New Autosomal Recessive Cerebellar Ataxias with Oculomotor Apraxia

*Isabelle Le Ber, MD, Alexis Brice, MD, and Alexandra Dürr, MD, PhD**

Address
*INSERM U679, Hôpital Pitié-Salpétrière, 47 boulevard de l'Hôpital, 75651 Paris Cedex 13, France.
E-mail: durr@ccr.jussieu.fr

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Autosomal recessive cerebellar ataxias (ARCAs) are a phenotypically and genetically heterogeneous group of diseases. Recently, a subgroup of ARCA associated with oculomotor apraxia (AOA) has been delineated. It includes at least four distinct genetic entities: ataxia-telangiectasia, ataxia-telangiectasia–like disorder, and ataxia with oculomotor apraxia type 1 (AOA1) and type 2 (AOA2). The phenotypes share several similarities, and the responsible genes, *ATM*, *MRE11*, *APTX*, and *SETX*, respectively, are all implicated in DNA break repair. As in many other DNA repair deficiencies, neurodegeneration is a hallmark of these diseases. Recently, the genes for two new autosomal recessive cerebellar ataxias with oculomotor apraxia, AOA1 and AOA2, were identified. Here, we report the phenotypic characteristics, genetic characteristics, and the recent advances concerning AOA1 and AOA2.

Introduction

Hereditary autosomal recessive cerebellar ataxias (ARCAs) are rare neurodegenerative diseases with many different phenotypes caused by mutations in a number of genes. The most common in whites is Friedreich's ataxia, which accounts for 30% to 40% of patients with ARCA [1]. Other ARCAs, including ataxia-telangiectasia (A-T), autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), ataxia with vitamin E deficiency (AVED), and spinocerebellar ataxia with neuropathy 1 (SCAN1), are less frequent.

Recently, a subgroup of ARCAs associated with oculomotor apraxia (AOA) was individualized. Oculomotor apraxia was initially described as the inability to generate voluntary horizontal saccades with a characteristic compensatory headthrusting and synkinetic blinking in children with congenital oculomotor apraxia [2]. This abnormality was later described in many other neurologic diseases, including A-T and several other autosomal recessive cerebellar ataxias. Aicardi *et al*. [3] first reported 14 patients with cerebellar ataxia and oculomotor apraxia that resembled A-T but without other characteristic features of A-T such as telangiectasia, recurrent infections, malignancies, or radiation sensibility and normal alpha-foetoprotein levels. The group of "ataxias with oculomotor apraxia" (AOA) was later distinguished by Barbot *et al*. [4], who identified 22 patients from 11 Portuguese families with an AOA phenotype. The relative frequency of AOA was 20% in Portuguese patients with ARCA [4]. Linkage studies recently identified two new ataxias: ataxia with oculomotor apraxia type 1 (AOA1) and AOA type 2 (AOA2).

The group of AOA actually includes four distinct genetic entities: A-T, A-T–like disorder, AOA1, and AOA2 (Table 1). Their phenotypes have many similarities and the responsible genes, *ATM*, *MRE11*, *APTX*, and *SETX*, respectively, are all implicated in DNA break repair. As in many other DNA repair deficiencies, neurodegeneration is a hallmark of all these diseases. A-T usually begins before the age of 5 years and associates cerebellar ataxia, oculomotor apraxia, choreoathoetosis, and characteristic extraneurologic signs including conjunctival and cutaneous telangiectasia, recurrent infections, and a predisposition to the malignancies [5,6]. Prognosis is severe, and death usually occurs around the age of 20 years [5]. Biologic markers are elevated levels of alpha-foetoprotein, carcinoembryonic antigen, and low levels of gamma-globulins. Hypersensitivity to ionozing radiation and chromosomal translocations, the most frequent of which is t(7;14), are additional features. A-T is caused by mutations in the A-T mutated gene (*ATM*), which encodes a phosphatidylinositol-3 kinase, the ATM protein [7]. More than 400 mutations throughout the 66 exons of the gene have been identified [8]. ATM acts at the initial phase of the response to the DNA damage and is activated by DNA double-strand breaks. ATM is intimately linked to the MRE11/Rab50/Nbs1 (MNR) protein complex, which is responsible for recognition and processing of double-strand breaks in DNA and is both an inductor and a target for the ATM protein. Neurodegeneration in A-T may result either from an inability to trigger apoptosis in the absence of ATM or from the persistence of unrepaired DNA double-strand breaks that may lead to neuronal dysfunction and degeneration [9]. Mutations in the *MRE11* gene also lead to neurodegeneration and a rare A-T–like phenotype (ATLD) characterized by early-onset cerebellar ataxia, oculomotor apraxia, and choreoathetosis but without elevated alpha-foetoprotein levels [10–16]. Finally, SCAN1, another autosomal recessive cerebellar ataxia with neuropathy but

Table 1. Comparisons of the phenotypes and biologic characteristics of cerebellar ataxias with oculomotor apraxia

Disease	A-T	ATLD	AOA1	AOA2
Gene	*ATM*	*MRE11*	*APTX*	*SETX*
Relative frequency	2%–10%	?	10%*	5%*
References	[5,6,56]	[11,13,15]	[30•]	[53•]
Mean age at onset (range)	< 5 y (2–42)	2 ± 2 y (1–6)	7 ± 5 y (2–18)	15 ± 4 y (9–25)
Cerebellar ataxia	+	+	+	+
Peripheral neuropathy	S or SM	S	SM	S or SM
Babinski sign	+	?	–	±
Cardiomyopathy	–	–	–	–
Oculomotor apraxia	+	+	+	+
Chorea/dystonia	+	+	+	+
Telangiectasia, malignancies	+	?	0	0
Alpha-foetoprotein levels	?	–	–	?
Albumin levels	–	–	?	–
Cholesterol levels	–	–	?	–
Cerebellar atrophy	+	+	+	+

*Frequency after exclusion of Friedreich's ataxia.
AOA—ataxia with oculomotor apraxia; A-T—ataxia-telangiectasia; ATLD—ataxia-telangiectasia–like disorder; S—sensory; SM—sensorimotor.

without oculomotor apraxia, is due to a mutation in the *TDP1* gene coding for a tyrosyl-phosphodiesterase, which is also involved in DNA repair [17,18]. We summarize the clinical and genetic characteristics of AOA1 and AOA2 and recent advances concerning these two newly identified forms ataxia with oculomotor apraxia.

Ataxia with Oculomotor Apraxia Type 1 (AOA1)

Ataxia with oculomotor apraxia 1, also called early-onset ataxia with ocular motor apraxia and hypoalbuminemia (EOAH), was initially described in Japanese patients presenting with early-onset cerebellar ataxia, oculomotor apraxia, mental retardation, hypercholesterolemia, and hypoalbuminemia [3,19–25]. A similar phenotype was reported in several Portuguese families [4]. Analyses of these families led to mapping of the locus designated AOA1 to chromosome 9p13 [26] and the identification of the *APTX* gene encoding aprataxin [27••,28••]. Aprataxin mutations have now been found in patients of various ethnic origins throughout the world [29•,30•,31,32]. The relative frequency of AOA1 varies among white populations from 6% to 11% [30•,32]. It is estimated to be the second cause of ARCAs after Friedreich's ataxia in Portugal and France [27••,30•] and the first cause in Japan, where Friedreich's ataxia does not exist [28••].

Phenotype

Onset usually occurs before the age of 10 years [30•], but a few patients with later ages of onset (28 and 29 years) have been reported [32]. At onset, most patients had cerebellar ataxia or chorea. Overall, 100% of the patients had cerebellar ataxia and 80% had mild to severe choreic movements, the severity of which decreases with the course of the disease.

Oculomotor apraxia is often absent at onset and appears after a mean disease duration of approximately 8 years [30•]. Oculomotor abnormalities are characterized by head-eye dissociation during conjugated movements, with the head reaching the lateral target before the eyes. This peculiarity results from the loss of vestibulo-ocular reflex cancellation. Horizontal saccade initiation is normal but it is hypometric and composed of multiple successive saccades of small amplitude [30•]. This is different than a true oculomotor apraxia, which is a failure in saccade initiation [2]. However, this term, employed in the first description of the disease, has been conserved.

The progression of the disease is characterized by a severe axonal sensorimotor neuropathy leading to motor deficit, distal amyotrophy, and foot deformities. Less frequently, mental retardation, scoliosis, and limb edema are present. The mean disease duration before confinement to wheelchair is approximately 10 years [30•]. The absence of cutaneous and conjonctival telangiectasia, immunosuppression, recurrent infections, or malignancies helps to distinguish AOA1 from A-T (Table 1). A marked cerebellar atrophy with vermian predominance is constantly observed on brain magnetic resonance imaging (MRI). Biologic markers are useful for the diagnosis of AOA1. Hypoalbuminemia is noted in 83% of the patients and hypercholesterolemia in 75%. At onset, however, these abnormalities are often absent. Their severity is correlated with disease duration [30•,33]. Alpha-foetoprotein and carcinoembryonic antigen levels are normal. Intrafamilial phenotypic variability may be noted [29•,30•], and atypical characteristics such as late age at onset [30•,32], absent oculomotor apraxia [29•], predominant severe chorea [30•], or generalized dystonia [34] have been described.

A recent study described an association between the W279X aprataxin mutation and a coenzyme Q10 deficiency

in four patients from a single family. They showed notable improvement of the cerebellar symptoms with coenzyme Q10 therapy [35]. The association of homozygous aprataxin mutation and the coenzyme Q10 deficit may be coincidental in this family, however, and additional studies in AOA1 patients are needed.

The *APTX* gene and aprataxin

The *APTX* gene encompasses seven exons and codes for aprataxin, a ubiquitously expressed nuclear protein [27••,28••]. Moreira *et al*. [27••] and Date *et al*. [28••] identified two isoforms resulting from alternative splicing involving exon 3. The longer human transcript is the major form in human cell lines and encodes a 342-amino acid protein. The shorter transcript encodes a 168-amino acid protein. Recently, Hirano *et al*. [36] identified six new alternative spliced variants resulting from alternative splicing of part of exon 2 (5 bases at the 5'end), part of exon 3 (115 bases at the 5' end), and all of exon 5 in various combinations. The expression levels of these variants are controlled in a tissue-specific manner and may contribute to the tissue-specific phenotype of AOA1. The high levels of the full-length transcript and the low levels of the different variants in cerebellum and liver suggest a critical role of full-length transcript in these organs [36].

Fourteen mutations, including missense (K197Q, A198V, R199H, H201Q, P206L, G231E, V263G, D267G, W279R), nonsense (W279X), frameshift (689insT, 8840delT), and splicing mutations (IVS5+1) or complete deletion of the gene have been described [27••,28••,29•,30•,31–33]. They are almost exclusively located in exons 5, 6, and 7 [27••,28••]. The most frequent mutation in Europe is W279X [27••,30•], whereas the 689insT and P206L mutations are the most common in Japanese patients [28••]. Interestingly, a homozygous deletion of all seven exons of the gene has been reported in a Tunisian family with a typical AOA1 phenotype. This indicates that total absence of the entire gene is not more deleterious than missense or other truncating mutations and suggests that these mutations lead to a complete loss of function of aprataxin [31].

Subcellular localization and function of aprataxin

Aprataxin is a ubiquitously expressed nuclear protein. Full-length aprataxin is detected in the nucleolus and uniformly and in small discrete foci in the nucleoplasm [37••,38••]. The major subcellular localization of the aprataxin variants is regulated by alternative splicing [39]. Full-length aprataxin is mostly located in the nucleus, whereas shorter variants are found in the cytoplasm [39]. The full-length protein contains three nuclear localizing signals (NLS) [40•]. The first NLS seems to play a critical role for the nuclear localization of full-length aprataxin [40•].

Homology searches revealed the presence of three putative functional domains in the full-length aprataxin [27••,28••]. Human aprataxin contains a central histidine triad motif suggesting it is a new member of the histidine triad (HIT) superfamily. Mutations are almost exclusively located in this domain of the protein. Proteins of the HIT superfamily are nucleotide hydrolases and transferases [41] that are divided in three branches: Hint (histidine triad nucleotide binding), Fhit (fragile histidin triad), and galactose-1-phosphate uridylyltransferase. Aprataxin is most homologous in the Hint subfamily [28••,37•,42]. Hint proteins bind nucleotides and have an adenosine 5'-monophosphoramidase (AMP) activity. They hydrolyze substrates in which AMP is linked to a lysine–side chain [43]. In addition, Hnt1, the yeast homolog of Hint, has a positive regulator effect on the components of the general transcription factor TFIIH [42], which also has a function in nucleotide excision repair. This suggests that it is indirectly involved in nucleotide excision repair, a subtype of single-strand break repair.

The N-terminal domain of aprataxin, known as PNKP-AOA1 N-terminal (PANT) or forkhead-associated (FHA) domain, is homologous to the N-terminal domain of the human polynucleotide kinase 3'-phosphatase (PNKP) [27••,28••]. PNPK protein interacts with other proteins such as DNA polymerase β, DNA ligase III, PARP-1, and XCCR1 to form the single-strand break repair complex (SSBR). The HIT and PANT motifs of aprataxin are both potentially involved in SSBR and suggest that the protein may function with or as a part of the SSBR complex [40•]. Moreover, the C-terminal motif of aprataxin is a zinc-finger domain that might enable aprataxin to bind to DNA [27••,28••].

Expression of the mutant aprataxin

The expression of the full-length protein is null or severely reduced in AOA1 cells with various truncating (689insT/840delT, W279X) or missense mutations (P206L/P206L, P206L/V263G) [37••,38••,40•]. By reverse transcriptase–polymerase chain reaction, Hirano *et al*. [39] demonstrated normal APTX mRNA levels but decreased protein levels in mutants (P206L, W279X, 689insT), suggesting that mutations in the *APTX* gene decrease the stability of the mutant protein.

Aprataxin and double-strand break repair

The ATM protein, which is deficient in A-T, plays a critical role in the double-strand break repair machinery. In normal cells, ATM is recruited and forms foci at the sites of DNA double-strand breaks. Many of the substrates of ATM are cell-cycle regulators that have essential functions in the cellular response to DNA damage and include p53, BRCA1, and the checkpoint kinase ChK2. A-T cells are typically deficient of ATM protein due to null mutations in both copies of the *ATM* gene [44].

Given the similarities between AOA1 and A-T, the nuclear localization, and the structure of the protein, a potential role of aprataxin in DNA repair and similarities with the A-T cellular phenotype were expected. The characteristic hallmarks of A-T cells are hypersensitivity to ionizing radiation, chromosomal instability, and cell checkpoint

defects with reduced or delayed phosphorylation of p53, Chk2, and H2AX following DNA damage. To investigate the physiologic role of aprataxin, DNA damage responses in AOA1 patient primary fibroblasts and lymphoblastoid cells expressing mutant protein were compared with A-T patient cells lacking ATM and control subjects [38••]. In AOA1 cell lines, ATM protein levels are normal and have the ability to form phopshorylated ATM foci at sites of DNA double-strand breaks. Moreover, AOA1 cells are different from A-T cell lines in respect to their milder sensitivity to ionizing radiations and lower level of chromosomal aberrations following X-ray irradiation [38••]. Experiments measuring sensitivity to genotoxic agents have yielded contradictory results. Clements *et al*. [38••] found that AOA1 cell lines were less sensitive to alkylating (MMS) and oxidizing (H_2O_2) agents, whereas Gueven *et al*. [37••] demonstrated hypersensitivity to these agents. This discrepancy may be explained by different cell types, mutations, and levels of cytotoxic agents employed in the two studies. Finally, phosphorylation of p53, Chk2, and H2AX is normal in AOA1 cell lines after exposure to H_2O_2 [38••]. Taken together, these results suggest that AOA1 cell lines do not share the cell-cycle checkpoint defects that are characteristic of A-T, and that aprataxin is not involved in recognizing double-strand breaks in DNA [37••,38••]. Clements *et al*. [38••] speculated that this difference accounts for the apparent lack of cancer in patients AOA1.

Interactions of *APTX* with SSBR proteins

Aprataxin shares homology with PNKP, a protein that interacts with XRCC1 (X-ray repair cross-complementing group 1). PNKP and XRCC1, together with PARP-1, DNA polymerase β, and DNA ligase III, form the SSBR complex. XRCC1 also interacts with PARP-1, DNA polymerase β, and DNA ligase III [45].

The expression of XRCC1 and PARP-1 is normal in AOA1 cell lines [37••,38••]. Based on yeast two-hybrid assays and co-immunoprecipitation experiments, several groups demonstrated that the full-length aprataxin interacts with the C-terminal domain of XRCC1, whereas the short form does not [37••,38••,40•,46]. This indicates that the N-terminal region of aprataxin, containing the FHA domain, is involved in the interaction with XRCC1 [40•]. Date *et al*. [46] showed the N-terminal 20 amino acid residue of the FHA domain of aprataxin is necessary for binding to XRCC1. In normal cells exposed to H_2O_2, XRCC1 aggregates in foci almost immediately after exposure and forms larger foci with time, with a peak at 30 minutes after treatment [37••]. In untreated AOA1 cell lines, XRCC1 foci are constitutively present and there is little change after H_2O_2 exposure [37••]. This shows that in absence of aprataxin, XRRC1 is abnormally distributed in the nucleus and the normal response to hydrogen peroxide is attenuated. Co-localization of aprataxin and XRCC1 was demonstrated along heavy ion-induced tracts but not in H_2O_2-induced foci [37••]. All these findings raise the possibility that aprataxin aggregates and co-localizes with XRCC1 at the break sites, and, therefore, plays a role in the SSBR through its interaction with XRCC1. AOA1 cell lines transfected with full-length aprataxin are reported to be less sensitive to genotoxic agents and have fewer chromosomal aberrations [37••].

Aprataxin also interacts with p53 and PARP-1 [37••]. P53 binds with both the FHA and HIT domains, whereas PARP-1 binds to a region including the FHA, NL, and HIT domains of aprataxin [37••]. Date *et al*. [46] suggested that aprataxin and PARP-1 could constitute a new SSBR complex with XRCC1 as the scaffold protein, and that aprataxin is likely to have novel function that is distinct from PNKP because it shares homology with the FHA domain of PNKP but not with its catalytic domain [46].

Finally, Gueven *et al*. [37••] also demonstrated that aprataxin interacts and co-localizes with nucleolin in nucleoli. Nucleolin binds most strongly to the FHA domain [37••]. Activation of the RNA binding properties of nucleolin is part of cellular response to genotoxic stress, which provides additional evidence for the role of aprataxin in the genotoxic stress response [37••,47].

Ataxia with Oculomotor Apraxia Type 2 (AOA2)

In 2000, Bomont *et al*. [48] and Nemeth *et al*. [49] independently established linkage to chromosome 9q34 in families with autosomal recessive ataxia resembling A-T, but with a later age at onset and without the extra-neurologic features characteristics of A-T. These results were based on the study of a large Pakistani family with oculomotor apraxia but normal serum alpha-foetoprotein level [49] and two Japanese families with elevated alpha-foetoprotein levels but no oculomotor apraxia [48,50]. The subsequent identification of families with both oculomotor apraxia and elevated alpha-foetoprotein levels suggested that this represents a new single entity, which was designated AOA2 [51]. The responsible gene, *SETX*, was identified in 2004 [52]. Patients with diverse geographic origins have now been reported, showing that AOA2 is present worldwide [53•,54].

Phenotype

The mean age at onset is 15 years (range, 2 to 25 years), which is later than in AOA1 patients [52,53•,54]. Most patients had cerebellar ataxia at onset. Choreic movements were less frequent and axonal sensorimotor neuropathy was less severe than in AOA1 patients. Oculomotor apraxia is present in 60% of patients. As in AOA1, eye-head dissociation caused by loss of vestibule-ocular reflex cancellation is observed. Furthermore, saccade initiation was also impaired in some patients with increased latencies [53•]. There was no mental retardation, telangiectasia, or malignancies. Brain MRIs showed marked cerebellar atrophy predominating in the vermis. Alpha-foetoprotein levels were elevated in 75% to 100% of patients and were

correlated with disease duration. The course of the disease is slowly progressive. Recently, Duquette *et al*. [54] reported 10 French-Canadian AOA2 families without oculomotor apraxia. The most frequent mutation associated with this phenotype was L1679R. This mutation was present in all families, suggesting a French-Canadian founder effect [54].

Interestingly, Chen *et al*. [55•] identified missense mutations in the *SETX* gene (T3I, L389S, R2136H) in three pedigrees with amyotrophic lateral sclerosis 4 (ALS4), an autosomal dominant form of motor neuronopathy. ALS4 is characterized by early distal weakness with amyotrophy and pyramidal signs, but with few or no sensory signs. There is a wide phenotypic variability in families with senataxin mutations; some have pure motor neuronopathy whereas others have spastic paraplegia. Severity is also variable. Some patients have only brisk reflexes whereas others are wheelchair-bound in their fifth or sixth decade [55•]. A pathologic study in one patient with ALS4 showed spinal cord atrophy with marked loss of anterior horn cells, corticospinal tracts, posterior columns, dorsal root ganglia, and the presence in axonal spheroids in the gray matter [55•].

SETX gene and senataxin

The *SETX* gene encoding senataxin, a 2677-amino acid protein, contains 24 exons [52]. Two major transcripts of 11.5 and 9.0 kb are expressed in all tissues, including brain and spinal cord [55•]. Little is known about the function of the human senataxin. The C-terminal region of senataxin is homologous with the yeast-splicing endonuclease 1 gene (*Sen1*), which has DNA and RNA helicases activity and might be a novel DNA/RNA helicase. Interestingly, recent studies have shown that several forms of human spinal muscular atrophy are associated with defects in protein complexes containing helicase activity. The SETX helicase domain of senataxin shares significant homology with two other members of the DexxQ-box family of helicase: the RENT1 and IGHMBP2 proteins [52]. RENT1 is involved in nonsense-mediated RNA decay. The IGHMBP2 protein is mutated in SMARD1, another form of spinal muscular atrophy [52,55•]. Chen *et al*. [55•] suggested, therefore, that DNA/RNA helicase dysfunction may play a major role in the development of lower motor neuron diseases. Furthermore, RENT1 and IGHMBP2 also play important roles in producing mature mRNA, which suggests that aprataxin may be implicate din mRNA biogenesis [55•].

Eighteen mutations located throughout the gene have been identified so far: seven missense (E65K, W305C, R332W, P413L, F1756S, L1976R, P2213L), four nonsense (R788X, Q868X, R1363X, Q1441X), and seven frameshift mutations (879delT, ins1690T, 2622-2625delAGTT, 2966-2970delGGAAA, 5070insT, 5249insT, 5264delC). Most AOA2 mutations are predicted to lead to a truncated protein [52]. The senataxin mutations responsible for ALS4 are missense mutations (T3I, L389S, R2136H). Chen *et al*. [55•] speculated that a dominant-negative effect, a partial loss of function, or a toxic gain of function could lead to the development of upper and lower motor neuron disease in autosomal dominant ALS4, whereas a putative autosomal recessive loss of function could lead to a more widespread disorder in AOA2.

Conclusions

The importance of the DNA repair system in neuronal cells has been evidenced in neurodegenerative disorders of impairment of the DNA repair system, such as A-T, A-T–like disorder, SCAN 1, Cockayne syndrome, and xeroderma pigmentosum. The gradual accumulation of DNA damage may lead to neuronal cell death, particularly in the cerebellum. How this leads to neurodegeneration and why DNA repair deficiencies predominantly affect the central nervous system, and in particular the cerebellum, need to be elucidated.

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Papers of particular interest, published recently,
have been highlighted as:

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