XERODERMA PIGMENTOSUM, TRICHOTHIODYSTROPHY AND COCKAYNE SYNDROME: A COMPLEX GENOTYPE–PHENOTYPE RELATIONSHIP

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Abstract—Patients with the rare genetic disorders, xeroderma pigmentosum (XP), trichothiodystrophy (TTD) and Cockayne syndrome (CS) have defects in DNA nucleotide excision repair (NER). The NER pathway involves at least 28 genes. Three NER genes are also part of the basal transcription factor, TFIIH. Mutations in 11 NER genes have been associated with clinical diseases with at least eight overlapping phenotypes. The clinical features of these patients have some similarities but also have marked differences. NER is involved in protection against sunlight-induced DNA damage. While XP patients have 1000-fold increase in susceptibility to skin cancer, TTD and CS patients have normal skin cancer risk. Several of the genes involved in NER also affect somatic growth and development. Some patients have short stature and immature sexual development. TTD patients have sulfur deficient brittle hair. Progressive sensorineural deafness is an early feature of XP and CS. Many of these clinical diseases are associated with developmental delay and progressive neurological degeneration. The main neuropathology of XP is a primary neuronal degeneration. In contrast, CS and TTD patients have reduced myelination of the brain. These complex neurological abnormalities are not related to sunlight exposure but may be caused by developmental defects as well as faulty repair of DNA damage to neuronal cells induced by oxidative metabolism or other endogenous processes. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

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XP

XP patients have marked skin sun sensitivity (Table 1). About half of the patients give a history of acute burning on minimal sun exposure. Typically the burn will appear about one day after the sun exposure. XP patients may develop blistering and severe redness that persists for days. The patients with the more severe burns tend to be those that later develop neurological abnormalities. Other XP patients do not experience sunburning but tan normally. However, following sun exposure all XP patients develop increased freckle-like pigmentation on exposed skin (Fig. 1A, B and C). The presence of these pigmented abnormalities in children under age 2 years is a clinical marker of XP patients.

With continued sun exposure the skin and the eyes become damaged. The skin of children with XP can develop pre-cancerous lesions such as actinic keratoses. XP patients develop skin cancers at a mean age of less than 10 years. This is a 50 year reduction in age of onset of skin cancer in comparison to the U.S. general population and thus XP represents a form of premature aging. Similarly, the eyes may have chronic UV-induced conjunctivitis and keratitis (Fig. 1C). These may progress to inflammatory lesions such as pungueculae (conjunctival growths limited to the bulbar conjunctiva) and pterygia (conjunctival growths that extend onto the corneal surface). In the general population, these lesions are rarely seen in children but have a fairly strong association with UV exposure in...
normal individuals such as farmers and sailors. The XP patients have 1000-fold increase in cancer of the skin and eyes (Kraemer et al., 1987, 1994). There is evidence that early diagnosis and rigorous sun protection will prevent more of the serious skin cancers in XP patients and prolong their life expectancy.

**XP WITH NEUROLOGICAL DISEASE**

About 30% of XP patients have a progressive neurological degeneration in addition to the skin abnormalities (Table 1). In contrast to CS, patients with XP neurological disease usually have normal sexual development. The course of the neurological degeneration is variable. The earliest clinical signs of the presence of XP neurological disease are diminished or absent deep tendon reflexes and high frequency hearing loss. Progression of sensorineural deafness may necessitate use of a hearing aid. Other changes may develop including abnormal gait, and difficulty walking eventually leading to the use of a wheelchair (Fig. 2A, B, and C) or to quadriplegic. During childhood, development may progress, with intellectual capacity initially increasing, however, this may be followed by deterioration over the course of years to decades. Swallowing difficulties may become severe leading to aspiration of food. At this late stage patients are often fed with an implanted gastric tube.

The MRI shows atrophy of the cerebrum and cerebellum with sparing of the white matter (Table 1). Enlarged ventricles may be seen early in childhood. This process may progress leading to greatly enlarged ventricles. The primary histological finding is neuronal degeneration without inflammation or abnormal depositions.

**TTD**

TTD patients have sulfur deficient brittle hair with characteristic alternating dark and light banding appearance (“tiger tail”) with use of a light microscope with polarizing filters (Fig. 3A, B, C and D) (Itin et al., 2001; Liang et al., 2005, 2006; Price et al., 1980). The clinical features in different patients are remarkably varied ranging from only hair involvement to severe neurological and somatic developmental abnormalities. Many TTD patients were born prematurely or were small for gestational age. Some patients may have a form of TTD called PIBIDS (for photosensitivity, ichthyosis, brittle hair, infertility, decreased intelligence and short stature). There is also a high frequency of congenital cataracts and of multiple infections. They may have skeletal abnormalities including peripheral osteopenia and central osteosclerosis. TTD patients, while sun sensitive, do not develop the pigmentary abnormalities of XP and do not have an increased frequency of skin cancer.

TTD patients may have developmental defects in the nervous system including microcephaly. While TTD patients may have intellectual impairment, they usually are very social and have an outgoing, engaging, friendly personality. Typically, standard intelligence tests appear to underestimate their capability for social interactions. The

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**Table 1. Comparison of features of XP, TTD and CS**

<table>
<thead>
<tr>
<th>Feature</th>
<th>XP</th>
<th>XP with neurological disease</th>
<th>TTD</th>
<th>CS</th>
<th>XP/CS complex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin sun sensitivity</td>
<td>Yes</td>
<td>Severe</td>
<td>Yes/No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Increased skin pigmentation</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sunlight-induced skin cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photophobia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes/No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Conjunctival growths</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cancer (anterior eyelids)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Not reported</td>
</tr>
<tr>
<td>Congenital cataracts</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pigmentary retinal degeneration</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>Somatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Short stature</td>
<td>No</td>
<td>No/Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Immature sexual development</td>
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<td>No</td>
<td>No/Yes</td>
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<td>Yes</td>
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<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sensorineural deafness</td>
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<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Progressive neurological degeneration</td>
<td>No</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary neuronal degeneration</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Dysmyelination</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Cerebral atrophy</td>
<td>No</td>
<td>Yes</td>
<td>No/Yes</td>
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<td>Cerebellar atrophy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Calcification (basal ganglia)</td>
<td>No</td>
<td>No</td>
<td>No/Yes</td>
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<td>Yes</td>
</tr>
<tr>
<td><strong>Disease mechanism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NER defect</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reaction to exogenous or endogenous damaging agents</td>
<td>Yes, severe</td>
<td>Yes, severe</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Developmental defect</td>
<td>No</td>
<td>Yes</td>
<td>Yes, severe</td>
<td>Yes, severe</td>
<td>Yes, severe</td>
</tr>
</tbody>
</table>

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patients may have ataxia. The MRI shows predominantly hypomyelination of the white matter of the cerebrum. Atrophy of the brain is not a major feature. Some patients may have calcification of the basal ganglia. At present the clinical course of TTD patients is not known.

**CS**

CS patients are often normal at birth but experience postnatal failure of brain growth (Nance and Berry, 1992; Rapin et al., 2000). They have a characteristic facies with deep set eyes, prominent ears and a wizened facial appearance. CS patients have extremely short stature and immature sexual development. They are sun sensitive but do not have the pigmentary changes or increased skin cancer frequencies seen in XP (Table 1). Unlike XP, where diminished deep tendon reflexes may be an early sign of neurologic involvement, deep tendon reflexes may be increased in CS. CS patients have a progressive sensorineural deafness beginning with high frequency hearing loss. The eye shows progressive visual loss with pigmentary retinal degeneration (“salt and pepper retinopathy”) and involvement of the lens and cornea (Dollfus et al., 2003). CS patients develop profound cachexia and often are fed with a gastric tube.

![Fig. 1. Skin and eye involvement in XP.](image-url)
Fig. 2. Progressive cachexia in XP patient XP12BE. At age 4 years she had prominent pigmentary changes on the sun-exposed portions of her body (face, arms) with sparing of her chest. By age 17 years she had had many basal cell and squamous cell carcinomas excised. Her main neurological abnormalities were loss of deep tendon reflexes and bilateral sensorineural hearing loss. By age 37 years she had become cachectic, was unable to swallow her food and required assistance to walk. Details of her neurological status up to age 22 years are described in Robbins et al. (1991). This patient inherited a defect in the XPA DNA repair gene (Cleaver et al., 1999).

Fig. 3. Clinical appearance of TTD. (A, B) Three year old female with short, brittle hair which is sparse and broken off at different lengths. She rarely has haircuts except to trim uneven areas. (C) Tiger-tail appearance of hair with polarizing microscopy. (D) Irregular, undulating hair shaft with light microscopy. From Liang et al. (2005).
Their clinical course typifies premature aging and usually results in early death. Like TTD patients, CS patients are very sociable with an outgoing affect. They develop progressive ataxia and loss of ability to walk and care for themselves. The brain MRI shows decreased or absent myelin. Cerebral atrophy may be present. CT scan may reveal prominent calcification of the basal ganglia and other areas in the brain (Fig. 4A and B). The primary histological finding in CS is a demyelinating neuropathy rather than the neuronal degeneration seen in XP.

**XP/CS COMPLEX**

Patients with the XP/CS complex have skin and eye disease of XP and the somatic and neurological abnormalities of CS (Table 1) (Lindenbaum et al., 2001; Rapin et al., 2000). Thus their skin is hypersensitive to sunlight and they develop the freckling and other pigmentary changes of XP. They have the short stature and immature sexual development as well as the retinal degeneration as in CS. The disease course is one of progressive neurological degeneration (Fig. 5A–G). Less than two dozen patients with the XP/CS complex have been reported in the literature.

**NER PATHWAY**

Patients with XP, TTD, CS and the XP/CS complex have defects in the NER pathway (Fig. 6) (Van Steeg and Kraemer, 1999). This pathway serves to remove DNA damage caused by exposure to ultraviolet radiation and some other exogenous and endogenous agents that cause bulky lesions or oxidative damage. There are at least 28 proteins in the NER pathway. They serve to recognize DNA lesions, unwind the surrounding DNA, excise the lesion and then fill in the resulting gap. Three of the proteins are also part of the 10 protein complex of the basal transcription factor, TFIIH. Thus the NER pathway is closely linked to transcription.

Repair of actively transcribing genes (transcription coupled repair) proceeds more rapidly than DNA repair of damage located in the remainder of the genome. DNA damage in these actively transcribing genes is signaled by CSA and CSB proteins along with other proteins. The XPC and XPE (DDB2) proteins are involved in recognition of DNA damage in the remainder of the genome (global genome repair). The XPB, XPD and TTDa proteins are part of the basal transcription factor TFIIH. The XPB and XPD helicases unwind the DNA. The XPF and XPG proteins are endonucleases that make asymmetric single strand breaks on either side of the damage about 30 nucleotides apart.

**RELATIONSHIP OF CLINICAL DISEASE TO NER MUTATIONS**

There is a complex relationship between the clinical diseases and the molecular defects in NER (Fig. 7) (Kraemer, 2004). Patients with one of several clinical disease may have inherited a defect in one of several different NER genes. Since the NER pathway functions in sequence, a defect in one portion of the pathway impairs the function of the subsequent steps. Thus patients with XP can have defects in XPA, XPB (ERCC3), XPC, XPD (ERCC2), XPE (DDB2), XPF (ERCC4) or XPG (ERCC5) genes. Conversely, different defects in one gene may lead to different
clinical diseases. Thus different mutations in the *XPD*(ERCC2) gene may lead to one of six different clinical disorders: XP, XP neurological disease, TTD, the XP/CS complex, XP/TTD complex or a severe form of CS known as COFS (cerebral, ocular, facial, skeletal syndrome).

**THEORETICAL MECHANISMS OF DISEASE**

The skin and eye disease in XP and the 1000-fold increased frequency of neoplasms in these sun-exposed organs is related to faulty repair of ultraviolet damage to
DNA. This results in increased cell killing and increased frequency of mutations in many of the genes in the surviving cells. Accumulation of mutations that activate oncogenes or inhibit tumor suppressor genes in dividing cells eventually leads to cancer.

In the XP patients who develop progressive neurological degeneration the brain is not exposed to ultraviolet radiation. The progressive nature of the degeneration suggests that there might be ongoing damage that is not repaired. Since neurons do not divide, unrepaired DNA...
damage could result in impaired cellular function and eventually in cell death. An effect of the damage might be to alter the process of transcription so that mutations might be introduced into newly synthesized RNA. This could impair functioning of essential proteins. The NER pathway is present in all cells in the body including those in the nervous system. Recent studies from several laboratories have reported the discovery of some bulky DNA lesions produced by oxidative damage that are substrates for the NER pathway. Unrepaired lesions such as cyclo-deoxyadenine or cyclo-deoxyguanine might accumulate in the DNA of neurons of patients with defective NER and lead to the progressive neurological degeneration (Brooks et al., 2000). There are many unanswered questions relating to this theory including why only some of the XP patients develop neurological degeneration and why certain parts of the brain are typically affected more than others.

Patients with TTD have neurological defects that appear to be mainly related to impaired development and maturation of the nervous system. They have decreased to absent myelin in the cerebrum. While not proven definitively, it seems that the myelin in these patients never formed properly (dysmyelination) rather than sustaining a loss of normally formed myelin (demyelination). This suggests the presence of a developmental defect as is also seen in the congenital cataracts in the eye, the problems during in utero growth, and the short stature. In addition TTD patients do not have an increased frequency of skin cancer. TTD patients have defects in XPD, XPE or TTD genes. These genes are part of the basal transcription factor, TFIIH as well as in NER. It has been proposed that the specific defects in these genes in TTD patients have a greater effect on the transcription activities of these genes than on their repair activities (Dubaele et al., 2003). A striking example is the finding that mutations in the XPD component of TFIIH result in beta-thalassemia in TTD patients without mutations in hemoglobin genes (Vipraka-sit et al., 2001). At present we have no evidence of progressive neurological degeneration in TTD patients.

CS patients have both developmental defects and progressive neurological degeneration. Like TTD patients there is primary involvement of the myelin in the brain. The CSA and CSB proteins have a role in transcription-coupled repair and may also be involved in transcription of undamaged genes. CSA and CSB proteins are involved in regulation of recruitment of chromatin remodeling and repair factors to stalled RNA polymerase II after UV damage (Fousteri et al., 2006). The transcriptional response after oxidative damage is defective in cells from patients with mutations in the CSB gene (Kyng et al., 2003). Thus the progressive neurological degeneration in CS may involve faulty repair of oxidative damage or of bulky DNA damage as in XP patients. However major questions remain such as the differences in the type of involvement—for example retinal degeneration is present in CS but not in XP—and the differences in cancer susceptibility.

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