

Differences in Peripheral Neuropathy in Xeroderma Pigmentosum Complementation Groups A and D

Tanya Lehky (✉ lehkyt@ninds.nih.gov)

NINDS: National Institute of Neurological Disorders and Stroke <https://orcid.org/0000-0001-6421-505X>

Paul E. Sackstein

Genetics and Developmental Biology Research Unit: Genetique et biologie du developpement

Deborah Tamura

Laboratory of Cancer Biology and Genetics, NCI, NIH

Martha Quezado

Laboratory of Pathology, NCI, NIH

Tianxia Wu

Clinical Trials Unit, NINDS, NIH

Sikandar G Khan

Laboratory of Cancer Biology and Genetics, NCI, NIH

Nicholas J Patronas

Radiology and Imaging Sciences, CC, NIH

Edythe Wiggs

Clinical Trials Unit, NINDS, NIH

Carmen C Brewer

Otolaryngology Branch, NIDCD, NIH

John J DiGiovanna

Laboratory of Cancer Biology and Genetics, NCI, NIH

Kenneth H Kraemer

Laboratory of Cancer Biology and Genetics, NCI, NIH

Research article

Keywords: Xeroderma pigmentosum, peripheral neuropathy, neurodegeneration, sensorineural hearing loss, DNA repair

Posted Date: March 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-351476/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

BACKGROUND

Xeroderma pigmentosum (XP) is a rare autosomal recessive genetic disorder with defective DNA nucleotide excision repair and associated with a high frequency of skin cancer. Approximately 25% of patients develop progressive neurological degeneration. Complementation groups XP-A and XP-D are most frequently associated with neurological disorders.

METHODS

This is a retrospective review of patients with XP who were evaluated at NIH from 1986 to 2015 and had nerve conduction studies (NCS). Audiological, brain imaging, neuropsychological assessments were also performed on most of the patients. Limited neuropathology of XP-A and XP-D patients were compared.

RESULTS

The 33 patients had NCS: XP-A (9 patients), XP-C (7 patients), XP-D (10 patients), XP-E (1 patient), XP-V (4 patients), and XP-unknown (2 patients). Peripheral neuropathy was documented only in two complementation groups: 78% (7/9) of XP-A patients had a sensorimotor neuropathy while 50% (5/10) of XP-D patients had a sensory neuropathy only. The severity of the neuropathy correlated with hearing loss.

CONCLUSIONS

Despite similar brain imaging and audiological findings patients, XP-A and XP-D complementation groups differ in the type of neuropathy, sensorimotor versus sensory alone. A few cases suggest that sensorineural hearing loss and absent deep tendon reflexes may precede abnormal NCS in XP and therefore serve as valuable clinical indicators of XP patients that will later develop peripheral neuropathy.

TRIAL REGISTRATION: Patients were evaluated under clinical protocols, NCT00001813 and NCT00046189, approved by the NIH Institutional Review Boards.

Background

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder involving defective DNA nucleotide excision repair (NER) that is characterized by extreme sensitivity to the damaging effects of ultraviolet radiation (UV) resulting in a greater than 2,000-fold increase in the frequency of melanoma and non-melanoma skin cancers; 25% of XP patients develop a progressive neurodegeneration.¹ XP is classified into 8 different complementation groups, denoted as XP A-G based on defects in DNA nucleotide excision repair (NER) genes and XP-Variant (XP-V) that has a defect in the *eta* polymerase gene.² Patients in complementation groups XP-A and XP-D have the highest frequency of neurological complications along with the greatest photosensitivity or burning on minimal sun exposure.³⁻⁵ A four-decade longitudinal study on the natural history of XP since 1971 showed that the leading cause of death in XP patients was skin cancer (34%, n=10). However, neurological degeneration was also a major cause of death (31%, n=9).¹ Brain atrophy, cerebellar and basal ganglia degeneration leading to ataxia and severe cognitive decline have all been observed in XP-A and XP-D patients.^{6,7} In conjunction with CNS deterioration, these patients have been observed to become areflexic and develop an axonal polyneuropathy as well as sensorineural hearing loss.⁸ Though visual loss occurs in XP, it is usually the result of direct UV-exposure of the anterior components of the eye rather than specific optic nerve deterioration.⁹

The frequency of peripheral neuropathy and its association with CNS degeneration, in different XP complementation groups remains unknown. In this study, we performed a retrospective review of nerve conduction studies of XP patients examined at NIH to assess the frequency and type of peripheral neuropathy among patients in different XP complementation groups. We

also examined MRI/CT, audiology, neuropsychological and clinical studies to determine if the peripheral neuropathy was associated with other neurological findings.

Methods

Patients: Patients were evaluated under clinical protocols, NCT00001813 and NCT00046189, approved by the NIH Institutional Review Boards. Written, informed consent and assent, was obtained from all patients. The patients underwent multimodality assessment including clinical¹⁰, genetic, MRI, neuropsychological, laboratory and electrodiagnostic evaluation. Records of deep tendon reflexes were available on most of the subjects evaluated. Absence of deep tendon reflexes were considered to be a clinical manifestation of peripheral neuropathy. Available data was retrieved by retrospective review of charts of patients with a clinically confirmed diagnosis of XP at the NIH from 1986-2018. For clarity in this paper, complementation group A subjects were designated XPA1-9 and complementation group D were designated XPD 1-10 but have also included the prior protocol designated subject numbers in the tables. The following subjects have been previously reported in other articles, XPA3 (XP19BE)⁴, XPA5 (XP12BE)^{3, 4, 8, 11}, XPA6 (XP360BE)¹², XPD1 (XP29BE)^{4, 13, 14}, and XPD4 (XP33BE)⁴.

Clinical Neurophysiology Studies: Nerve conduction studies were performed using standard methodology on a Nicolet Viking Select equipment (Natus, Middleton, WI) for the studies performed after 2004 and were compared to department-based normative values. All prior studies used earlier versions of the Nicolet Viking equipment. In most patients, the median and sural sensory nerves and the median and fibular motor nerves were tested although other nerves were selected for clinical indications. No needle EMG studies were performed. For consistency, the studies were reviewed by one neurologist (TJL).

Audiological evaluations: Audiologic testing included pure-tone air-conduction (0.25–8 kHz) and bone-conduction (0.25–4 kHz) thresholds and speech audiometry using clinical audiometers in double-walled sound suites that met American National Standards Institute criteria. Audiology results were presented as the 4F-PTA, a four frequency (0.5/1/2/4-kHz) pure-tone average using the right ear results only. Classification of the hearing loss is: < 20 dBHL = normal hearing, >20-40 dBHL = mild hearing loss, >40-70 dBHL = moderate hearing loss, >70-95 = severe hearing loss, > 95 profound hearing loss. For consistency, the studies were reviewed by one audiologist (CCB).

Brain Imaging: MRI or CT imaging of brain was performed at NIH or reviewed from outside sources. Cerebral and cerebellar atrophy were classified on a four-point scale: normal (0), mild (1), moderate (2), or severe (3) depending on the extent of volume loss at each patient's age. For consistency, the studies were reviewed and graded by one neuroradiologist (NP).

Neuropsychological studies: Wechsler scales appropriate for age were performed to yield a Full-Scale IQ. Those XP patients unable to do the Wechsler test because of limited cognitive ability or very young age, were excluded. For the Full-Scale IQ, a score of less than 80 was considered to be abnormal. For consistency, the studies were reviewed by one neuropsychologist (EW).

Neuropathology: Pathology slides from autopsy were available for one XP-A patient (XPA5) and one XP-D patient (not evaluated by NCS) for review. These autopsy reports had been previously published³, and available specimens of muscle and nerve were reexamined. New H&E stained sections of peripheral nerve and muscle were prepared from formalin-fixed paraffin embedded material. For consistency, the studies were reviewed by one neuropathologist (MQ).

Data Analysis: Demographic and clinical results are given as means \pm standard deviations (SD) in tables and two-sample t-test was used to evaluate the difference between XP complementation groups. For each of nerve conduction outcomes, motor and sensory amplitudes, analysis of covariance (ANCOVA) was performed to examine the interaction between group and hearing level. Pearson correlation analysis was used to evaluate the association between hearing level and each of

nerve conduction outcomes. The correlation analysis was performed for XP-A and XP-D combined (interaction effect: $p > 0.05$) or separately depending on the interaction test.

Data Availability Policy: Anonymized data will be shared by request from any qualified investigator.

Results

Demographics: For the study, 106 patients had been evaluated for XP phenotype/genotype over 40 years (Figure 1). Electrodiagnostic studies were performed on 54 of the patients. The majority of the electrodiagnostic studies were performed between 2004-2015, though 7 patients had studies performed between 1986-1993. Twelve patients had XP-TTD complex¹ and were not included in the final analysis. Nine patients were excluded from the analysis because of confounding comorbidities or incomplete studies. In the XP-C complementation group, six patients were excluded; one patient had multiple sclerosis, one patient was treated with alpha interferon and had a preexisting neuropathy, one patient was the product of a close consanguineous relationship and had atypical features of nonprogressive early hearing loss, another patient was also the product of close consanguinity and had fetal alcohol syndrome. Two patients lacked lower extremity nerve conduction studies. In the XP-D complementation group, one patient was excluded for coexistence of limb girdle muscular dystrophy. One patient with XP-E was excluded for a prior history of transverse myelitis, and one patient with XP-G had a possible Cockayne syndrome presentation. Of the remaining 33 patients (Table 1), 9 (27%) patients were in complementation group XP-A, 7 (21%) patients were in XP-C, 10 (30%) patients were in XP-D, 1 (3%) was in XP-E, 4 (12%) were in XP-V, and 2 (6%) had an unknown mutation causing XP (Table 1).

Of the XP patients who underwent NCS, there were 14 males and 19 females and the mean age at initial NCS study was 20.7 ± 13.6 years (range 3-54 years). The patients in XP-A, XP-C, and XP-D complementation groups were generally younger than the XP-E and XP-V complementation groups. For the XP-A and XP-D complementation groups used in the analysis of peripheral neuropathy characteristics, there was no significant difference in age ($p = 0.48$) in the two groups (mean \pm standard deviation, range; XP-A -18.5 ± 2.1 , 3-24, XP-D -16.7 ± 9.0 , 5-43). Six patients in the XP-A and XP-D complementation groups had follow-up electrodiagnostic evaluations. Summary of patients with NCS, audiology, MRI or CT imaging and were evaluated for deep tendon reflexes testing is in Table 1.

XP-A Findings:

Seven of the nine (78%) XP-A patients had axonal sensorimotor polyneuropathy on nerve conduction studies with the findings summarized in Table 1,2. The 4F-PTA showed that six of these patients (XPA1-6) also had mild to severe sensorineural hearing loss and MRI abnormalities. One subject (XPA-7) with neuropathy, a 3 year old, did not have audiology testing. MRI findings was noted in the same subjects with neuropathy include cerebral atrophy, cerebellar atrophy and in 2 pediatric patients, hypomyelination was noted. Six XP-A patients had Full-Scale IQ testing and all were abnormal, regardless of the presence or absence of neuropathy. XP-A patients who had neuropathy, expectedly, also had absent DTRs. However, one XP-A patient (XPA-9) eventually lost her DTRs though her NCS remained normal.

XP-D findings:

In the XP-D patients, 5 patients of 10 studied (XPD1-5) or 50% had evidence for an axonal sensory neuropathy with the findings summarized in Table 1,3. These patients (XPD1-5) also had mild to moderate sensorineural hearing loss and abnormal MRIs of the brain. The MRI findings included varying degrees of cerebral and/or cerebellar atrophy. XP-D patients without neuropathy had normal hearing and brain imaging, though one patient (XPD6) showed development of cerebral atrophy between ages 9 and 14. Low Full-Scale IQs was observed in all patients with neuropathy and in two patients without neuropathy. All XP-D patients with peripheral neuropathy had absent DTRs while only one patient without peripheral neuropathy (XPD6) had absent DTRs. This was the same patient noted to be developing recent signs of brain atrophy in brain imaging.

Other XP complementation group findings:

In the XP-C patients, the NCS (7 patients), audiology (6 patients), and brain imaging studies (2 MRI and 2 CT) were all normal and only one patient (XPC1) had a low Full-scale IQ at age 5. Patients in the XP-E, XP-V and XP-U complementation groups had normal nerve conduction studies. These patients had normal hearing with the exception of one XP-E patient had a mild unilateral hearing loss and one XP-V patient developed mild high frequency hearing loss over 5 years. The XP-V had normal MRIs of the brain with the exception of a few punctate white matter lesions observed in one MRI (XPV4).

Comparison of XP-A and XP-D Complementation Groups:

Comparison of the nerve conduction studies between the XP-A and XP-D complementation groups, using a two-sample t-test, showed a significant difference in the fibular motor amplitudes ($p = 0.0208$) but not the sural sensory, median sensory and median motor amplitudes. There was no significant difference in the hearing loss, cortical atrophy on MRI imaging and Full-scale IQ between the two complementation groups.

Association evaluations (XP-A and XP-D):

For sural and median sensory amplitude (Figure 2a,b), ANCOVA showed that the interaction between XP complementation groups (XP-A vs. XP-D) and hearing loss was not significant ($p = 0.635$, Figure 2a), indicating that the relationship between SNC response and hearing was consistent across the two groups and reflecting deterioration together in sensory and hearing functions in both complementation groups. The difference in sural sensory amplitudes between XP-A and XP-D complementation group was not significant ($p=0.0792$) and the interactions for MRI severity and Full-Scale IQ were also not significant. Therefore, Pearson correlation analysis based on the combined XP-A and XP-D groups was used to examine the linear correlations between sural sensory amplitude and hearing loss, MRI severity, and Full-scale IQ. The analysis showed that the linear correlation was significant for hearing loss ($r=-0.845$, $R^2=0.714$, $p<0.001$), MRI severity ($r=-0.796$, $R^2=0.634$, $p<0.001$), and Full-Scale IQ ($r=0.520$, $R^2=0.27$, $p=0.047$). The difference in median sensory amplitudes between XP-A and XP-D complementation group was also not significant ($p=0.3351$). Pearson correlation analysis for the combined XP-A and XP-D groups showed that the linear correlation was also significant for hearing loss ($r=0.842$, $R^2=0.709$, $p<0.001$) and MRI severity ($r=0.865$, $R^2=0.748$, $p<0.001$) but not IQ.

For fibular motor amplitude, ANCOVA indicated that interaction between XP complementation group (XP-A vs XP-D) and hearing loss was significant ($p=0.050$, Figure 2c), with only the XP-A group showing significant negative linear correlation with hearing ($r = -0.828$, $R^2=0.686$, $p=0.022$), while the XP-D group not showing the significant linear correlation ($r=0.007$, $p=0.985$). This is in keeping with the sparing of motor nerve abnormalities in the XP-D complementation group. The interactions for MRI severity and Full-Scale IQ were not significant ($p=0.171$ for MRI, $p=0.508$ for Full-Scale IQ), but the difference in fibular motor amplitude between XP-A and XP-D groups was significant ($p = 0.0208$). Thus, the association with MRI severity and Full-Scale IQ was also examined separately for the two complementation groups. For XP-A complementation group, the linear correlation was significant for MRI severity ($r=-0.761$, $R^2=0.58$, $p=0.0285$) similar to the sural sensory analysis, not significant for Full-scale IQ ($r=-0.254$, $p=0.6270$). For XP-D complementation group, the linear correlation was not significant for either MRI or Full-Scale IQ ($p>0.6$). For median motor amplitude (Figure 2d), ANCOVA showed that the interaction between XP complementation group (XP-A vs XP-D) and hearing loss was not significant. Linear correlation analyses were not significant for hearing, MRI severity, or Full-Scale IQ.

Follow-up Evaluations:

Follow-up evaluations were available on two XP-A and four XP-D patients . Patient XPA3 (XP19BE) was evaluated at age 14, 35, and 37 years and had neurologic deterioration during this time (Figure 3a). Sural sensory nerve amplitude decreased from 10.8 μV to 3 μV over the first 19 years but did not change any further when retested two years later. The initial study was performed on an older EMG machine which may have affected the results. Sequential nerve conduction studies of

lower extremity motor nerves were not available. Patient XPA8 (XP337BE) did not have overt signs of neurologic deterioration and motor and sensory NCS at age 14 and 23 years have remained stable.

In the XP-D complementation group, the two patients, XPD1 (XP29BE) and XPD4 (XP33BE) with peripheral neuropathy (XPD-1 and XPD-4) and neurological deterioration showed a minimal decline in the sensory responses with stable motor responses (Figure 3b). Patient XPD6 (XP116BE), an initially neurologically normal patient with recent signs of cerebral atrophy on CT brain images, had a 50% decrease in sural sensory response (25 μ V to 12 μ V) over 4 years. Patient XPD9 (XP341BE), also neurologically normal, showed no change in the median and sural sensory nerve amplitudes in a three-year follow-up period. There were no decreases in the motor responses for any of the XPD patients.

Neuropathology:

Nerve and muscle pathology was compared between the XP-A and XP-D patient (Figure 3) and previously reported³. XPA5 (XP12BE) patient passed away at age 44, was cachectic (<3%tile wt.), nonambulatory, no DTRs, with hearing loss and optic atrophy⁵. The XP-D patient (XP18BE) passed away at age 45 and was not cachectic (50% tile wt.) but was nonambulatory, with no detectible DTRs, and had hearing loss⁵. There were no available nerve conduction studies for this XP-D patient. Both patients had had adequate nutrition maintained through g-tubes.

The significant pathology for the XP-A patient was severe end-stage muscle degeneration and fat infiltration. Electron microscopy of the vagus nerve showed axonal degeneration and degenerative changes of the myelin sheath consistent with an axonal neuropathy (not shown) even though median nerve did not show significant degeneration. The XP-D patient had showed mild neurogenic findings on muscle pathology. The nonspecified nerve from the arm under light microscopy had normal architecture as well as pathology of a dorsal root ganglion (not shown).

Discussion

Consistent with observations in past studies, patients with mutations in XP-A and XP-D develop neurological complications including peripheral neuropathy, brain atrophy, hearing loss, and low IQ. These neurological findings are generally not found in patients with mutations in XP-C, XP-E or XP-V. Though there is a limited number of patients in each group, our findings suggests that the peripheral nerve manifestations differ between these two complementation groups with the XP-A patients having a sensorimotor neuropathy and XP-D patients having only a sensory neuropathy.

Sensorimotor neuropathy has been reported in XP-A patients¹⁵ though selectivity of XP-D neuropathies to the sensory nerve has not been previously described. In both XP-A and XP-D complementation groups, the peripheral neuropathy becomes evident within the first or second decade and appears to progress slowly as shown by the gradual decline in sural sensory responses in the follow-up studies.

We also demonstrated that there were correlations between the sural sensory amplitude and the other three markers of neurodegeneration; hearing loss, cortical atrophy on MRI and low IQ. This suggests that the neurodegeneration is affecting the different parts of the nervous system may be occurring concurrently. The correlations for the fibular motor amplitude were more limited, reflecting the differences between the XP-A and XP-D neuropathy presentations. The relative sparing of the median motor nerve in XP-A suggests that there is likely a length-dependent motor nerve degeneration.

The neuropathology of the PNS of the XP-A patient shows an axonal neuropathy associated with chronic neurogenic denervation of the muscles consistent with the sensorimotor neuropathy noted on electrodiagnostic studies. This finding was not observed in the neuropathology of the XPD patient.

In XP, perturbations in the NER pathway result in helix-distorting lesions in the DNA which leads to various end organ damage.¹⁶⁻¹⁸ Neuronal and glial cell injury, both in mature nonreplicating cells and immature replicating cells, are subject to oxidative stress which is normally repaired by a host of DNA repair mechanisms.¹⁹ The XPC and XPE proteins are responsible for damage recognition, the XPA protein is involved in the verification and complex formation at the site of

DNA damage. The XPD protein is one of the helicases involved in unwinding the DNA prior to excision and repair. The other XP gene products are involved in DNA complex stabilization, DNA cleavage, and finally repair of the DNA strand with polymerases and ligases. Clearly, the integrity of the NER pathway and the XP gene complementation groups is crucial for maintenance of DNA repair in the central and peripheral nervous systems though the exact mechanism is not known. Since neuronal cells are not predisposed directly to the injurious effects of ultraviolet (UV) radiation, other mechanisms for neuronal injury in XP patients have been proposed.²⁰ One suggested mechanism may be generation of oxidative stress. The reactive oxygen species (ROS) are constantly generated during aerobic metabolism. One of the ROS is hydroxyl radical, the key endogenous source of DNA damage. Hydroxyl radicals induce many different base lesions including cyclopurine deoxynucleosides (CyPU) that are known to be removed by the NER pathway.²¹⁻²⁴ Accumulation of cyPU in neuronal cells with inability to undergo DNA repair may lead to neurodegeneration.²⁵ Other suggested mechanisms may be mitochondrial dysfunction and role of these proteins in non-DNA repair pathways.²⁰ Generation of neural stem cells and post-mitotic neurons from XP-A patient induced pluripotent stem cells (iPSCs) showed hypersensitivity to DNA damage-induced apoptosis following UV exposure.²⁶ The neurophysiological findings in this paper suggests that there may be slightly different mechanisms of neurodegeneration associated with XP-A and XP-D complementation groups that, at least in the peripheral nervous system, result in two types of neuropathy. Better understanding of pathways may be beneficial in designing clinical studies that address neurotoxicities in XP-A and XP-D since controlled clinical studies in this area have been limited to date.^{27, 28}

Conclusions

The findings in this study are notable for the distinction between XP-A and XP-D on the basis of the type of peripheral neuropathy. CNS deterioration and hearing loss does not appear to differ between the two XP complementation groups. Because XP is a rare disease, the number of subjects in each complementation group is small and limits the robustness of our findings. However, it supports the importance of DNA NER in the survival of central and peripheral neurons with defects in the pathway resulting in variable forms of peripheral nerve degeneration. Continued studies on the peripheral nerve manifestations of XP-A and XP-D may help to further elucidate the role of the XP gene defects in the pathogenesis of neuropathy, particularly as related to the DNA NER pathway.

Abbreviations

XP – xeroderma pigmentosum

NCS – nerve conduction studies

PN - Peripheral neuropathy

IQ – Intellectual quotient

CNS – Central nervous system

NER - Nucleotide excision repair

MRI – Magnetic resonance imaging

CT- Computed tomography

4F-PTA – four frequency (0.5/1/2/4-kHz) pure-tone average

dB HL – decibel hearing level

SNHL – sensorineural hearing loss

DTR – deep tendon reflexes

TTD -- trichothiodystrophy

UV – ultraviolet radiation

Declarations

Disclosures of the authors/Competing Interests: The authors declare that they have no competing interests.

Acknowledgments: We are grateful to the patients and their families for their commitment and time to this study.

Sponsorship/Funding: This research was supported by the National Institutes of Health Intramural Research Programs of National Institute of Neurological Disorders and Stroke (NINDS), National, National Institute on Deafness and Other Communication Disorders (NIDCD) and National Cancer Institute (NCI).

Data Availability Policy: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: See appendix at end of manuscript.

References

1. DiGiovanna JJ, Kraemer KH. Shining a light on xeroderma pigmentosum. *J Invest Dermatol* 2012;132:785-796.
2. Lindenbaum Y, Dickson D, Rosenbaum P, Kraemer K, Robbins I, Rapin I. Xeroderma pigmentosum/cockayne syndrome complex: first neuropathological study and review of eight other cases. *Eur J Paediatr Neurol* 2001;5:225-242.
3. Lai JP, Liu YC, Alimchandani M, et al. The influence of DNA repair on neurological degeneration, cachexia, skin cancer and internal neoplasms: autopsy report of four xeroderma pigmentosum patients (XP-A, XP-C and XP-D). *Acta Neuropathol Commun* 2013;1:4.
4. Totonchy MB, Tamura D, Pantell MS, et al. Auditory analysis of xeroderma pigmentosum 1971-2012: hearing function, sun sensitivity and DNA repair predict neurological degeneration. *Brain* 2013;136:194-208.
5. Anttinen A, Koulu L, Nikoskelainen E, et al. Neurological symptoms and natural course of xeroderma pigmentosum. *Brain* 2008;131:1979-1989.
6. Ueda T, Kanda F, Nishiyama M, Nishigori C, Toda T. Quantitative analysis of brain atrophy in patients with xeroderma pigmentosum group A carrying the founder mutation in Japan. *J Neurol Sci* 2017;381:103-106.
7. Ueda T, Kanda F, Aoyama N, Fujii M, Nishigori C, Toda T. Neuroimaging features of xeroderma pigmentosum group A. *Brain Behav* 2012;2:1-5.
8. Viana LM, Seyyedi M, Brewer CC, et al. Histopathology of the inner ear in patients with xeroderma pigmentosum and neurologic degeneration. *Otol Neurotol* 2013;34:1230-1236.
9. Brooks BP, Thompson AH, Bishop RJ, et al. Ocular manifestations of xeroderma pigmentosum: long-term follow-up highlights the role of DNA repair in protection from sun damage. *Ophthalmology* 2013;120:1324-1336.
10. Nakano E, Takeuchi S, Ono R, Tsujimoto M, Masaki T, Nishigori C. Xeroderma Pigmentosum Diagnosis Using a Flow Cytometry-Based Nucleotide Excision Repair Assay. *J Invest Dermatol* 2018;138:467-470.
11. Ramkumar HL, Brooks BP, Cao X, et al. Ophthalmic manifestations and histopathology of xeroderma pigmentosum: two clinicopathological cases and a review of the literature. *Surv Ophthalmol* 2011;56:348-361.
12. Christen-Zaech S, Imoto K, Khan SG, et al. Unexpected occurrence of xeroderma pigmentosum in an uncle and nephew. *Arch Dermatol* 2009;145:1285-1291.

13. Ueda T, Compe E, Catez P, Kraemer KH, Egly JM. Both XPD alleles contribute to the phenotype of compound heterozygote xeroderma pigmentosum patients. *J Exp Med* 2009;206:3031-3046.
14. Zhou X, Khan SG, Tamura D, et al. Abnormal XPD-induced nuclear receptor transactivation in DNA repair disorders: trichothiodystrophy and xeroderma pigmentosum. *Eur J Hum Genet* 2013;21:831-837.
15. Tsuji Y, Ueda T, Sekiguchi K, et al. Progressive length-dependent polyneuropathy in xeroderma pigmentosum group A. *Muscle Nerve* 2020;62:534-540.
16. McKinnon PJ. Maintaining genome stability in the nervous system. *Nat Neurosci* 2013;16:1523-1529.
17. Cleaver JE, States JC. The DNA damage-recognition problem in human and other eukaryotic cells: the XPA damage binding protein. *Biochem J* 1997;328 (Pt 1):1-12.
18. Liu H, Rudolf J, Johnson KA, et al. Structure of the DNA repair helicase XPD. *Cell* 2008;133:801-812.
19. Feltes BC, Bonatto D. Overview of xeroderma pigmentosum proteins architecture, mutations and post-translational modifications. *Mutat Res Rev Mutat Res* 2015;763:306-320.
20. Rizza ERH, DiGiovanna JJ, Khan SG, Tamura D, Jeskey JD, Kraemer KH. Xeroderma Pigmentosum: A Model for Human Premature Aging. *J Invest Dermatol* 2021.
21. Kamakura N, Yamamoto J, Brooks PJ, Iwai S, Kuraoka I. Effects of 5',8-cyclodeoxyadenosine triphosphates on DNA synthesis. *Chem Res Toxicol* 2012;25:2718-2724.
22. Brooks PJ. The 8,5'-cyclopurine-2'-deoxynucleosides: candidate neurodegenerative DNA lesions in xeroderma pigmentosum, and unique probes of transcription and nucleotide excision repair. *DNA Repair (Amst)* 2008;7:1168-1179.
23. Brooks PJ, Wise DS, Berry DA, et al. The oxidative DNA lesion 8,5'-(S)-cyclo-2'-deoxyadenosine is repaired by the nucleotide excision repair pathway and blocks gene expression in mammalian cells. *J Biol Chem* 2000;275:22355-22362.
24. Kuraoka I, Bender C, Romieu A, Cadet J, Wood RD, Lindahl T. Removal of oxygen free-radical-induced 5',8-purine cyclodeoxynucleosides from DNA by the nucleotide excision-repair pathway in human cells. *Proc Natl Acad Sci U S A* 2000;97:3832-3837.
25. Brooks PJ. The cyclopurine deoxynucleosides: DNA repair, biological effects, mechanistic insights, and unanswered questions. *Free Radic Biol Med* 2017;107:90-100.
26. Fu L, Xu X, Ren R, et al. Modeling xeroderma pigmentosum associated neurological pathologies with patients-derived iPSCs. *Protein Cell* 2016;7:210-221.
27. Abeti R, Zeitlberger A, Peelo C, et al. Xeroderma pigmentosum: overview of pharmacology and novel therapeutic strategies for neurological symptoms. *Br J Pharmacol* 2019;176:4293-4301.
28. Evangelisti C, Cenni V, Lattanzi G. Potential therapeutic effects of the MTOR inhibitors for preventing ageing and progeria-related disorders. *Br J Clin Pharmacol* 2016;82:1229-1244.

Tables

Table 1. Demographics of XP Patients with Nerve Conduction Studies

	Complementation Group					
	XP-A	XP-C	XP-D	XP-E	XP-V	XP unk
Number	9	7	10	1	4	2
Mean Age	16.7±9.0	13.1±6.9	18.5±2.1	42	43.5±9.1	12, 36
± Std Dev						
(Range)	(3-24)	(5-25)	(5-43)		(34-54)	
Gender (F:M)	5:4	4:3	4:6	1:0	3:1	1:1
Abn SNCS	7/9	0/7	5/10	0/1	0/4	0/2
Abn MNCS	7/9	0/7	0/10	0/1	0/4	0/2
Abn Hearing	6/8	0/6	5/10	0/1	0/3	0/1
Abn MRI	7/8	0/4	0/9			0/1
Abn IQ	5/6	0/4	0/9			0/1

Abbreviations: XP-A – xeroderma pigmentosum complementation group A, XP-C – xeroderma pigmentosum complementation group C, XP-D – xeroderma pigmentosum complementation group D, XP-E – xeroderma pigmentosum complementation group E, XP-V – xeroderma pigmentosum variant, XP unk – xeroderma pigmentosum – Unknown mutation, F- female, M- male, Abn – abnormal, SNCS – sensory nerve conduction studies, MNCS – motor nerve conduction studies (fibular nerve), MRI – magnetic resonance imaging, IQ – intelligence quotient, Std dev – Standard deviation

Table 2. XP-A Patient Findings.

Patient	Age	Gender	Neuropathy		Audiology	MRI/CT Imaging		IQ Testing		DTR
ID # (Protocol designated ID)			Abn SNC	Abn MNC	SNHL	Cerebral Atrophy	Cerebellar Atrophy	Hypo-myelination	IQ<80	Absent
XPA1 (XP81BE)	18	F	+	+	Mod	1	1	-	+	+
XPA2 (XP79BE)	24	M	+	+	Mild	2	1	-	+	+
XPA3 (XP19BE) ^a	33	M	+	+	Mod	2	2	-	+	+
XPA4 (XP460BE)	9	F	+	+	ND	1	1	+	ND	+
XPA5 (XP12BE) ^{a-d}	19	F	+	+	Severe	3	2	-	+	+
XPA6 (XP360BE) ^e	10	M	+	+	Mod	2	1	+	ND	+
XPA7 (XP53BE)	3	F	+	+	ND	1	0	-	ND	-
XPA8 (XP337BE)	21	M	-	-	Normal	0	0	-	+	-
XPA9 (XP631BE)	13	F	-	-	Normal	0	0	-	+	-

Abbreviations: XPA – xeroderma pigmentosum – A, F- female, M- male, Abn – abnormal, SNC – sensory nerve conduction studies, MNC – motor nerve conduction studies (fibular nerve), MRI – magnetic resonance imaging, CT - Computed tomography, IQ – intelligence quotient, DTR – deep tendon reflexes, ND – not done, Mod-Moderate

Footnotes: ^a Totonchy MB, et al. 2014 (Ref. 4), ^b Lai JP, et al. 2013 (Ref. 3), ^c Viana LM, et al. 2013 (Ref. 8), ^d Ramkumar HL, et al. 2011 (Ref. 11), ^e Christen-Zaech S, et al. 2009 (Ref. 12)

Table 3. XP-D Patient Findings.

Patient	Age	Gender	Neuropathy		Audiology	MRI/CT Imaging			IQ Testing	DTR
ID # (Protocol designated ID)			Abn SNC	Abn MNC	SNHL	Cerebral Atrophy	Cerebellar Atrophy	Hypo-myelination	IQ<80	Absent
XPD1 (XP29BE) ^{a-c}	22	M	+	-	Mod	3	2	-	+	+
XPD2 (XP528BE)	19	M	+	-	Mild	1	0	-	+	+
XPD3 (XP32BE)	42	M	+	-	Mild	2	1	ND	ND	+
XPD4 (XP33BE) ^a	31	F	+	-	Mod	2	1	-	+	+
XPD5 (XP400BE)	17	M	+	-	Mild	1	0	-	+	+
XPD6 (XP116BE)	5	F	-	-	Normal	0	0	-	-	+
XPD7 (XP82BE)	11	F	-	-	Normal	0	0	-	-	ND
XPD8 (XP30BR-D)	13	M	-	-	Normal	0	0	-	-	ND
XPD9 (XP341BE)	3	M	-	-	Normal	0	0	-	+	-
XPD10 (XP416BE)	13	F	-	-	Normal	0	0	-	+	-

Abbreviations: XPD – xeroderma pigmentosum – D, F- female, M- male, Abn – abnormal, SNC – sensory nerve conduction studies, MNC – motor nerve conduction studies (fibular nerve), MRI – magnetic resonance imaging, CT - Computed tomography, IQ – intelligence quotient, DTR – deep tendon reflexes, ND – not done, Mod-Moderate

Footnotes: ^a Totonchy MB, et al. 2013 (Ref. 4), ^b Ueda T, et al. 2009 (Ref. 13), ^c Zhou X, et al. 2013 (Ref. 14)

Figures

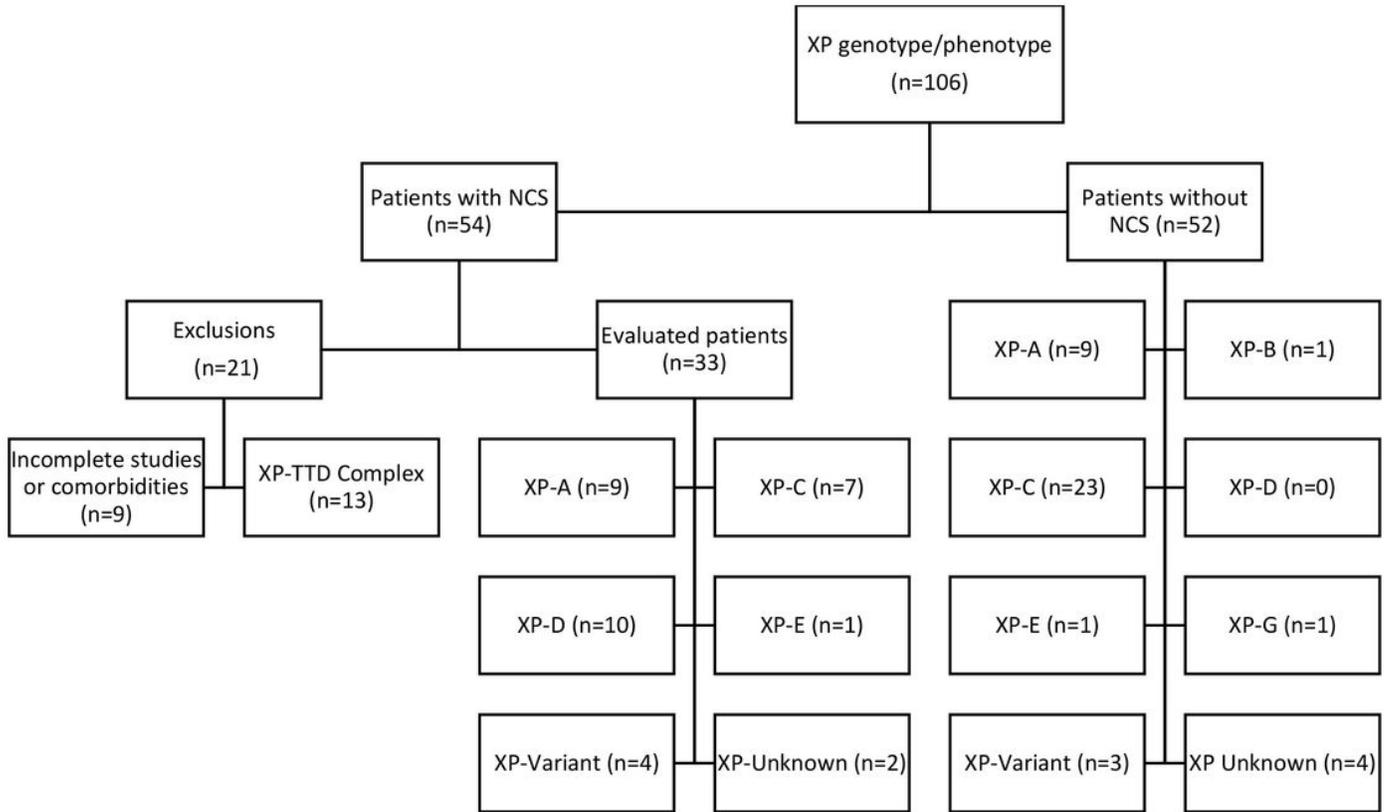


Figure 1

Algorithm of Subjects Studied. Of the 106 subjects with an XP genotype/phenotype, 54 subjects had nerve conduction studies and 33 subjects were included in the final evaluation. NCS – nerve conduction studies, XP – xeroderma pigmentosum.

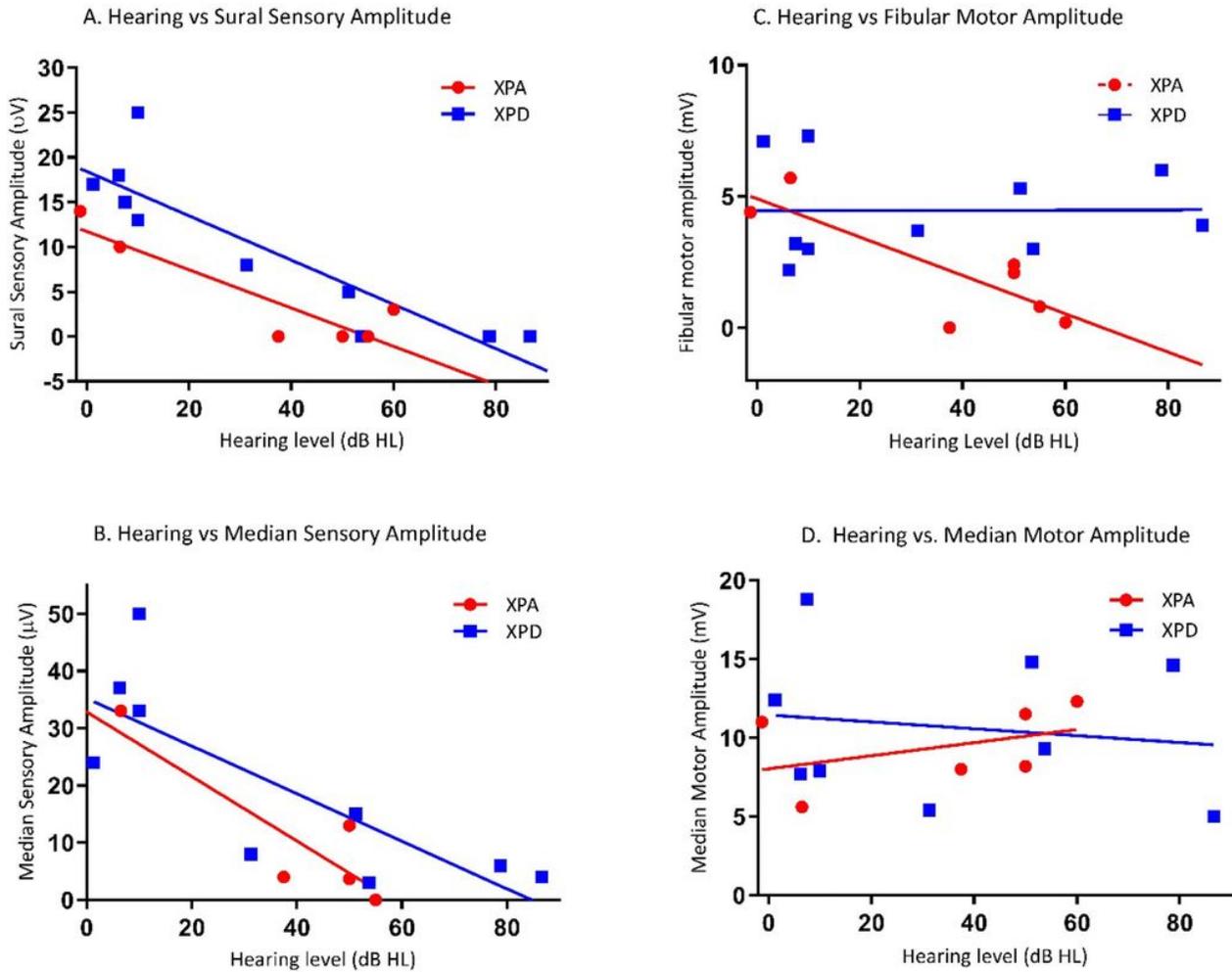


Figure 2

Hearing loss vs nerve conduction studies in XP-A and XP-D. The right ear 4F-PTA, defined as the four frequency (0.5/1/2/4-kHz) pure tone average, was plotted against the amplitudes of the following: A. Sural sensory nerve, B. Median sensory nerve, C. Fibular motor nerve, D. Median motor nerve. ANCOVA was used to study the interaction between complementation group and hearing level. Normal hearing: 4F-PTA \leq 20 dB HL. Normal NCS findings: sural sensory \geq 6 μ V, median sensory \geq 15 μ V, fibular motor \geq 2.5 mV, median motor \geq 4.5 mV.

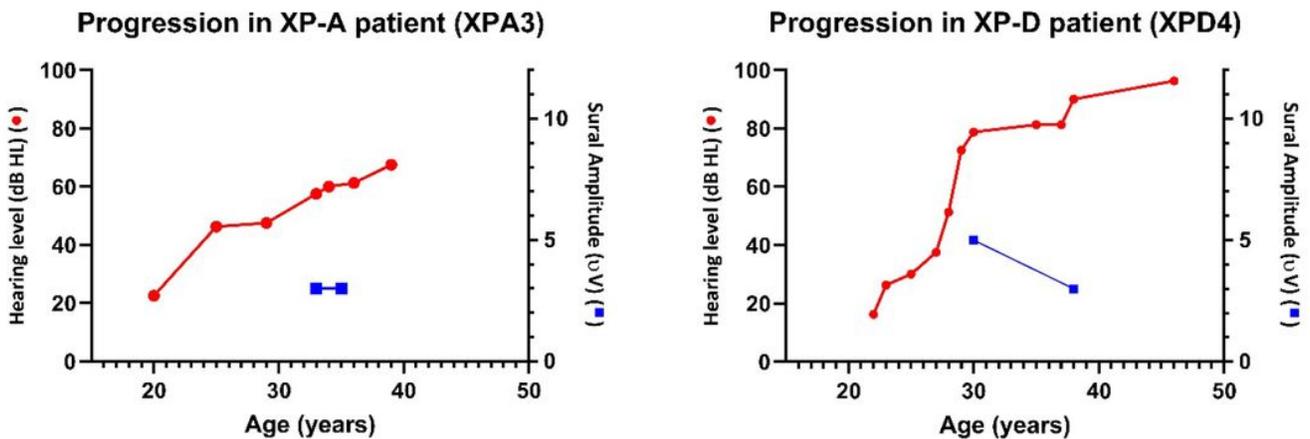


Figure 3

Follow-up hearing and sural sensory nerve studies. A. Patient XPA3 (neurological involvement) B. Patient XPD4 (neurological involvement). Age of patient (X axis) plotted versus hearing (dB HL) (left Y axis) and sural amplitude (μV) (right Y axis). Normal hearing: 4F-PTA ≤ 20 dB HL. Normal NCS findings: sural sensory ≥ 6 μV , fibular motor ≥ 2.5 mV.

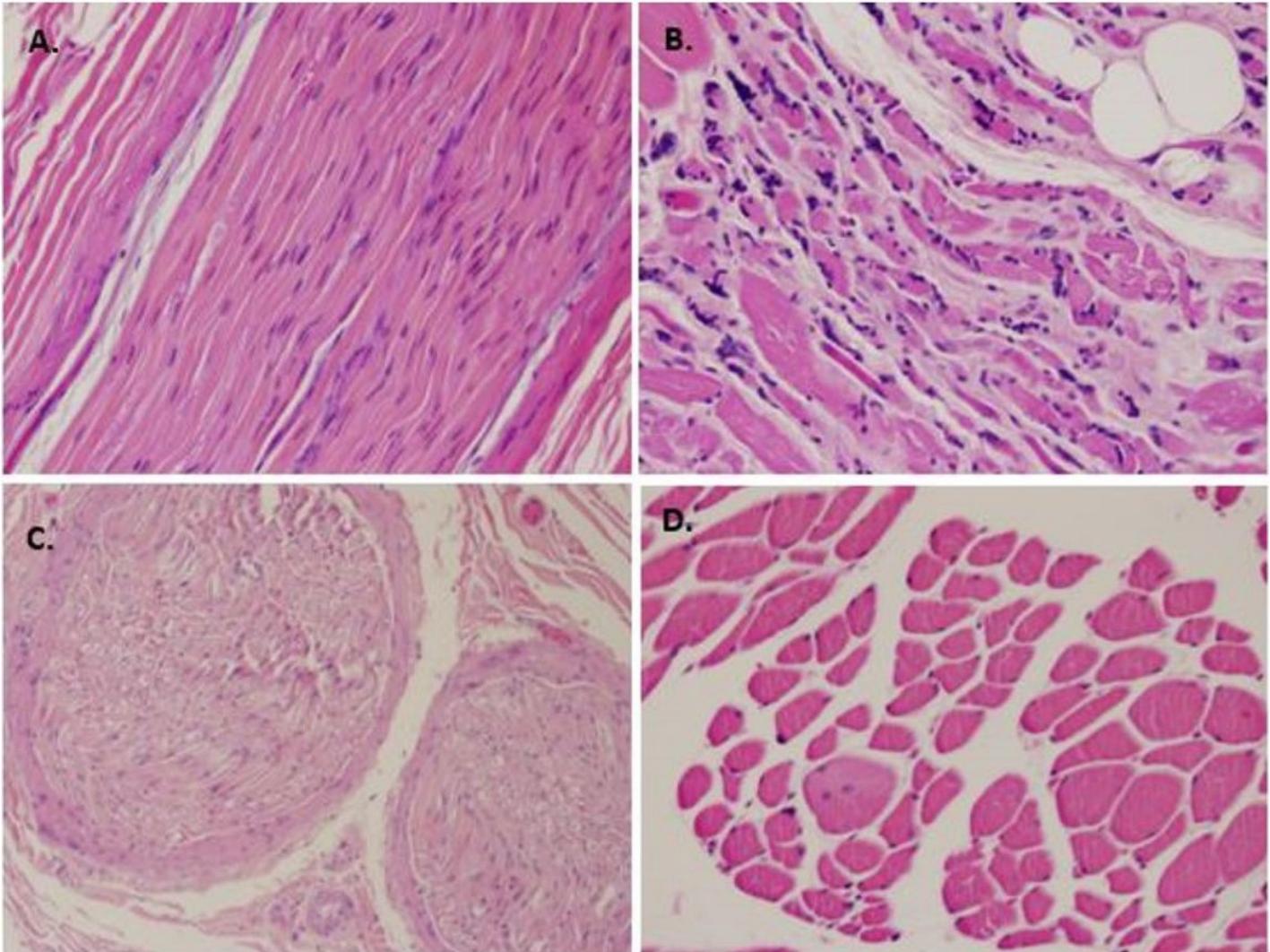


Figure 4

Nerve and muscle pathology of XP-A and XP-D patients. A. XPA (XP5 - XP12BE) patient median nerve - H&E, 20x, normal nerve architecture on longitudinal section. B. XP-A (XP5 - XP12BE) patient. muscle - H&E, 20x, marked variation in myofiber size characterized by the presence of many rounded and angular atrophic fibers, approaching panfascicular atrophy in some areas with fatty infiltration. Numerous pyknotic nuclear clumps are also present. C. XP-D patient nerve from arm but not specified - H&E, 10x, normal nerve architecture on cross-section. D. XP-D patient muscle - H&E, 20x, mild variation of muscle fiber size with occasional small-sized angulated fibers. (Modified from JP Lai, et al 2013, permission by Dr. K. Kraemer)