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INVITED REVIEW

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Peripheral neuropathies associated with DNA repair disorders

Melissa Maguina MS[1] | Peter B. Kang MD[2,3] | Ang-Chen Tsai PhD[4] | Christina A. Pacak PhD[2]

[1]Medical Education Program, Nova Southeastern University, Fort Lauderdale, Florida

[2]Department of Neurology, Paul and Sheila Wellstone Muscular Dystrophy Center, University of Minnesota Medical School, Minneapolis, Minnesota

[3]Institute for Translational Neuroscience, University of Minnesota Medical School, Minneapolis, Minnesota

[4]Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida

Correspondence
Christina A. Pacak, Department of Neurology, University of Minnesota Medical School, 420 Delaware Street SE, MMC 295, Minneapolis, MN 55455.
Email: cpacak@umn.edu

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Abstract

Repair of genomic DNA is a fundamental housekeeping process that quietly maintains the health of our genomes. The consequences of a genetic defect affecting a component of this delicate mechanism are quite harmful, characterized by a cascade of premature aging that injures a variety of organs, including the nervous system. One part of the nervous system that is impaired in certain DNA repair disorders is the peripheral nerve. Chronic motor, sensory, and sensorimotor polyneuropathies have all been observed in affected individuals, with specific physiologies associated with different categories of DNA repair disorders. Cockayne syndrome has classically been linked to demyelinating polyneuropathies, whereas xeroderma pigmentosum has long been associated with axonal polyneuropathies. Three additional recessive DNA repair disorders are associated with neuropathies, including trichothiodystrophy, Werner syndrome, and ataxia-telangiectasia. Although plausible biological explanations exist for why the peripheral nerves are specifically vulnerable to impairments of DNA repair, specific mechanisms such as oxidative stress remain largely unexplored in this context, and bear further study. It is also unclear why different DNA repair disorders manifest with different types of neuropathy, and why neuropathy is not universally present in those diseases. Longitudinal physiological monitoring of these neuropathies with serial electrodiagnostic studies may provide valuable noninvasive outcome data in the context of future natural history studies, and thus the responses of these neuropathies may become sentinel outcome measures for future clinical trials of treatments currently in development such as adeno-associated virus gene replacement therapies.

KEYWORDS
ataxia telangiectasia, Cockayne syndrome, DNA repair disorders, neuropathies, peripheral neuropathy, trichothiodystrophy, Werner syndrome, xeroderma pigmentosum

Abbreviations: AT, ataxia telangiectasia; BER, base excision repair; CNS, central nervous system; CS, Cockayne syndrome; DDR, DNA damage response; DSBR, double-strand break repair; GG-NER, global genomic; HR, homologous recombination; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; ROS, reactive oxygen species; SSBR, single-strand break repair; TC-NER, transcription-coupled; TTD, trichothiodystrophy; UV, ultraviolet; WS, Werner syndrome; XP, xeroderma pigmentosum.

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The objectives of this activity are to: 1) Become familiar with several DNA repair and genome stability pathways so as to be able to understand the phenotypic consequences; 2) Recognize the neuropathies associated with 5 DNA repair disorders: xeroderma pigmentosum, trichothiodystophy, Cockayne syndrome, Werner syndrome, and ataxia telangiectasia; 3) develop and implement appropriate pharmacologic and non-pharmacologic interventions for individuals with these 5 DNA repair disorders.

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1 | INTRODUCTION

Peripheral neuropathy represents one of the many complex clinical manifestations that can be present in patients with DNA repair disorders and, as such, symptoms related to this may be overshadowed by other complications.[1] As these are inherited disorders that impair ubiquitous biological processes, the peripheral neuropathy that occurs tends to be a polyneuropathy rather than a mononeuropathy. Although the true incidence is likely underreported, a review of current literature shows documentation of sensory, motor, and sensorimotor peripheral neuropathies in patients with DNA repair or genome instability disorders. Depending on the specific underlying deficiency, these can present as either demyelinating or axonal peripheral neuropathies. In each of these cases, differences exist among patients regarding the age of susceptibility, precise anatomical distribution of the neuropathy, and overall severity. Regardless of the specific manifestations, peripheral neuropathies add to the burden of patients with DNA repair disorders and an improved understanding of how the underlying disease mechanisms influence the development of neuropathies in these patients would support the development and assessment of effective therapies.

The human body relies upon multiple levels of quality control mechanisms that serve to correct injuries that occur due to both endogenous and exogenous factors. Oxidative DNA base damage from reactive oxygen species (ROS) represents one of the most common endogenous sources of DNA damage and is an inevitable, constant byproduct of normal cellular metabolism.[2] In healthy cells, ROS are generally maintained at manageable levels. However, in situations of persistent cell stress, such as that found in DNA repair disorders and other diseases, ROS can become problematic due to increased production and decreased abilities to manage its effects. A nonexhaustive list of exogenous factors that activate DNA repair pathways includes: DNA lesions caused by ultraviolet (UV) radiation (cyclobutane pyrimidine dimers [CPDs] and pyrimidine [6-4] pyrimidone photoproducts), X ray and gamma-ray exposure, mutagenic chemicals (hydrogen peroxide, vinyl chloride, and polycyclic aromatic hydrocarbons), viruses, and heat stress.[3–5]

A variety of DNA damage response (DDR) pathways exist, each of which is responsible for a specific DNA-editing function. These pathways include nucleotide excision repair (NER), base excision repair (BER), mismatch repair, homologous recombination (HR), nonhomologous end joining (NHEJ), single-strand break repair, and double-strand break repair (DSBR).[6] DNA repair disorders occur when genetically inherited mutations lead to dysfunctions in proteins that are responsible for a particular component of the DDR mechanism. Among these, neuropathies have been observed specifically in patients with deficiencies in proteins involved in NER and DSBR and as well as those involved in the maintenance of genome stability.

Due to the high energetic burden associated with maintaining precise ion gradients across long distances and relaying electrophysiological signals on a regular basis, the metabolic activity of neurons and other cells associated with the nervous system is more robust when compared with many other cell types throughout the body. This exposes both the central and peripheral nervous systems to high levels of oxidative stress that are associated with vulnerability to an accumulation of DNA damage. Thus, it is not surprising that DNA repair disorders are frequently associated with neurological complications, including peripheral neuropathies.

The neuropathies associated with DNA repair disorders vary regarding sensory, motor, or sensorimotor involvement. It remains a puzzle why defects in the same overall biological process can have different manifestations, often in consistent patterns depending on the subtype. One possible explanation is that some of these proteins involve overlapping but somewhat distinct aspects of DNA repair defects. Another possible explanation is that individual proteins involved in these diseases have functions distinct from their direct role in DNA repair.[7]

The following is a review of the current literature regarding the association of neuropathies with these disorders. We discuss five diseases in detail---xeroderma pigmentosum (XP), trichothiodystrophy (TTD), Cockayne syndrome (CS), Werner syndrome (WS), and ataxia telangiectasia (AT)---due to evidence in the literature for peripheral neuropathy presentation. In this review we highlight aspects of these disorders that are relevant to neuromuscular specialists.

2 | DNA REPAIR AND GENOME STABILITY PATHWAYS

These repair pathways have been extensively reviewed elsewhere,[8–12] but we briefly summarized these in what follows. NER is responsible for the removal of lesions caused by ultraviolet (UV) rays and other environmental carcinogens. It is divided into two forms: global genomic (GG) and transcription-coupled (TC) and is the only DNA repair system capable of removing sun-induced UV DNA damage in mammals.[13,14] The sequential steps involved include lesion recognition, lesion removal, DNA repair patch synthesis, and ligation. Each of these steps proceeds with a careful orchestration of recruitment, binding, and release of repair machinery components.

GG-NER is the subpathway that is able to detect helix distortions caused by structural nucleotide lesions and can function anywhere in the genome.[15] In GG-NER, once the DNA helix distortions are recognized, repair is initiated by the GG-NER–specific DNA-damage–binding XP type C (XPC)-Rad23B complex and sometimes the UV-damaged DNA-binding complex (UV-DDB).[15] After damage recognition, the remaining steps occur in a manner similar to TC-NER as other repair proteins are recruited to the lesion to verify the damage, unwind the helix, excise the damaged DNA strand, and fill in the repair patch using the complementary strand as a template.[16] When the DNA-damage recognition machinery is deficient, recognition of the DNA helix distortion does not occur and repair machinery fails to localize to the lesion. Defects in the GG-NER pathway–specific proteins typically lead to cancer predisposition and associated disorders, such as XP.[15]

TC-NER is responsible for the repair of lesions located on the transcribed strand of active genes and does not require XPC or DDB proteins for lesion recognition in mammalian cells.[15] TC-NER initiation differs from GG-NER in DNA damage recognition step, as the recognition signal is the stalling of RNA polymerase at a lesion in DNA. Defects in TC-NER are associated with TTD, CS, XP, and XP-CS.

Although some DNA repair disorders reveal clear deficiencies in only GG or TC-NER, studies have revealed that some deficiencies impact the function of both repair pathways.[17]

Double-strand break repair is one of two repair mechanisms that involve HR repair.[9] DNA double-strand breaks (DSBs) are the primary form of DNA lesions responsible for formation of chromosomal aberrations and can be induced by ionizing radiation, topoisomerase-mediated DNA cleavage, spontaneous DSBs during DNA replication, various recombination mechanisms, and BER when operating on near but opposite strands.[9] Two different DSBR repair strategies exist: HR and NHEJ.[18] In HR, a mechanism involving DNA resection, strand invasion, and exchange provides primers for repair synthesis. It is this requirement for a homologous template that restricts HR to the S and G2 phases of the cell cycle. NHEJ, however, requires no homology with a second DNA duplex and little to no homology between the two severed DNA ends.[18] Although more efficient, NHEJ is also more error-prone and, in contrast, although less efficient (slower), HR is more accurate.[19]

The affected gene in AT, AT-mutated (*ATM*), encodes a serine/threonine protein kinase important for damage signaling in response to DSBs.[20–22] Clinical observations demonstrated chromosomal instability, immunodeficiency, and radio-sensitivity that suggested impaired DSBR in AT patients.[23] Previous studies using different models and experimental conditions reached conflicting conclusions regarding the precise role for ATM in DSBR, but compelling evidence has shown that it facilitates repair of DSBs associated with heterochromatin.[24,25] Other studies focused on the telangiectasias in AT have uncovered a key role for oxidative stress in the disruption of cellular responses in this disorder.[26–28]

The accelerated aging disorder WS is caused by defects in the WS protein (WRN). Although WRN has a role in the maintenance of genomic DNA stability, its precise function has yet to be elucidated. The WRN protein has been shown to have DNA-binding capabilities and is recruited to DSBs, where it may play a role in DNA unwinding through its helicase activities.[29–31]

3 | NEUROPATHIES IN DNA REPAIR AND GENOME INSTABILITY DISORDERS

3.1 | XP

Xeroderma pigmentosum is a rare, autosomal recessive genetic disorder that affects an estimated 2.3 per million livebirths in Western Europe, 1 in 22 000 in Japan, and 1 per million in the United States.[32,33] The disease affects males and females equally and is statistically more common in certain regions, including Japan, North Africa, and the Middle East.[32] Patients with XP are hypersensitive to DNA damage from UV radiation and typically experience severe sunburns, increased freckles, and increased susceptibility to skin cancer.[34] In 60% of XP cases, extreme sensitivity to sunlight is apparent within the first few weeks of life. The remaining 40% of cases typically display freckle-like pigmentation on sun-exposed skin by 2 years of age.[35]

The degree of UV sensitivity can vary between XP patients and basal- and squamous-cell carcinomas are the most prevalent types of skin tumors.[36] XP is caused by pathogenic variants in one of multiple XP genes that encode proteins involved in NER (Table 1).[37] Although the resulting deficiency in NER is consistent throughout XP, the various functions of specific XP proteins and the severity of the pathogenic variant (null variants versus partial impairments) can both influence disease presentation in XP patients.[38] The central nervous system is affected in ~25% of XP patients, and an estimated 20% to 30% display sensorineural abnormalities that include ataxia, hearing loss, as well as sensory and sensorimotor peripheral neuropathies (Table 2).[35,39–45] Of the XP genetic subtypes, XPA, XPB, XPD, XPF, and XPG are those that have been found to be associated in some cases with neurological symptoms, with XPA and XPD being the genetic subtypes most frequently associated with neurological degeneration.[46] Conversely, patients with XPC and XPE rarely display neurological manifestations, although there is one published case of an XPC patient developing a peripheral neuropathy at age 47.[41,47]

One recent study showed that 78% of XPA patients evaluated had an axonal sensorimotor polyneuropathy, whereas 50% of XPD patients evaluated had an axonal sensory neuropathy.[46] The investigation also showed that the development of neuropathy in XPA tended to be earlier than in XPD patients and that sensorineural hearing loss may precede abnormal nerve conduction studies in XP.[46]

The main course of treatment for XP is prevention of complications through protective measures against UV radiation. In utero XP screening for families with a history of the disease is recommended and facilitates early implementation of sun protection measures.[35,39,40] Regular multidisciplinary clinical evaluations that include dermatology, neurology, and ophthalmology can help capture various symptoms in the early stages and identify beneficial preventive strategies to minimize the detrimental effects of DNA damage.[48] As of yet, there are no reports of medications that are effective for the neurological aspects of XP.

3.2 | TTD

Trichothiodystrophy is a rare, autosomal recessive disorder that is characterized by sulfur-deficient, short, brittle hair and nails, with a range of disease severity and a prevalence in the United States of ~1 per 1 000 000 with males and females being equally affected.[14,49,50] The age of onset is early and often associated with premature birth and low birthweight with prenatal diagnoses documented in some patients with a family history of the disease.[51] Mildly affected patients may only display the characteristic tiger-tail-banding hair phenotype, whereas more severely affected patients will often develop photosensitivity, ichthyosis, intellectual impairment, developmental delay, hematological abnormalities, microcephaly, decreased fertility, accelerated aging, and recurrent infections.[14,52] Forty to 50% of TTD patients have photosensitivity.[53] The photosensitive form of this disorder is caused by pathogenic variants in any one of the three genes: *ERCC2*, *ERCC3*, or *GTF2H5* (Table 1). Each of these genes encodes a subunit of the DNA repair and transcription factor TFIIH.[52,54] Genetic variants in *ERCC2* XPD are the most common causes of photosensitive TTD.[55]

TABLE 1 Key features of DNA repair disorders

DNA repair disorders	Affected protein/gene	DNA repair pathway/s affected	Notes on general neurological presentation and frequencies
Xeroderma pigmentosum	XPA (*XPA*), XPB (*ERCC3*), XPC (*XPC*), XPD (*ERCC2*) XPE (*DDB2*), XPF (*ERCC4*), XPG (*ERCC5*), XPV (*POLH*)[a]	NER[a] translesion synthesis[128]	• Of the genes affected, XPC, XPE, and XPV rarely show signs of neurological abnormalities[39] • The central nervous system is affected in ~25% of XP patients[35,39] • Approximately one third of XP patients have progressive neurodegeneration with neuronal loss[39] • 78% of XPA patients show sensorimotor neuropathy and 50% of XPD patients show a sensory neuropathy[46]
Photosensitive trichothiodystrophy	XPB (*ERCC3*), XPD (*ERCC2*), TTDA (*GTF2H5*)	NER	• Frequencies of neurological presentations in TTD patients: peripheral neuropathy 2%, intellectual impairment 75%, developmental delay 68%, impaired motor control or psychomotor retardation 37%[51,53]
Cockayne syndrome	CSA (*ERCC8*), CSB (*ERCC6*),	NER	• CS is associated with a progressive demyelinating neuropathy that correlates with clinical severity[71] • Parkinson-like symptoms often develop in CS adolescents[70] • A CS imaging study reported brain calcifications in 16 of 18 CS patients, white matter hypoattenuation in 10 of 18 patients, and cerebral atrophy in all 18 patients evaluated[129]
Werner syndrome	WRN (*WRN*)	Genome stability	• Accelerated aging of the brain is a common finding in WS[130]
Ataxia telangiectasia	ATM (*ATM*)	DSBR	• Cerebellar gait ataxia is the most common form of ataxia in AT with truncal ataxia, and limb ataxia presenting in a smaller number of AT patients[86] • Movement disorders are common in these patients[86]

Abbreviations: AT, ataxia telangiectasia; CS, Cockayne syndrome; DSBR, double-strand break repair; NER, nucleotide excision repair; TTD, trichothiodystrophy; WS, Werner syndrome; XP, xeroderma pigmentosum.
[a]Indicates that XPV is unique in that it is involved in translesion synthesis not NER.

TABLE 2 Type of peripheral neuropathy associated with DNA repair disorders

DNA repair disorder	Sensory vs motor neuropathy	Axonal vs demyelinating neuropathy	Age of neuropathy onset
Xeroderma pigmentosum	Sensorimotor (XPA), sensory (XPD)	Axonal	Detected as early as 3 years for XPA, detected as early as adolescence for XPD[46]
Trichothiodystrophy	Motor	Demyelinating	Detected as early as 6 months of age[56]
Cockayne syndrome	Sensorimotor	Demyelinating	Severe slowing of conduction velocities observed at 2 years of age[71]
Werner syndrome	Sensorimotor	Axonal and demyelinating	Neuropathy has been detected in the fourth decade of life and later, onset unclear[80–82]
Ataxia telangiectasia	Sensorimotor	Axonal	Childhood onset with progression over time[131]

Abbreviation: XP, xeroderma pigmentosum.

TFIIH is important for both NER and transcription initiation. Although TFIIH's role in NER can explain the photosensitivity observed in TTD, the other features of this disease are thought to be a result of deficiencies in TFIIH's ability to initiate transcription.[14]

Neurological complications associated with TTD include peripheral neuropathy, intellectual impairment, developmental delays, and impaired motor control/psychomotor skills.[51,56] A systematic review of TTD showed a 2% frequency of peripheral neuropathies in TTD patients.[51] In one published case study, motor nerve conduction studies performed at 6, 14, and 24 months of age demonstrated a slow conduction velocity, indicating demyelinating physiology (Table 2).[56]

As with many of the other disorders in this review, TTD patients typically have complex health-care needs and require multidisciplinary clinical care that can include neurology, dermatology, ophthalmology, orthopedics, rehabilitation medicine, immunology, and genetics.[51] Treatments for mildly affected TTD patients typically include symptomatic management using sun-protection measures and moisturizers for the dermatological aspects of the disease (ichthyosis, dry skin, and UV sensitivity).[50] A recent study has demonstrated successful treatment of the skin features of TTD (improved erythema and reduced itching) with the monoclonal antibody dupilumab.[57] As of yet, there are no reports of medications being effective for the neurological aspects of TTD.

3.3 | CS

Cockayne syndrome is a rare, autosomal recessive, multisystem disorder with an estimated incidence of 1 in 250 000 live births in the United States, with no known gender, ethnic, or racial clustering.[1,58] The genes affected in this disorder are CSA (*ERCC8*) and CSB (*ERCC6*), which encode proteins responsible for TC-NER (Table 1).[59] CS is characterized by microcephaly, failure to thrive (in weight and size), progressive dementia, and developmental delay. CS is divided into three types based on age of onset. In CS type 1, the progressive symptoms are typically apparent after 1 year of age. CS type 2 is congenital and typically a severe form of the disease. CS type 3 is characterized by a late onset after the age of 2 years and is typically a milder form of the disease.[58]

Cockayne syndrome is recognized as the first NER disorder associated with mitochondrial impairment and it is thought that this dysfunction contributes to the accelerated aging and neurodegeneration phenotypes observed in CS.[60] Other compelling data suggest that CSB is involved in the regulation of gene expression and that this (as opposed to deficient TC-NER) may be the main cause of neurological dysfunction in CS.[61] In addition, the CS proteins also appear to play a role in the maintenance of mitochondrial homeostasis through NAD^+ signaling.[62,63]

Among CS patients, ~25% of cases result from pathogenic variants in CSA/*ERCC8*, whereas 75% of cases are caused by CSB/*ERCC6*.[58] In the setting of CSA or CSB deficiency, DNA damage remains unrepaired and RNA polymerase progression halts at lesion sites on the transcribed strand of active genes. The detrimental effects of unrepaired DNA damage accumulate, simultaneously impeding expression of many active genes, causing various degrees of cellular dysfunction. This continuous accrual of unrepaired DNA damage likely compounds CS neurological abnormalities that include brain atrophy (Table 1), brain calcifications and vascular defects, demyelinating peripheral neuropathy, hypomyelination (central and peripheral), and the accelerated aging phenotype, all common characteristics of CS (Table 2).[64–69]

The most common form of peripheral neuropathy observed in CS patients is sensorimotor demyelinating polyneuropathy, although other polyneuropathies have also been described.[1,70,71] CS patients display white matter demyelination in the central nervous system (CNS), atrophy of the cerebrum and cerebellum, and perivascular calcifications in the basal ganglia and cerebellum.[1] One study assessed peripheral nerve involvement in CS through a retrospective evaluation of neurophysiological data on a series of 25 CS patients to determine whether there was evidence of correlations between neurophysiological, clinical, and molecular data.[71] The study showed that all 25 patients displayed an electrophysiological pattern that was suggestive of primary sensorimotor demyelinating neuropathy with a correlation between the severity of the neuropathy and overall disease severity.

Supportive care and regular evaluations with a multispecialty clinical team will help facilitate management of complications.[72,73] Specialties that may be helpful for CS patients include audiology, cardiology, dentistry, dermatology, otolaryngology, endocrinology, gastroenterology, genetics, neurology, nephrology, nutrition, ophthalmology, pulmonology, and urology.[73] Some CS patients develop tremors, which could originate from basal ganglia lesions, neuropathy, or both. Tremors due to basal ganglia lesions may in some cases be managed successfully with the dopamine agonist carbidopa-levodopa, which is used in Parkinson's disease.[70]

3.4 | WS

Werner syndrome is an autosomal recessive disease that causes dramatic, progressive, accelerated aging and is estimated to affect 1 in 200 000 individuals in the United States and 1 or 2 per 40 000 in Japan.[74] Affected individuals typically undergo healthy development until puberty, when no growth spurt materializes.[74] The accelerated aging aspects of the disease typically begin to appear in the third decade of life. Additional WS characteristics include cataracts, skin ulcers, osteoporosis, type 3 diabetes, and some forms of cancer.[74]

WS is caused by pathogenic variants in the *WRN* gene, which encodes a helicase protein that is important for the unwinding of DNA (Table 1).[74,75] This important protein supports genome stability and telomere maintenance.[76,77] Myelopathy and polyneuropathy have been reported in WS for over 30 years.[78,79] Based on electrophysiological and biopsy studies, the polyneuropathy in WS has variable sensorimotor involvement with axonal and demyelinating physiology, accompanied at least in some cases by clinical and electrophysiological evidence for long tract and dorsal column dysfunction in the spinal cord (Table 2).[80–83] This association suggests that WS can affect both the CNS and peripheral nervous system. Current treatments for WS involve symptomatic and supportive care with a multidisciplinary clinical team of specialists able to meet the affected individual's needs.[75] Specialty clinicians who may be needed include orthopedists, cardiologists, ophthalmologists, endocrinologists, and neurologists.[75] As of yet, there are no medications known to be effective for the neurological aspects of WS.

3.5 | AT

Ataxia telangiectasia, also known as Louis-Bar syndrome, is a rare, inherited disorder that affects 1 or 2 per 100 000 live births

worldwide.[84] AT is an autosomal recessive disorder caused by mutations in the ataxia telangiectasia mutated (*ATM*) gene that encodes the protein ATM (Table 1). AT impacts multiple systems throughout the body including the nervous and immune systems and is associated with an increased predisposition for cancer and neurodegeneration.[60] The initial presentation of AT is typically an unsteady gait at around 1 or 2 years of age.[85,86] Patients with AT can develop a broad range of clinical phenotypes, including progressive cerebellar ataxia, axonal polyneuropathy, oculocutaneous telangiectasia, variable immunodeficiencies, tremors, increased susceptibility to malignancies, and metabolic dysfunction.[87,88]

The *ATM* gene is located on 11q22-q23 and encodes a serine/threonine protein kinase that assists in recognizing damaged or broken DNA strands.[21,22] When ATM is deficient, p53 signaling is not activated and the cell cycle continues without allowing for DNA repair or activating apoptosis. This allows for replication of abnormal cells and, ultimately, leads to complications that include a primary immunodeficiency disease involving both cellular and humoral immune systems.[89] Due to the increased susceptibility of AT patient cells to X rays, radiotherapy, and some forms of chemotherapy, these exposures should be avoided if possible.[84] Sensorimotor axonal polyneuropathy has been observed in AT patients (Table 2).[90] Although it can develop as young as 5 years of age, the acquired deformity of the feet (pes cavus) is common in AT patients and becomes apparent by 10 or 11 years of age.[84,91]

Investigators have studied the ability of several pharmacological interventions to mitigate neurological manifestations in AT patients.[92] Amantadine, fluoxetine, and buspirone can improve balance, speech, and coordination, whereas tremors in AT patients have been mitigated with gabapentin, clonazepam, and propranolol, and dystonia has been successfully treated with trihexyphenidyl.[92,93]

The use of glucocorticoids (dexamethasone and betamethasone) has also been shown to improve neurological symptoms in AT.[94] However, the use of these medications can increase the frequency of infections and have an influence on inflammatory and immune responses.[94] The use of nutritional antioxidants is another approach that may slow the progress of neurodegeneration. Vitamin E and alpha-lipoic acid have both been shown to improve mitochondrial function in ATM-deficient lymphoblastoid cells.[95] Clinically, current disease management for AT is focused on symptomatic and supportive care.

4 | MANAGEMENT AND TREATMENT

Currently, there are no US Food and Drug Administration–approved therapies for any of the DNA repair disorders, so management of these diseases and their complications, including the neuropathies, remains challenging. As these diseases have multiorgan system involvement, and diagnostic testing for neuropathy, particularly electrodiagnostic (EDx) testing and nerve biopsy, is not uniformly performed, the incidence of these neuropathies is likely underrecognized and underreported. The variable origins of pain due to individual physiological, emotional, or cognitive states is another factor that can impede recognition that one of these patients may be experiencing symptoms of a neuropathy.[96,97] Although more research has been performed to evaluate neuropathic pain in diabetic patients, understanding the underlying mechanisms associated with pain has been challenging even in such a common disease.[98] An added diagnostic difficulty in younger children within this population involves the struggle they experience in effectively communicating specific discomforts.

Despite the challenges, many patients with DNA repair disorders do receive comprehensive multidisciplinary care. A common thread throughout the five DNA repair disorders described herein is the importance of increased awareness among patients, families, and health-care providers of the importance of obtaining the most up-to-date clinical care for the patient. Having multidisciplinary care further advances patient needs in a collaborative setting.[99] This benefits patient quality of care through the development of disease management plans that anticipate symptoms and provide disease-specific supportive care and advice whenever possible.[72,73]

Although the supportive approaches just described are important, other existing neuropathy therapies have been tested in some of these disorders and may be worth considering on an individual basis. Knowing that a therapy is effective and has been safely administered to other patients with specific DNA repair disorders can help to avoid tragedies such as those that have occurred after metronidazole use in both CS and XP/TTD patients.[100,101]

One potential therapeutic target for these disorders may be mitochondrial function. Multiple research groups have documented mitochondrial deficiencies in CS, WS, and AT and observed how multiple disease phenotypes (including peripheral neuropathies) overlap with those of certain classic mitochondrial disorders.[102–107] Several of these observations point toward a possible increase in ROS, suggesting that antioxidants may be beneficial in these disorders, which have been supported by studies in disease models.[104,108–110] Thus far, however, antioxidant therapy has not been studied systematically in human patients. Another aspect of mitochondrial dysfunction that is relevant for CS, XP, AT, and WS is defective mitophagy, which is a decreased ability to degrade damaged mitochondria.[102,103,106,111–115] NAD^+ augmentation has been shown to restore some functions in WS, AT, and CS disease models, likely through improved mitophagy mechanisms.[63,113,115] Such an approach has not yet been tested in human patients but is likely on the horizon. It will be of interest to see the impact of such NAD^+ supplementation strategies on neuropathies.

Other therapies are currently under development for DNA repair disorders. Gene therapies are designed either to transfer a healthy copy of a defective gene to cells and tissues impacted by a disorder or to transfer genome-editing machinery to correct specific pathological variants.[116] Gene replacement strategies are broadly applicable across patients with pathogenic variants in the same affected gene, but, depending on factors such as the target tissue(s) and the timing of treatment, the therapeutic effect may be diluted over time due to growth and cell division. In contrast, most genome editing techniques are designed in variant-specific ways that potentially benefit subsets of patients harboring specific pathogenic variants, sometimes also including biologically related variants. Either approach could

potentially prevent or improve neuropathies in these disorders and we are pursuing active preclinical studies testing gene replacement strategies for treatment of the neurological aspects of CS and XP-CS.[117] Other investigators have shown promising results after *ATM* cDNA delivery to fibroblasts where the cell-cycle abnormalities and cellular radiosensitivity were restored in the treated cells.[118]

Another interesting therapeutic approach that is dependent on the specific type of pathogenic variant is read-through of aberrant stop codons (nonsense mutations) and the potential for epigenetic therapies. A preclinical study using cells from patients with WS demonstrated successful read-through of nonsense mutations using pharmacological treatments. Both aminoglycosides and ataluren restored full-length protein expression and WRN function in cellular disease models of WS.[119] Another study demonstrated successful read-through of *XPC* mRNA, functional XPC protein expression, localization of XPC to sites of UV-induced DNA damage, and successful repair in XP-C–deficient patient cells using G418 sulfate and gentamicin, and subsequently similar efficacy with reduced toxicity using small-molecule non-aminoglycoside compounds (PTC124, BZ16, or RTC14).[120] Although promising results have been achieved in preclinical models for a variety of disorders, it is not yet clear how efficacious these approaches are in human patients.[120–122]

A major question as new therapies are being developed is how feasible it will be for the peripheral nerves to be a target organ for these treatments, and whether the status of any neuropathy should be an outcome measure for human clinical trials, either for the sake of improving the neuropathy itself or as a surrogate marker for improvement in the CNS. If the latter, the peripheral nerves have the distinction of being more easily accessible for direct functional testing than the CNS. There is precedent for using various configurations of EDx as outcome measures for human clinical trials. For example, compound muscle action potentials were used in a pivotal trial of gene therapy for spinal muscular atrophy (SMA),[123] and motor unit number estimation has been studied as a potential outcome measure in the setting of SMA[124,125] and amyotrophic lateral sclerosis.[126,127] The use of these noninvasive neurophysiological measures and derivatives of these measures in clinical trials will likely expand to other diseases in the future, including DNA repair disorders.

5 | CONCLUSIONS

The DNA repair deficiencies are a category of rare disorders representing multiple individual ultrarare populations that can display overlapping disease phenotypes, including neuropathies. Although significant advances are being made to better understand the natural progression of these disorders and their underlying disease mechanisms, more detailed preclinical experiments and human natural history studies for DNA repair disorders are needed to prepare novel therapies for translation into human clinical trials and to determine optimal outcome measures for such trials, respectively. We anticipate that the peripheral nerves will have an important role in the development of new therapies, either as a target organ or as the nexus for a surrogate biomarker. There is cause to be optimistic about future therapeutic development for these serious inherited disorders.

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The authors declare no potential conflict of interest.

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ORCID

Peter B. Kang https://orcid.org/0000-0002-4270-7325
Christina A. Pacak https://orcid.org/0000-0002-7430-124X

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