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REVIEW ARTICLE

DNA repair abnormalities leading to ataxia: shared neurological phenotypes and risk factors

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Abstract Since identification of mutations in the *ATM* gene leading to ataxia-telangiectasia, enormous efforts have been devoted to discovering the roles this protein plays in DNA repair as well as other cellular functions. Even before the identification of *ATM* mutations, it was clear that other diseases with different genomic loci had very similar neurological symptoms. There has been significant progress in understanding why cancer and immunodeficiency occur in ataxia-telangiectasia even though many details remain to be determined, but the field is no closer to determining why the nervous system requires *ATM* and other DNA repair genes. Even though rodent disease models have similar DNA repair abnormalities as the human diseases, they have no consistent, robust neuropathological phenotype making it difficult to understand the neurological underpinnings of disease. Therefore, it may be useful to reassess the neurological and neuropathological characteristics of ataxia-telangiectasia in human patients to look for potential commonalities in DNA repair diseases that result in ataxia. In doing so, it is clear that ataxia-telangiectasia and similar diseases share neurological features other than merely ataxia, such as length-dependent motor and sensory neuropathies, and that the neuroanatomical localization for these symptoms is understood. Cells affected in ataxia-telangiectasia and similar diseases are some of the largest single nucleated cells in the body. In addition, a subset of these diseases also has extrapyramidal movements and oculomotor apraxia. These neurological and neuropathological similarities may indicate a common DNA repair related pathogenesis with very large cell size as a critical risk factor.

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Introduction

Ataxia-telangiectasia (A-T) is an autosomal recessive disease that has long fascinated clinicians and scientists alike (OMIM #208900) [1]. A-T was likely originally described in 1926 [2] and again in 1941 [3]. However, it was not until a series of patients described by Boder and Sedgewick [4] as well as Wells and Shy [5] that A-T became widely appreciated as a clinical syndrome. Although rare, with an estimated incidence of 1 in 40,000 to 100,000 births [6–8], A-T has been of significant interest because of patients' unusual combination of neurological degeneration, cancer predisposition, immunodeficiency, radiation sensitivity, and telangiectasia (capillary dilatation on the face and sclera most prominently) as well as specific laboratory abnormalities (such as elevated alpha fetal protein levels) that aid in diagnosis. Cancer and diseases of the respiratory system (possibly secondary to immunodeficiency) are the most common causes of death, but neurological degeneration results in significant disability over the majority of a patient's life [8]. Cells derived from A-T patients were found to be sensitive to ionizing radiation and have chromosome rearrangements, first suggesting ATM's role in DNA repair and genome stability [9–12]. After the genetic cause was identified, mutations in the gene *ataxia-telangiectasia mutated* (*ATM*) [13], a great deal of excellent work has focused on understanding the myriad of functions of this protein. Through this research, there is a reasonable insight into the causes of both immunodeficiencies and cancer [14]. However, there is still no clear mechanistic understanding of neurological degeneration.

In addition to A-T, there are several other DNA repair associated neurological diseases that have extremely similar neurological symptoms. Different symptoms have variable

penetrance and severity at different times during the course of disease, but common symptoms suggest or have been demonstrated to have similar neuropathological localization between diseases. The similarities in neurological and neuropathological phenotypes in multiple DNA repair diseases suggest the possibility of a similar neuropathological mechanism(s). Neurologists and neuropathologists who study A-T and similar diseases may have limited understanding of the details of DNA repair. Basic scientists who study DNA repair may not understand the nuances of A-T's neurological pathology. This is an attempt to partially bridge that gap. Since the goal is to examine neurological aspects of A-T and similar diseases, the neurological symptoms will remain the focus and other clinical phenotypes may be only briefly mentioned.

A-T has been a distinct genetic disease for over 5 decades and is well characterized both neurologically and pathologically so it will be the source for comparison to other diseases. Very similar neurological symptoms are found in other DNA repair diseases including A-T-like disease (*MRE11*) (OMIM #604391) [15]; ataxia, early onset, with oculomotor apraxia and hypoalbuminemia (EAOH) (a.k.a. ataxia with oculomotor apraxia 1) (*APTX*) (OMIM #208920) [16, 17]; spinocerebellar ataxia, autosomal recessive 1 (SCAR1) (a.k.a. ataxia with oculomotor apraxia 2) (*SETX*) (OMIM #606002) [18]; and spinocerebellar ataxia with neuropathy (*TDP1*) (OMIM #607250) [19], and in some patients with epileptic encephalopathy, early infantile, 10 (a.k.a microcephaly with seizures) (*PNKP*) (OMIM #605610) [20, 21]. Even though ataxia is not the only neurological symptom, this group of genetic conditions will be referred to as DNA repair ataxia diseases for this phrase's relative succinctness.

Multiple groups have created mouse models of DNA repair ataxia diseases, including *Atm* [22–28]. While *Atm* knockout mice have abnormalities in DNA repair and develop cancer and immunodeficiency, they lack dramatic neuropathology such as neuronal loss with some having subtle or variable neurological phenotypes (reviewed by Lavin [29]). Similarly, murine disease models with mutations in *Mre11a* [30], *Tdp1* [31–33], *Aptx* [34], and *Setx* [35] do not have dramatic neuropathological phenotypes similar to the human diseases even though they also replicate the DNA repair abnormalities. The lack of a robust neuropathological phenotype has limited the ability to test hypotheses concerning mechanisms for neurodegeneration. This emphasizes the importance of understanding the human neurological pathology.

Neurological features of A-T

The neurological symptoms and neuropathology will be discussed as a way of illuminating the specific requirements for *ATM* and other genes in the nervous system. The correlations between a neurological phenotype and loss of specific cell types are typically quite strong for the symptoms discussed. The pathogenesis in Purkinje versus granule cells in the cerebellum will be detailed, but one cannot be certain in which cell type the defect resides since animal models with neurological phenotypes are needed to make definitive determinations. Because of their unknown clinical significance, neuropathological features not clearly associated with A-T's specific neurological deficits as well as inconsistent or rare pathological findings will not be discussed in detail. Childhood neurological diseases are frequently categorized as degenerative, a function that was previously present but lost, or developmental, deficient development of a function. DNA repair ataxia diseases are degenerative as patients lose functions they previously possessed. The age of onset of neurological symptoms in A-T seems to be affected by mutation severity and can be separated into two categories, early childhood and mid-childhood [36–38]. While later onset neurological symptoms are different in terms of timing and severity, both have the same neuropathological features [38, 39] and early onset neurological disease will be the focus. Many neurological diseases that typically start in childhood, such as mitochondrial or metabolite processing diseases, frequently have milder cases that present in a patient's 30's, 40's, or even later in life. However, A-T neurological symptoms seem to always start prior to adulthood.

In early onset A-T, ataxia and cerebellar degeneration, a particular form of lack of motor coordination, is typically the initial symptom and is found in essentially all patients at some point [8]. Cerebellar atrophy is common but not universal in genetic ataxias. Neurological symptoms in A-T generally start with ataxia, although other symptoms such as extrapyramidal symptoms can predominate at first in later onset disease and weakness can rarely be the earliest symptom [40, 38]. Although not proven, Purkinje cell loss is likely to be the primary cause of cerebellar atrophy and is a universal finding in A-T. Granule cells proliferate, migrate, and synapse to Purkinje cells starting in utero and continuing the first year or two of life when A-T ataxia can start in early onset cases, suggesting that granule cells may be primarily defective (Fig. 1). However, Purkinje cell loss is universal and granule cell loss is not as severe and occasionally not apparent, making ATM more likely required in Purkinje cells [41, 42]. In addition, mouse studies suggest that intrinsic loss of granule cells does not seem to result in severe Purkinje cell losses [43, 44]. Therefore, while it is not definitive, evidence supports Purkinje cells as primarily affected in the cerebellum. Dysarthria or slurred speech is common in A-T. Dysarthria is often difficult to localize neuroanatomically because it can have many different causes. The dysarthria associated with A-T is similar to other forms of ataxia and may be cerebellar in origin [45]. However, drooling is also common in A-T but not a universal symptom in cerebellar ataxias, so involvement of brainstem nuclei controlling the oral pharynx is possible but not clear [8].

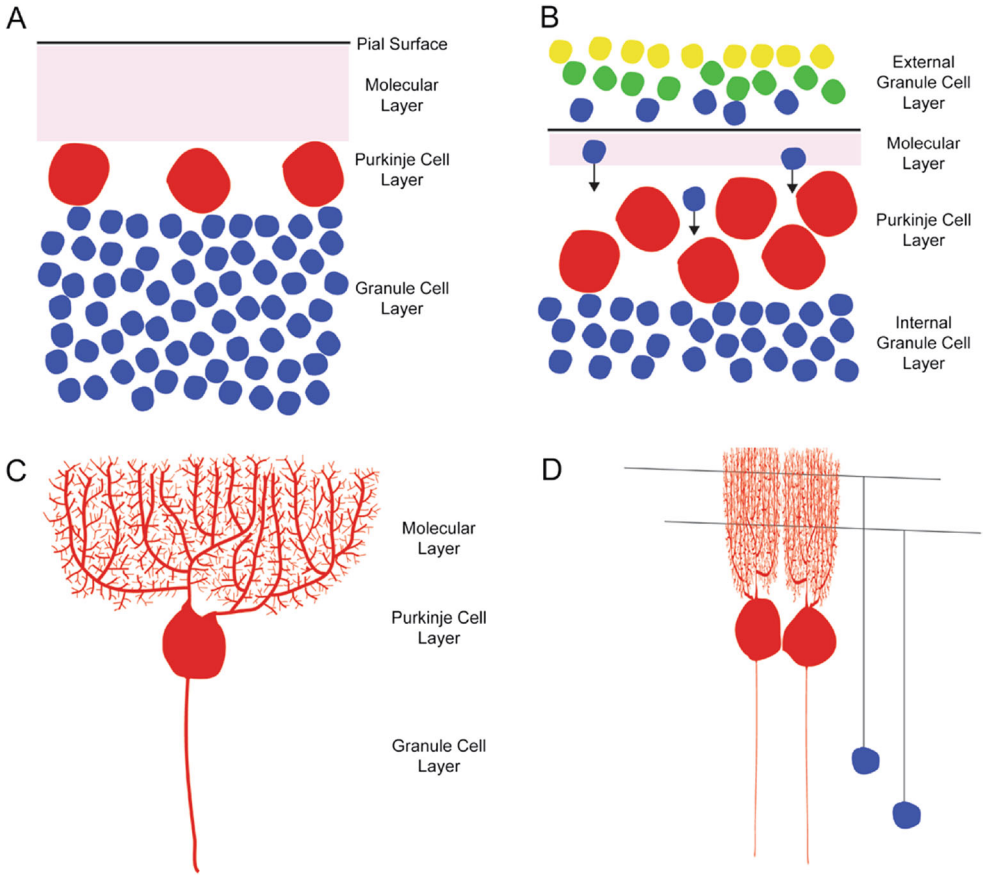

Fig. 1 Diagram of cerebellum and development. **a** The mature cerebellar cortex has three layers. Adjacent to the pial surface (outer surface) is the molecular layer (*light pink/blue*) containing Purkinje cell dendrites, granule cell axons, and a few sparse cells not depicted. Next is a single cell layer of large Purkinje cell bodies (*red*) followed by the highly abundant granule cell bodies (*blue*). **b** Purkinje cells are "born" significantly before granule cell proliferation begins. Granule cells migrate across the pial surface to cover the developing cerebellum forming the external granule cell layer. Granule cell precursors divide (*yellow*), start to differentiate (*green*), and when mature (*blue*) migrate into the cerebellum. As the granule cells migrate through the molecular layer, they extend their axons and form synapses on Purkinje cell dendrites. Granule cell bodies migrate past the Purkinje layer and into the internal granule cell layer with their axons trailing behind. **c** A cartoon underrepresenting the elaborate arborization of a human Purkinje cell dendrite. The dendrite is planar and viewed here sagittally. **d** Two Purkinje cells (turned 80° from view seen in **c**) with two granule cell parallel fibers (axons) extend in the horizontal plane making synapses on multiple Purkinje cell dendrites. Granule cell synapses are required to form the very large Purkinje cell dendritic tree. Therefore, granule cell proliferation is associated with dramatic increases in Purkinje volume via dendritic growth (Color figure online)

In early onset A-T, weakness from loss of motor neurons generally starts to become an issue later in childhood (Fig. 2, left side). In A-T, neuropathy is consistent with loss of axons in the nerve (as opposed to loss of myelin that covers axons) as well as the motor neuron cell bodies within the spinal cord, most pronounced within the lumbar regions (lower spinal cord that innervates the legs) [46–49, 39]. The neuropathy is most severe for the longest axons with distal muscle wasting of the feet and hands common late in disease. Muscle loss is consistent with loss of neurons as opposed to a primary defect in muscle fibers based upon muscle histological pattern, group atrophy [50, 39]. The length-dependent nature of the neuropathy is illustrated by a patient who cannot move his toes and barely his ankles but has normal or near normal strength at shoulders and hips [51].

A-T patients lose sensation from loss of sensory neurons (Fig. 2, right side), particularly position and vibration as well as losing deep tendon reflexes, but have relative sparing of cold and pain sensation [45, 49]. Like motor neurons, the neuropathy is axonal and also includes loss of sensory neuronal cell bodies in dorsal root ganglia [50, 46, 8, 49, 39]. The spinal cord shows a striking loss of sensory axons carrying position and vibration sense within the posterior portion of the spinal cord from the leg regions with arm regions relatively intact [50, 45, 39]. The axons that convey joint position and vibration are larger in diameter than those that carry pain and temperature, and the large caliber fibers are lost in A-T nerves [47]. Taken together, this shows that neurons are lost in a length-dependent (longer>shorter), as well in an axonal diameter-dependent (larger>smaller), manner [39]. The loss of deep tendon reflexes in A-T patients is likely due to the loss of sensory neurons, motor neurons, or both [8].

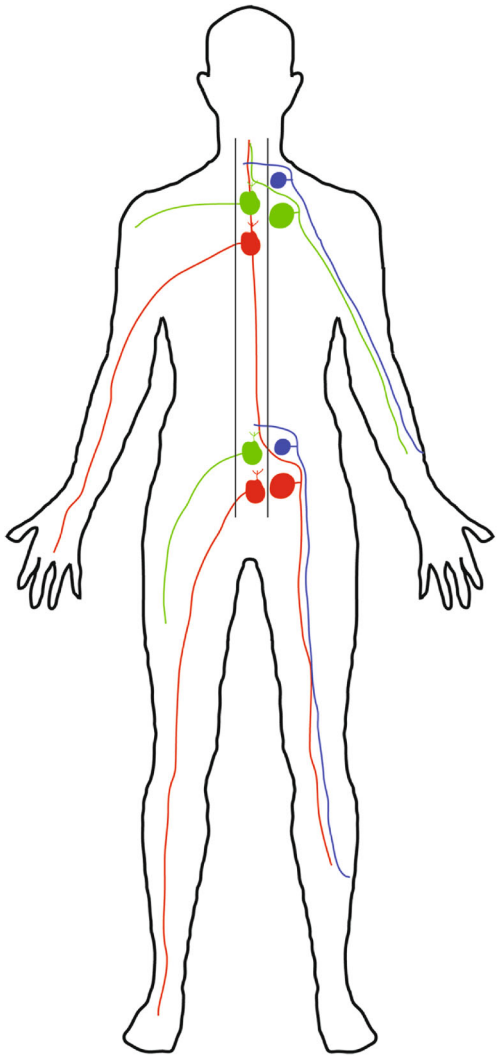

Fig. 2 Illustration of the relative vulnerability of motor and sensory neurons in A-T. The *thin black lines* in midline represent the spinal cord. On the *left* are motor neurons with cell bodies residing within the spinal cord whose axons extend to muscles. The motor neurons with the longest axons (*red*) are most affected in A-T while the motor neurons with shorter axons (*green*) are less affected. On the *right* are sensory neurons with cell bodies just outside of spinal cord in clusters, the dorsal root ganglia. A single axon extends out into the periphery as well as into the spinal cord. The most vulnerable neurons have large diameter cell bodies and axons and a single large caliber axon that carries vibration sense or position information (*red*) from the legs to the brain stem. Sensory neurons with small cell bodies and smaller axonal caliber carry pain or temperature sensation (*blue*), convey information from the periphery, synapse in the spinal cord at the approximate level they enter (not in the brain stem), and are less affected in either the upper or lower extremities of A-T patients compared to vibration and proprioceptive neurons (Color figure online)

Many A-T patients have prominent movement disorders that appear extrapyramidal in nature [2, 5, 8, 52]. A-T patients' extrapyramidal symptoms frequently include abnormal posture, tremor (shaking), myoclonus (rapid single jerks of a limb), and/or choreoathetoid movements (slow dancing and/or writhing-like) [8, 52]. Extrapyramidal symptoms are often associated with injury to the basal ganglia but can also come from injury to regions of the thalamus or brainstem such as the substantia nigra. In early onset A-T, extrapyramidal symptoms are prominent later in the course of the disease but at times can predominate to the extent that two early descriptions of A-T described the disease as extrapyramidal as opposed to ataxic in nature [2, 5]. Only a few neuropathological studies have found any potential pathology in the basal ganglia while others found abnormalities in the locus coeruleus and the substantia nigra [53–55, 48, 45, 56, 39]. A-T patients have metabolic changes in their basal ganglia indicative of dysfunction even though the neuroanatomical localization of the extrapyramidal neuropathology remains to be definitely determined [57].

A-T patients can have peculiar eye movements known as oculomotor apraxia that are distinct from those usually found in other ataxic diseases [58, 8]. Oculomotor apraxia is a rare condition where patients have the ability to move eyes in all directions when tracking (following) an object but cannot voluntarily move their eyes to a different location, as when looking back and forth between two different objects [59]. The neuroanatomical localization for oculomotor apraxia is not known in A-T or any other condition [59].

While affecting multiple different types of neurons, A-T does not appear to be a universally progressive neurological disease. As noted above, A-T is a degenerative disease and several different cell types are lost, but the vast majority of the neurons in the brain appear unaffected in A-T. For instance, patients do not seem to have significant cognitive degeneration during the course of their disease. Early impressions were that intellectual disability was present in A-T, but much of that was due to slowness in responses secondary to motor dysfunction [60, 48, 45]. When followed over time, A-T patients can stop acquiring intellectual gains as opposed to losing intellectual capacity that typically occurs during cerebral cortical degeneration. In addition, there is little definitive structural MRI or pathological change in the cerebral cortex, thalamus, or basal ganglia neurons or axons, although it is possible that subtle changes may have not yet been consistently identified. Abnormalities in small blood vessels are present in the brain, but they seem to occur later in disease and are not necessarily correlated with neurodegeneration, so their contribution to neurodegeneration is uncertain [48, 8, 61]. A-T patients have cells with hyperchromatic nuclei with bizarre shapes, but these abnormalities are found in many organs with no correlation to tissue pathology and their clinical significance remains undetermined [46, 62, 55, 48].

Neurological features of other DNA repair ataxia diseases

The other DNA repair ataxia diseases were recognized more recently. Therefore, the clinical and neuropathological literature is not as extensive. Neurological similarities to A-T will

only be summarized and neuropathological similarities when known are not detailed due to space constraints (Table 1). Mutations in *MRE11A* can produce ataxia-telangiectasia-like disorder (ATLD) with degenerative cerebellar ataxia, dysarthria, drooling, oculomotor apraxia, loss of sensation, loss of reflexes, weakness with distal muscle wasting, and extrapyramidal symptoms [63, 64, 15, 65, 66]. Mutations in the *aprataxin* (*APTX*) gene lead to ataxia, early onset, with oculomotor apraxia and hypoalbuminemia (EAOH) (a.k.a. ataxia with oculomotor apraxia I, AOA1) with degenerative cerebellar ataxia, dysarthria, extrapyramidal abnormalities, oculomotor apraxia, loss of position and vibration sense, and length-dependent weakness with muscle wasting of the distal extremities [67, 16, 17, 68–75]. *Senataxin* (*SETX*) mutations can lead to a disease called spinocerebellar ataxia, autosomal recessive 1 (SCAR1) (a.k.a. ataxia with oculomotor apraxia 2, AOA2) with degenerative cerebellar ataxia, extrapyramidal abnormalities, loss of reflexes, motor and sensory neuropathy particularly affecting vibration and position sense, oculomotor apraxia, some evidence of loss innervation to the spinal motor neurons from the cerebral cortex (a.k.a. upper motor neuron signs), and dysarthria [76, 18, 77–83]. Mutations in *tyrosyl-DNA phosphodiesterase 1* (*TDP1*) result in spinocerebellar ataxia, autosomal recessive with axonal neuropathy (SCAN1) with cerebellar degenerative ataxia, distal muscle weakness, length-dependent loss of vibration and position sense, dysarthria, and loss of reflexes [19]. Patients with mutations in polynucleotide kinase 3-prime phosphatase (*PNKP*) were first reported with microcephaly, developmental delay, and seizures, called epileptic encephalopathy, early infantile 10 (EEEI 10, a.k.a. microcephaly with seizures) [20]. Subsequently, it was found that some patients in later childhood developed cerebellar degenerative ataxia, as well as sensory and motor neuropathy [21]. Mutations in the DNA repair gene *TDP2* lead to intellectual disability, epilepsy, and ataxia, but this very recently identified condition requires more clinical characterization before it is clear how patients with *TDP2* mutations may relate neuropathologically to the other DNA repair ataxia diseases [84]. Also currently not included is a single family with a compound homozygous polymorphism in phosphoinositide-3-kinase, regulatory subunit 5 *(PIK3R5*) (OMIM# 615217) because even though they neurologically appear very similar to other DNA repair ataxia diseases, evidence for PIK3R5 dysfunction in the patients is not yet definitive [85].

In summary, patients with A-T (*ATM*), ATLD (*MRE11A*), EAOH (AOA1) (*APTX*), SCAR1 (AOA2) (*SETX*), and SCAN1 (*TDP1*) and some with EEEI10 (*PNKP*) have nearly identical neurological symptoms including prominent cerebellar ataxia, dysarthria (likely secondary to cerebellar degeneration), length-dependent motor neuropathy, and length-dependent sensory axonal neuropathy of vibration and position sense with loss of reflexes likely secondary to neuropathy (Table 1). Mutations in *ATM*, *MRE11A*, *APTX*, and *SETX* can lead to prominent extrapyramidal symptoms and oculomotor apraxia. Ataxia is consistent with cerebellar degeneration most likely secondary to loss of Purkinje cells. Weakness is predominately due to loss of motor neurons as opposed to loss of myelination or muscle disease. Sensory changes, predominately position and vibration, are also likely secondary to loss of sensory neurons/axons and not an abnormality of myelin. Loss of reflexes is likely secondary to loss of sensory neurons, although loss of motor neurons may also contribute. There is length-dependent axonal loss of the largest diameter axons. The neuropathological localizations for the extrapyramidal symptoms and oculomotor apraxia are not well understood,

Table 1 Summary of neurological symptom and neuropathological correlate if known

	A-T (*ATM*)	ATLD (*MRE11A*)	EAOH (a.k.a. AOA1) *APTX*	SCAR1 (a.k.a. AOA2) *SETX*	SCAN1 *TDP1*	EEEI 10 (a.k.a. MCSZ) *PNKP*
Ataxia	Prominent, 2° to Purkinje cell loss	Prominent, 2° to Purkinje cell loss	Prominent, 2° to Purkinje cell loss	Prominent, 2° to Purkinje cell loss	Prominent, cerebellar degeneration	In some, with cerebellar degeneration
Length-dependent neuropathy (motor)	Yes, distal weakness, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss	In some patients with distal weakness
Length-dependent neuropathy (sensory)	Yes, distal vibration and position, 2° to axonal loss	Yes, distal vibration and position, 2° to axonal loss	Yes, distal vibration and position, 2° to axonal loss	Yes, distal vibration and position, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss	In some patients
Extrapyramidal symptoms	Yes, neuronal localization unknown	Yes, neuronal localization unknown	Yes, neuronal localization unknown	Yes, neuronal localization unknown	No	No
Oculomotor apraxia	Yes, neuronal localization unknown	Yes, neuronal localization unknown	Yes, neuronal localization unknown	Yes, neuronal localization unknown	No	No
Spasticity	Rare	Occasional	No	Occasional	No	No

although one might suspect that they are similar as these symptoms are quite rare in other degenerative ataxia diseases. In addition, it is also important to note the rather restricted and very specific neurons affected in these diseases as A-T and similar diseases do not appear to have widespread neuronal degeneration.

The neurological symptoms associated with DNA repair ataxia diseases are distinct from other ataxia diseases. Autosomal recessive cerebellar degeneration with both motor and sensory neuropathies is not common but present in all DNA repair ataxia diseases. In autosomal recessive ataxias that do have neuropathy, some are demyelinative while A-T and similar diseases have axonal neuropathies [86]. The most common genetic ataxia, Friedreich's ataxia (OMIM #229300), has some clinical similarities, but several key differences, generally making this disease reasonably easy to clinically distinguish from DNA repair ataxia diseases [87]. Friedreich's ataxia is often characterized by ataxia and neuropathy similar to A-T, but neuroimaging of the cerebellum is normal early in disease [88, 86]. In Friedreich's, some of the ataxia may be mediated via loss of the sensory input to the cerebellum via the spinocerebellar tract as well as prominent loss of the cerebellar dentate neurons (as opposed to Purkinje cells) [89]. Additional features of Friedreich's ataxia include some overlapping features with DNA repair abnormalities associated with ataxia including dysarthria, sensory neuropathy with loss of reflexes, and length-dependent weakness. However, unlike A-T, Friedreich's ataxia often has evidence of loss of the connection from cerebral cortex to the spinal cord motor neurons (a.k.a. upper motor neuron signs) early, and scoliosis is prominent while some have bladder disturbances, optic atrophy, and hearing loss. Extraneurological symptoms include frequent and potentially lethal cardiac abnormalities and diabetes mellitus [88, 90]. Friedrich's ataxia is more likely to be confused clinically with a different disease, ataxia with vitamin E deficiency (*TTPA*) (OMIM #277460), because of overlapping neurological features [91–93]. Dominant ataxias, sometimes called spinocerebellar ataxias (SCA), have nearly 40 different genetic loci. Some have neuropathy and some have extrapyramidal movements, but it would be rare that they would be clinically confused with DNA repair ataxia diseases because of the combination of neurological symptoms and age of onset [94, 95]. When all neurological symptoms are considered, the neurological similarities between DNA repair ataxia diseases are striking when compared to other ataxia diseases.

DNA repair activities

This is not intended to be a comprehensive review of biochemical roles and mechanisms of DNA repair proteins as many excellent reviews have been previously written [96–99, 14, 100–108]. However, a brief elaboration of DNA repair activities is required to establish some context. ATM is a serine/threonine protein kinase that plays a very central role in many aspects of DNA repair signaling, particularly well studied in double-strand break repair. For example, ATM and its paralog ATR phosphorylate over 700 different proteins after ionizing radiation [109]. In addition to ATM's role in double-strand break repair, it has been implicated in single-strand break repair, response to hypoxia, oxidative stress, insulin signaling, mitochondrial activity, histone acetylation, and other functions (recently reviewed in Hoche et al. [104] and Shiloh and Ziv [107]). MRE11 is required for optimal activation of ATM under multiple stressors (upstream of ATM activation), is phosphorylated by ATM, and has ATM-independent roles as well [98].

Unlike ATM and MRE11, the other DNA repair ataxia disease proteins seem to have much more simple roles in DNA repair, likely having direct enzymatic repair roles on DNA itself. ATPX, TDP1, and PNKP can interact with single-strand break repair machinery [96, 97, 102, 100]. APTX can remove failed ligase products and other abnormalities that are covalently attached to DNA [34, 110]. TDP1 can help remove arrested topoisomerase I covalently bound to DNA and can process damaged bases during single-strand break repair [111–115]. PNKP can interact with multiple DNA repair pathways in its role as a DNA 3′ phosphate and 5′ kinase [116–118, 20, 119]. SETX is a putative RNA/DNA helicase that may repair DNA damage associated with transcription [120–124]. It is certainly possible that ATM and MRE11 control broad/homeostatic signaling pathways during DNA repair or even have a critical non-DNA repair related role required in neurons. However, APTX, SETX, TDP1, and PNKP are not directly involved in signaling and likely have limited, direct enzymatic repair activities on DNA itself, and it would be surprising that non-DNA repair functions would be discovered for all four proteins. Therefore, since DNA repair ataxia diseases share similar neurological phenotypes, it is reasonable to postulate a common DNA repair pathway/mechanism between these various genes in neurons. Recent evidence of a biochemical relationship between ATM and TDP1 supports the possibility of critical shared DNA repair pathways [125].

Potential stressors that require DNA repair

Understanding the underlying pathological mechanisms can be critical for developing therapeutic interventions in any disease. Although the reasons for differential susceptibility of specific neuronal populations remain elusive in many neurological diseases, it may be useful to consider why specific cells are preferentially lost in DNA repair ataxia diseases. As noted, it is reasonable to propose that DNA repair ataxia diseases result from abnormalities in DNA repair. Currently,

there is no evidence that the DNA repair pathways in neurons are significantly different than other cells, and patterns of gene expression have yet to provide insight. Alternatively, it is possible that all cells have similar levels of DNA damage and the limited types of affected neurons are more sensitive to DNA damage than other cells, but evidence for that hypothesis is currently lacking. Therefore, it is possible that the affected cells have more DNA damage. Shared characteristics of affected neurons might suggest "stressors" that lead to DNA damage that requires repair.

Purkinje cells, motor neurons, and sensory neurons are "born," meaning that they complete their last cell division and become terminally differentiated in utero, years prior to becoming clinically dysfunctional. Therefore, if defects are intrinsic to the dying cells, any required DNA repair activities are more likely to be associated with G1 (sometimes referred to as G0 in neurons since they are incapable of becoming proliferative) and not activities specific to S, G2, and M phases. DNA damage secondary to reactive oxygen species is a commonly proposed mechanism for neurodegeneration in A-T and similar diseases. However, there are several reasons to question this hypothesis as the exclusive source of DNA damage. Cardiac muscle and kidney are not affected in DNA repair ataxia diseases even though they use nearly two times the energy by weight as the brain (brain ~240 kcal/kg/d, heart and kidney ~440 kcal/kg/d) [126]. In addition, the brain does not appear to accumulate more somatic DNA damage than other organs [127, 128], although other studies contradict that assertion [129, 130]. It is also not obvious why only a few cell types appear to be lost in DNA repair ataxia diseases since DNA damage secondary to oxidative damage would presumably be widespread. Finally, the hypothesis that reactive oxygen causes accumulation of DNA damage has never been proven due to the difficulty of altering the amount of reactive oxygen generated or present (via anti-oxidant therapy). Therefore, it may be fruitful to explore additional explanations of the nervous system's requirements for ATM and other ataxia-associated DNA repair proteins.

Clinical features of motor and sensory neurons indicate that large cellular volume is correlated with vulnerability in DNA repair ataxia diseases. The longest motor and sensory neurons as well as the largest caliber sensory neurons (motor neuron axons are more uniform in diameter) are the most severely affected. In addition, huge dendrites of Purkinje cells (Fig. 1c) that grow in the first few years of life are their distinguishing and unique characteristic, but it is very difficult to estimate their volume. Motor and sensory neurons are likely the largest single nucleated cells in the body, but how much bigger they are than other cells in the body can be unappreciated. For instance, the longest motor neurons are >10,000 times larger than an average hepatocyte. The volume of a cell body that is roughly spherical can be calculated as a sphere and an axon a cylinder. A hepatocyte has an approximate diameter of 20 μm and volume of 4.2×10^{-9} cm^3. A motor neuron cell body can have a diameter of 50 μm and volume of 65×10^{-9} cm^3, not including the dendrites. In adults, axons that extend to the foot can be 1 m long (or greater) and can have a diameter of up to 20 μm and volume of $310{,}000\times10^{-9}$ cm^3. This shows that motor neurons are orders of magnitude larger than other cell types, and the vast majority of the volume of a motor neuron is within the axon. The lack of clear neuropathology in murine models of DNA repair ataxia diseases may be explained by the much smaller sizes of motor and DRG neurons as well as Purkinje cells in mice relative to humans.

The extreme growth in volume of motor and sensory neurons and other vulnerable cells may cause unique stressors for these very large, single nucleated cells. DNA repair ataxia diseases' neurological symptoms develop in childhood at the time the affected cells need to grow to achieve their very large sizes. While these cells require proportionally larger amounts of amino acids, energy (glucose and fatty acids), etc., absorbing these building blocks may not be limiting because of these cells' proportionally large surface area. Energy production could be an issue as mitochondria along with their intrinsic mitochondrial genome would presumably be required in proportionally very large numbers. Critically, mitochondria are produced via fission (each mitochondria can divide forming two mitochondria) so their growth can be logarithmic. Defects in mitochondria proliferation dynamics, particularly producing a sufficient number of mitochondria or maintaining them, could be important and have been implicated in multiple neurodegenerative diseases [131, 132] while ATM has been shown to play a role in mitochondrial function [133–136]. An additional potential stressor for producing these huge volumes may be the increase in transcriptional requirements. Most tissues grow dramatically in size via cell proliferation. Every cell division doubles the number of transcriptional units (genomes) and allows for growth in volume of a tissue. Very large neurons must achieve their enormous sizes with the same complement of DNA found in every cell with increases in transcription and translation. Not surprisingly, large cells have large nuclei and nucleoli (sources of rRNA transcription and ribosomes) as well as high rates of transcription, making transcription a potential source of DNA damage [137, 138].

In summary, A-T neurological features have potentially important lessons for understanding the requirements for ATM-related neuropathology. Both neurological and neuropathological studies suggest that the localization of neuronal defects in A-T is restricted to a reasonably small number of cell types, including cerebellar Purkinje cells, motor and sensory neurons, and likely some others that have not been definitively determined. The other DNA repair ataxia diseases seem to have very similar clinical phenotypes both in terms of neurological features and neuropathology including cerebellar ataxia and motor and sensory neuropathy (position and vibration) as well as some having extrapyramidal movements and

peculiar eye movements distinguishing these diseases from other forms of ataxia. The size of neurons, particularly during their periods of cell volume growth, may be a critical risk factor for neuronal susceptibility in DNA repair ataxia diseases. This susceptibility is illustrated by the size of cells lost, particularly motor and sensory neurons via the length-dependent nature of the neuropathies. In addition, neurological symptoms present as neurons are growing in volume during childhood or early teen years and not later in adulthood after cell volume increases have ceased. Purkinje cells are often affected when their huge dendrites are growing as granule cells are forming synapses. Size as a risk factor may also explain why rodent disease models do not display neuropathological changes found in the much larger human cells. The DNA repair ataxia disease gene proteins may eventually be tied to a single cellular insult such as oxidative damage, mitochondrial production/repair, transcription-related damage, or other processes. Understanding the particular vulnerabilities in the neurons lost in DNA repair ataxia diseases may be critical to developing potential therapies as well as providing insight into other neurological diseases affecting very large neurons.

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