapping. Among the recessive ataxias, 2 larger groups of disorders can be delineated, one including FRDA and AVED that is associated with mitochondrial dysfunction and oxidative stress and another group including ataxia telangiectasia (AT) associated with defective DNA repair mechanisms. In addition, there are numerous disorders that cannot be categorized in these 2 groups (Table 3).⁹

Fragile X-associated tremor/ataxia syndrome (FXTAS) was established as a novel disorder that occurs in male and less frequently in female *FMR1* premutation carriers. CGG expansions of the 5' untranslated region of the *FMR1* gene beyond a critical threshold of 200 are the cause of fragile X syndrome (FXS), the most common inherited form of mental retardation in boys. FXTAS arises from *FMR1* premutations, with a repeat length ranging from 55 to 200. The clinical spectrum of FXTAS includes progressive cerebellar ataxia with prominent tremor, often accompanied by cognitive decline, parkinsonism, neuropathy, and autonomic failure.¹⁰

Clinical

The new genetic discoveries yielded numerous clinical reports that led to a firm understanding of the genotype-phenotype relationship in the common hereditary ataxias. One of the great surprises was the finding that Machado-Joseph disease (MJD), a dominantly inherited movement disorder with a variable phenotype that had been first described in families of Azorean origin,¹¹ was genetically identical to SCA3, an autosomal dominantly inherited ataxia with a worldwide distribution.¹²

Clinical research in the 1990s established that SCA1, SCA2, and SCA3 patients typically present

TABLE 2. Spinocerebellar ataxias (SCAs): molecular genetics and clinical phenotype

Disorder	Mutation	Gene product	Clinical phenotype
SCA1	Translated CAG repeat expansion	Ataxin-1	Ataxia, pyramidal signs, neuropathy, dysphagia, restless legs syndrome
SCA2	Translated CAG repeat expansion	Ataxin-2	Ataxia, slow saccades, neuropathy, restless legs syndrome
SCA3/Machado-Joseph disease (MJD)	Translated CAG repeat expansion	Ataxin-3	Ataxia, pyramidal signs, ophthalmoplegia, neuropathy, dystonia, restless legs syndrome
SCA4	Unknown	Unknown	Ataxia, sensory neuropathy
SCA5	Point mutation	Beta-III spectrin (SPTBN2)	Almost purely cerebellar ataxia
SCA6	Translated CAG repeat expansion	Calcium channel subunit (CACNA1A)	Almost purely cerebellar ataxia
SCA7	Translated CAG repeat expansion	Ataxin-7	Ataxia, ophthalmoplegia, visual loss
SCA8	3' Untranslated CTG repeat expansion	Ataxin-8	Ataxia, sensory neuropathy, spasticity
SCA10	Intronic ATTCT repeat expansion	Ataxin-10	Ataxia, epilepsy
SCA11	Insertion, deletion	Tau tubulin kinase 2 (TTBK2)	Almost purely cerebellar ataxia
SCA12	5' Untranslated CAG repeat expansion	Phosphatase subunit (PP2A-PR55 β)	Ataxia, tremor
SCA13	Point mutation	Potassium channel (KCNC3)	Ataxia, mental retardation
SCA14	Point mutation	Protein kinase C γ (PKC γ)	Ataxia, myoclonus, dystonia, sensory loss
SCA15/16	Deletion	Inositol 1,4,5-triphosphate receptor, type 1 (ITPR1)	Almost purely cerebellar ataxia
SCA17	Translated CAG repeat expansion	TATA binding protein (TBP)	Ataxia, dystonia, chorea, dementia, psychiatric abnormalities
SCA18	Unknown	Unknown	Ataxia, sensory neuropathy, neurogenic muscle atrophy
SCA19/22	Unknown	Unknown	Ataxia, myoclonus, cognitive impairment
SCA20	Unknown	Unknown	Ataxia, dysphonia
SCA21	Unknown	Unknown	Ataxia, parkinsonism
SCA23	Unknown	Unknown	Ataxia, sensory neuropathy, pyramidal signs
SCA25	Unknown	Unknown	Ataxia, sensory neuropathy
SCA26	Unknown	Unknown	Almost purely cerebellar ataxia
SCA27	Point mutation	Fibroblast growth factor 14 (FGF14)	Ataxia, tremor, mental retardation
SCA28	Missense	ATPase family gene 3-like 2 (AFG3L2)	Ataxia, ophthalmoparesis, pyramidal signs
SCA30	Unknown	Unknown	Almost purely cerebellar ataxia
SCA31	Pentanucleotide (TGGAA) repeat insertion	Unknown	Almost purely cerebellar ataxia

TABLE 3. Autosomal recessive ataxias: gene products and function

Disorder	Gene product	Function
Mitochondrial/oxidative stress		
Friedreich ataxia (FRDA)	Frataxin	Synthesis of iron-sulfur clusters
Mitochondrial recessive ataxia syndrome (MIRAS)	Polymerase gamma (POLG)	Mitochondrial DNA proofreading
Infantile onset spinocerebellar ataxia (IOSCA)	Twinkle	Mitochondrial DNA proofreading
Autosomal recessive cerebellar ataxia type 2 (ARCA2, SCAR9)	ADCK3	Coenzyme Q10 synthesis
Ataxia with isolated vitamin E deficiency (AVED)	α -Tocopherol transport protein	Vitamin E
Abetalipoproteinemia	Microsomal triglyceride transfer protein	Vitamin E
DNA repair		
Ataxia telangiectasia (AT)	ATM protein	Phosphoinositol-3 kinase activity: cell-cycle checkpoint control and DNA repair
Ataxia telangiectasia-like disorder (ATLD)	MRE11	Double-stranded DNA repair
Ataxia with oculomotor apraxia type 1 (AOA1)	Aprataxin	Single-stranded DNA repair
Ataxia with oculomotor apraxia type 2 (AOA2, SCAR2)	Senataxin	Single-stranded DNA repair
Spinocerebellar ataxia with axonal neuropathy 1 (SCAN1)	Tyrosyl-DNA phosphodiesterase-1 (TDP1)	DNA replication
Other mechanisms		
Refsum disease	Phytanoyl-CoA hydroxylase	Oxidation of phytanic acid
Cerebrotendinous xanthomatosis (CTX)	Sterol-27 hydroxylase	Sterol hydroxylation
ARSACS	Sacsin	Proteasomal system
Marinesco-Sjögren syndrome (MSS)	SIL1	ER glycoprotein
Autosomal recessive cerebellar ataxia type 1 (ARCA1, SCAR8)	SYNE1	Member of spectrin family
Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC)	ABHD12	Endocannabinoid metabolism: hydrolysis 2-arachidonoyl glycerol (2-AG)

with ataxia in combination with various additional symptoms, whereas SCA6 is an almost purely cerebellar disorder. SCA6 is also different in that it begins between ages 50 and 60 years, whereas SCA1, SCA2, and SCA3 have an onset between 30 and 40 years.¹³ More detailed clinical work revealed that the phenotypic variability of these disorders could be partly attributed to differences in repeat length of the expanded allele. Thus, in SCA3, large expanded alleles were found in patients with early disease onset and marked pyramidal and extrapyramidal features, whereas those with prominent ataxia and ophthalmoplegia and patients with late disease onset and marked peripheral involvement had smaller expansions.¹⁴ Although these “common” SCAs are caused by translated CAG repeat mutations, many of the rarer SCAs that were subsequently found are caused by untranslated repeat mutations and by conventional nonrepeat mutations. In general, these SCAs were found to take a more benign course, in some instances resembling developmental rather than degenerative disorders.

The clinical studies following the discovery of the FRDA mutation demonstrated that the clinical spectrum of FRDA was broader than previously thought. Up to 30% of FRDA patients have “late” disease onset, after the age of 20 years, and/or retained tendon reflexes.¹⁵ Following FRDA, ataxia with oculomotor apraxia type 2 (AOA2) is the second most common recessive ataxia. Interestingly, only half of AOA2 patients have oculomotor apraxia, whereas the prevalence of polyneuropathy in AOA2 is almost 100%.¹⁶

One of the greatest breakthroughs in the understanding of the sporadic ataxias was the clinical delineation of multiple system atrophy (MSA), defined as sporadic, adult-onset disease presenting with either sporadic ataxia or levodopa-unresponsive parkinsonism in combination with severe autonomic failure.¹⁷ In a large case series of sporadic ataxia patients with adult-onset, MSA accounted for about 30% of all cases.¹⁸

Pathological

After the delineation of the first ataxia disorder by Friedreich in 1863, the field was dominated by neuropathology for more than a century. In the past 25 years, however, clinicians and geneticists rather than neuropathologists left their marks on ataxia research. Nevertheless, numerous new insights came from neuropathological studies, the most important one being the recognition of intracellular proteinaceous inclusions as pathological hallmarks of a number of ataxia disorders. In brains of patients with the polyglutamine ataxias SCA1, SCA3, SCA7, and SCA17, neuronal intranuclear inclusions (NIIs) containing the expanded disease protein were observed.¹⁹ On the other hand, NIIs are less frequent or absent in SCA2

and SCA6, disorders that also belong to the group of polyglutamine diseases. Although most scientists agree that the large inclusions seen inside neurons in brain disease are not the primary culprits causing neurons to die, they do represent a pathological hallmark reflecting a chronic problem with protein homeostasis.

Following the clinical delineation of MSA as a disease entity, glial cytoplasmic inclusions (GCIs) were discovered in oligodendroglial cells of MSA brains.²⁰ A major component of GCIs is α -synuclein, an observation that placed MSA in the group of synucleinopathies together with Parkinson disease and Lewy body dementia.²¹

Epidemiologic

The past 25 years have seen a number of epidemiological studies that attempted to determine the prevalence of certain ataxias in defined regions. Nevertheless, a reliable estimation of the prevalence of all ataxias is still not possible. In Europe, FRDA is the most frequent recessive ataxia with a prevalence ranging between 1.7 and 3.7 per 100,000,²² whereas it is almost absent in the East Asian population. Dutch and Norwegian surveys found a prevalence of dominantly inherited SCAs of 3.0 and 4.2 per 100,000, respectively.^{23,24} Studies of sporadic ataxia performed in the Aosta valley (Italy) and in southeastern Wales (United Kingdom) reported a prevalence of 6.9 and 8.4 per 100,000, respectively.^{25,26} In the Japanese population, the prevalence of sporadic ataxias including MSA was determined to be 18.5 per 100,000.²⁷ Epidemiological studies of acquired ataxias are widely lacking.

On the basis of the available figures, it can be estimated that the overall prevalence of ataxias is at least 15 per 100,000 and may approach 20 per 100,000. Thus, ataxia appears to be more frequent than generally assumed. Nevertheless, ataxia remains an orphan disease according to current definitions of the National Institutes of Health and the European Commission.

Therapeutic

Although the genetic defects of many hereditary ataxias were discovered in the past 25 years, this has not yet led to new therapies. Etiological treatment approaches are available only for some rare forms of ataxia with known biochemical defects, such as Refsum's disease, CTX, and AVED. In most other types of hereditary and nonhereditary degenerative ataxias, only supportive treatment is possible. Repeated claims that centrally acting drugs such as 5-hydroxytryptophan, buspirone, physostigmine, thyrotropin-releasing hormone, and D-cycloserine have an antiataxic action and temporarily improve cerebellar ataxia, often based on uncontrolled observations in small patients samples, did not stand up to subsequent larger trials.^{28,29}

Where We Are Now

Classification

Following the discovery of the genes and mutations causing hereditary ataxias and elucidation of the molecular causes of many nonhereditary ataxias, a wide consensus about the proper classification of ataxias was reached. According to current aetiology-based classifications, the ataxias can be subdivided into 3 major groups: the hereditary ataxias, the nonhereditary degenerative ataxias, and the acquired ataxias, which have exogenous or endogenous nongenetic causes (Table 1).^{6,9,30}

Cohort Studies and Clinical Scales

In clinical research, the focus has shifted from cross-sectional studies that aimed to define the phenotype of a specific ataxia disorder to prospective studies of large cohorts of ataxia patients. Worldwide, consortia have been formed that are conducting large prospective studies.^{31,32} An important precondition for these studies was the development of validated clinical assessment methods. The Scale for the Assessment and Rating of Ataxia (SARA) is based on a semiquantitative assessment of cerebellar ataxia on an impairment level. SARA underwent a rigorous validation procedure involving 4 clinical trials in large groups of SCA and non-SCA ataxia patients and controls. Compared with the previously used International Cooperative Ataxia Rating Scale (ICARS), SARA has favorable biometric properties and is easier to handle.³³

Studies in various neurodegenerative disorders have shown that quality of life is only partly related to disease-related factors assessed by clinical instruments such as SARA or ICARS. Other factors such as emotional well-being, coping strategies, and comorbidity may play a role in health perception. Therefore, patient-based measures are increasingly considered important for outcome assessment in interventional trials. There is intense ongoing research aiming to assess quality of life in ataxias and to identify the factors that determine it.³⁴

Understanding Molecular Pathogenesis

The wide range of genes implicated in degenerative ataxias suggests that multiple pathways can induce cerebellar dysfunction and atrophy.⁶ Fortunately, however, certain pathogenic themes keep surfacing. In particular, 5 recurrent themes stand out: (1) dynamic repeat expansions cause many dominant ataxias, as well as at least 1 key recessive ataxia and 1 X-linked ataxia; (2) polyglutamine expansion is a shared mutational mechanism for the most common dominant ataxias; (3) perturbations in ion channel function, either directly through mutations or indirectly through involvement of electrophysiological pathways, underlie some ataxias; (4) defects in DNA repair are the cause

of some recessive ataxias, and the nucleus plays a key role in many other ataxias beyond DNA repair; and (5) mitochondrial perturbation resulting from mutations in mitochondrial or nuclear-encoded genes or from specific nutritional deficiencies (vitamin E) is increasingly appreciated as the basis of ataxia.

As outlined above, 1 group of ataxia disorders is caused by dynamic repeat expansions.³⁵ Some repeat-expansion diseases result in expansions in the encoded proteins, whereas others occur in non-protein-coding regions of the gene. Although it is not yet certain how noncoding repeat expansions cause neurodegeneration, the prevailing theory is that at least some of them act through a dominant toxic mechanism occurring at the RNA level, much like myotonic dystrophy.³⁶ Fragile X-associated tremor ataxia syndrome (FXTAS) belongs to this class of diseases. Another noncoding repeat disease is SCA8, which is associated with a large CAG/CTG repeat expansion. The mechanism of pathogenesis in SCA8 is debated, with recent studies suggesting bidirectional expression that could lead to both RNA-mediated and protein-mediated toxicity.

SCA1, SCA2, MJD/SCA3, SCA6, SCA, and SCA17 are caused by polyglutamine-encoding CAG repeat expansions. Most studies, from the test tube to animal models, suggest that the toxic action of polyglutamine expansion occurs primarily at the protein level.^{35,37} The idea that abnormal protein aggregation reflects a failure in protein quality control in the brain may apply beyond the ataxias to Parkinson's and Alzheimer's disease. A failure in protein homeostasis could precipitate numerous deleterious consequences, ranging from aberrant gene expression to dysfunction of organelles to defects in axonal transport or synaptic activity.

Many research groups now study the biochemical process of polyglutamine protein aggregation, with increasing focus on the earliest steps in the aggregation pathway because oligomers or misfolded monomers may drive toxicity rather than the larger downstream amyloid fibrils. Efforts are also underway in many labs to harness the quality control machinery in cells (molecular chaperones, ubiquitin-proteasome, lysosome-autophagy pathway) to enhance the clearance of mutant polyglutamine proteins. Drug screens are beginning to identify compounds that reduce steady-state levels of the mutant proteins and/or facilitate their degradation; some of these compounds likely act through chaperone pathways, whereas others may facilitate autophagy.

Despite their shared mutations, the various polyglutamine SCAs do not have precisely the same clinical features. The marked clinical differences among these disorders illustrate the importance of disease-protein context to pathogenesis. The mutant proteins must affect the brain somewhat differently in each disease.

For example, the set of interacting proteins with which a given disease protein interacts is bound to differ: whereas ataxin-1, ataxin-2, and ataxin-3 may bind some of the same proteins, the differences in their protein interactions will far outweigh their commonalities. This difference may help to explain the disease-specific consequences of each disease protein. SCA1 provides a compelling example of this phenomenon. The first identified polyglutamine ataxia, SCA1 remains better understood than other SCAs. When the disease protein ataxin-1 contains an expansion, its ability to form the correct ratios of specific protein complexes inside the nucleus is disrupted, contributing to neurotoxicity.³⁸

Channel dysfunction in ataxia can occur directly or indirectly.³⁹ The 2 most common forms of dominantly inherited episodic ataxia, EA1 and EA2, are caused by mutations in a voltage-gated potassium channel (KCNA1) and a voltage-gated calcium channel (CACNA1A4), respectively. EA-2 is a result of mutations in the same gene that is mutated in both SCA6 and familial hemiplegic migraine, demonstrating the phenomenon of allelic heterogeneity, in which different mutations in the same gene can cause distinct clinical syndromes. SCA13 is caused by mutations in the *KCNC3* gene, which encodes a voltage-gated potassium channel (Kv3.3) that is highly enriched in the cerebellum. Mutations in this gene have a dominant effect on electrophysiological properties of this multi-subunit channel. A particularly exciting area of investigation now is the likelihood that channel function is indirectly perturbed in various ataxias caused by mutations with no direct link to ion channels.

Interest is growing in the nucleus as a central site of toxicity in many ataxias, not simply the well-defined DNA repair ataxias. Several recessive ataxias including AT result from mutations in genes linked to DNA repair. Their existence suggests that single-stranded DNA damage, and perhaps even double-stranded DNA damage, harms the postmitotic neuron over time.⁴⁰ The nucleus is implicated in many other ataxias as well, including the polyglutamine ataxias. Although the disease genes in these disorders may not directly affect DNA, they alter the precise, regulated expression of specific genes. Most polyglutamine proteins normally reside in the nucleus or become concentrated in the nucleus during disease; thus, the hypothesis that they trigger disease in part by perturbing nuclear gene expression is attractive. Expanded polyglutamine proteins can engage in aberrant protein interactions in the nucleus, including with transcription factor complexes and chromatin proteins. Several polyglutamine disease proteins are even directly involved in transcription: the SCA3 protein ataxin-3 is a transcriptional corepressor, the SCA7 protein ataxin-7 is part of a transcriptional complex, and the SCA17 protein is

the basal transcription factor TATA-binding protein. Because transcriptional dysregulation caused by mutant polyglutamine proteins partly reflects changes in histone acetylation, this suggests a potential route to therapy: histone deacetylase inhibitors that reverse some of the gene repression occurring in disease.

Mutations in the mitochondrial genome certainly cause important forms of ataxia, and mutations in the nuclear gene encoding polymerase gamma (POLG) are now recognized to be an important cause of progressive ataxia because of mitochondrial dysfunction. Perhaps the most important mitochondrial disease, however, is FRDA. The nuclear-encoded disease protein frataxin acts inside the mitochondria, and the consensus is that the causative mutation impairs mitochondrial function.⁴¹ GAA repeat expansions lead to transcriptional silencing, resulting in reduced levels of frataxin mRNA and protein. Frataxin deficiency causes accumulation of iron within mitochondria and signs of oxidative stress. The protein is critically important for the biosynthesis of iron-sulfur cluster enzymes in mitochondria, leading to the compelling hypothesis that disease pathogenesis reflects oxidative stress from impaired mitochondrial energetics.

FRDA is probably the leading success story in the burgeoning ataxia field: in little more than a decade, scientists have proceeded from discovering the mutation to understanding the basic problem to testing rational therapies in humans. The coenzyme Q10 analogue idebenone has already been tested in a phase III trial.⁴² This success notwithstanding, it is still uncertain how reduced levels of this key mitochondrial protein cause selective neurodegeneration of certain regions of the nervous system.

Future Directions

The greatest challenge for ataxia research is the development of effective therapies. So far, only idebenone in FRDA has made its way to a phase III trial, which then unfortunately failed.⁴² In the future, it will be of vital importance for academic research and the pharmaceutical industry to join forces to establish an effective research pipeline including development of standardized criteria for the rigorous evaluation of molecular targets, of pathogenic mechanisms, and of therapeutic approaches that will finally result in successful clinical trials. The possible therapeutic strategies are diverse and range from conventional pharmaceutical approaches to gene therapy.

Silencing of disease genes using RNA interference (RNAi) is a novel experimental therapeutic approach that appears to be specifically suitable for polyglutamine SCAs. The therapeutic value of this approach in SCAs has already been shown in transgenic disease models.⁴³ However, numerous problems related to

safety, delivery, and dosage remain to be solved before RNAi will become a viable alternative to conventional pharmacological approaches. In FRDA, boosting levels of the deficient protein frataxin is a promising strategy. This may be achieved by enhancing transcription using histone deacetylase inhibitors.⁴⁴

A promising strategy for the development of therapies is the selection of an appropriate drug target based on an understanding of the molecular mechanisms leading to ataxia or a specific ataxia disorder. This approach is greatly facilitated by knowledge of the gene mutations causing the common hereditary ataxia disorders and the availability of transgenic animal models. Examples of drug candidates that have emerged from this approach are lithium,⁴⁵ the rapamycin ester temsirolimus,⁴⁶ and dantrolene⁴⁷ for SCAs, as well as antioxidants for FRDA. Given the central role of protein aggregation in pathogenesis, the search for antiaggregation compounds may yield a compound that acts on all polyglutamine diseases.

An alternative approach is treatments that aim to normalize disturbed neuronal activity in the cerebellum and thereby exert a “symptomatic” antiataxic effect. Such a treatment approach has the advantage of not being limited to one particular ataxia disorder but may be beneficial in a larger group of ataxias that share common effector mechanisms such as Purkinje neuron dysfunction. In the current scientific discussion on treatment strategies in neurodegenerative diseases, these “symptomatic” approaches play an increasingly important role because it is recognized that the early phases of neurodegeneration are characterized by neuronal dysfunction, whereas impaired neuronal cell metabolism and cell death are events that occur later in the disease course. It is also conceivable that early interference with neuronal dysfunction may not only temporarily improve symptoms but also have a disease-modifying effect. One possible approach is interference with small-conductance calcium-activated potassium (SK) channels, which play a critical role in the regulation of neuronal activity in the cerebellar cortex and deep cerebellar nuclei.³⁹ In the future, detailed functional analysis of cerebellar circuits in transgenic models of ataxia will therefore play an increasingly important role in identifying novel drug targets.

Genetic research of the past 25 years has identified an impressively large number of ataxia genes. Nevertheless, a significant proportion of ataxia patients still cannot be assigned to a proper diagnosis.^{18,48} For the early-onset ataxias, most of which are autosomal recessively inherited, it is expected that novel genes will be found with refined mapping and sequencing technology. However, most of these new genes will be responsible for only a very small number of families. New dominant genes will similarly account for only a limited number of families. For clinical practice, it will be more important to offer comprehensive genetic

testing in a cost-effective way. A promising strategy toward this aim is the use of microarray technology. The situation is different in sporadic ataxia with adult-onset disease, where monogenic mutations probably account only for few cases. In these patients, the search for novel acquired causes has to be continued. On the other hand, it is conceivable that these disorders nevertheless have a genetic background that can be elucidated by genome-wide association studies. This underlines the need to recruit, characterize, and follow large patient cohorts. ■

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