

Trichothiodystrophy: Update on the sulfur-deficient brittle hair syndromes

Peter H. Itin, MD,^a Alain Sarasin, PhD,^b and Mark R. Pittelkow, MD^c
Aarau, Switzerland, Villejuif, France, and Rochester, Minnesota

Trichothiodystrophy (TTD) refers to a heterogeneous group of autosomal recessive disorders that share the distinctive features of short, brittle hair and an abnormally low sulfur content. Within the spectrum of the TTD syndromes are numerous interrelated neuroectodermal disorders. The TTD syndromes show defective synthesis of high-sulfur matrix proteins. Abnormalities in excision repair of ultraviolet (UV)-damaged DNA are recognized in about half of the patients. Three distinct autosomal recessive syndromes are associated with nucleotide excision repair (NER) defects: the photosensitive form of TTD, xeroderma pigmentosum, and Cockayne syndrome. The unifying feature of these conditions is exaggerated sensitivity to sunlight and UV radiation. In contrast to patients with xeroderma pigmentosum, no increase of skin cancers in patients with TTD has been observed. Genetically, 3 complementation groups have been characterized among photosensitive patients with TTD. Most patients exhibit mutations on the two alleles of the *XPD* gene. Rarely, mutated *XPB* gene or an unidentified *TTD-A* gene may result in TTD. In UV-sensitive TTD, the TFIIH transcription factor containing XPB and XPD helicase activities necessary for both transcription initiation and DNA repair is damaged. Beyond deficiency in the NER pathway, it is hypothesized that basal transcription may be altered leading to decreased transcription of specific genes. Depressed RNA synthesis may account for some clinical features, such as growth retardation, neurologic abnormalities, and brittle hair and nails. Therefore the attenuated expression of some proteins in differentiated cells is most likely explained by a mechanism distinct from DNA repair deficiency. The first transgenic mouse models for NER deficiencies have been generated. The TTD mouse as well as related cell models will provide important tools to understand the complex relationships between defects in DNA repair, low-sulfur hair shaft disorders, and the genotype-phenotype correlates for this constellation of inherited disorders, including the lack of predisposition to cancer in patients with TTD. (J Am Acad Dermatol 2001;44:891-920.)

Learning objective: At the completion of this learning activity, participants will have a current understanding of the expanded and further defined clinical spectrum of the TTD syndromes. Participants will have gained new insight into the genetic and molecular characteristics and causes for the low-sulfur hair disorders.

TRICHOIODYSTROPHY SYNDROMES: DEFINITION, CLASSIFICATION, AND CLINICAL FEATURES

Definition and diagnosis

The term *trichothiodystrophy* (TTD) was coined by Price in 1979-1980¹⁻³ based on a series of cases,

including the early report by Pollitt, Jenner, and Davies⁴ in 1968, of a family with mental and physical retardation and "trichorrhaxis nodosa" with abnormal amino acid composition of the hair. Brown et al⁵ in 1970 specifically described the congenital hair defect, consisting of trichoschisis, "alternating birefringence," and low-sulfur content. The designation for this unique hair shaft disorder is derived from Greek: *tricho*, hair; *thio*, sulfur; *dys*, faulty; and *trophe*, nourishment. Clinical features of patients with TTD are highly variable in expression and severity, and phenotypes range from those with an isolated hair defect to those with severe neuroectodermal findings and, rarely xeroderma pigmentosum (XP)-like changes (Fig 1).

We reviewed the clinical features of TTD extensively in this Journal in 1990 and proposed a dysmorphic

From the Department of Dermatology, University of Basel and Kantonsspital Aarau^a; the Laboratory of Molecular Genetics, Institut de Recherches sur le Cancer, Villejuif^b; and the Department of Dermatology, Mayo Clinic and Mayo Foundation, Rochester.^c

Reprint requests: Mark R. Pittelkow, Department of Dermatology, Mayo Clinic and Mayo Foundation, 200 First St SW, Rochester, MN 55905.

Copyright © 2001 by the American Academy of Dermatology, Inc. 0190-9622/2001/\$35.00 + 0 **16/2/114294**
 doi:10.1067/mjd.2001.114294

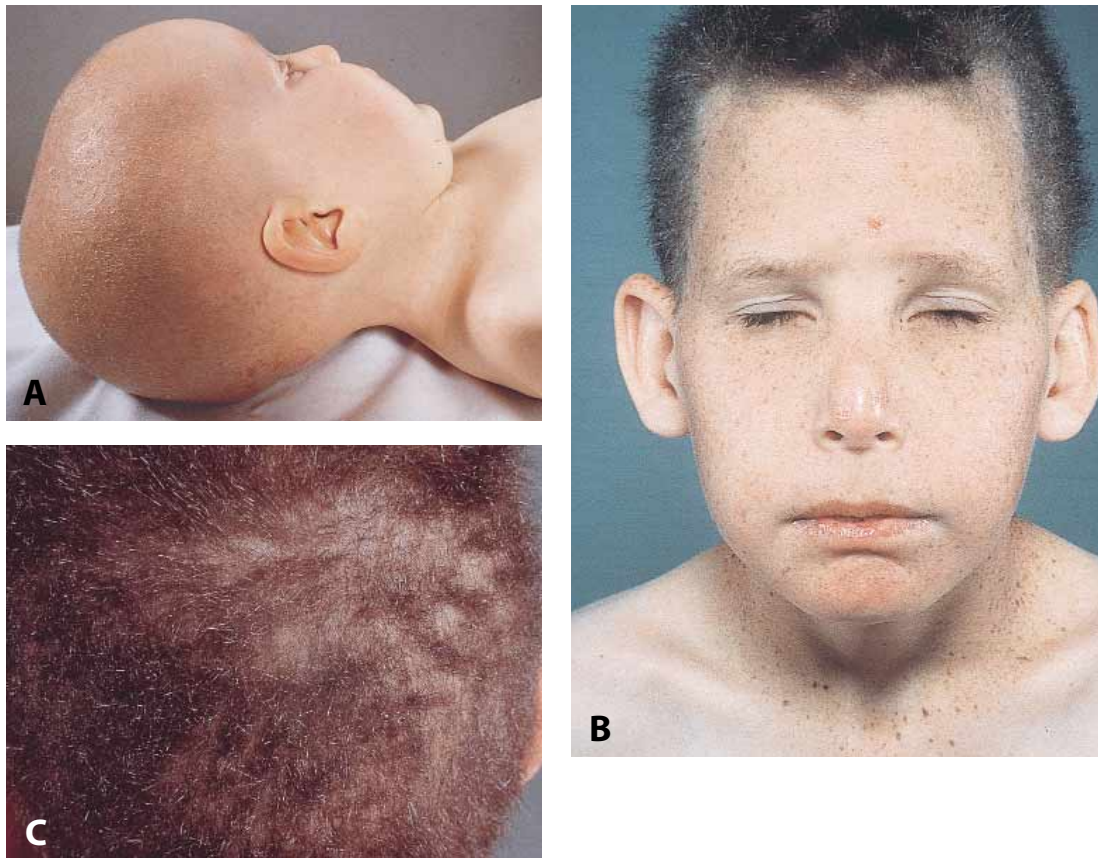


Fig 1. Clinical spectrum of TTD. **A**, TTD and psychomotor retardation in a 2-year-old girl. TTD and photosensitivity in a 9-year-old boy showing **(B)** distinctive facial features and **(C)** hair abnormality. The patient also had ichthyosis and was found to have mutations within the *XPD* gene (see text).

Abbreviations used:

CPD:	cyclobutane pyrimidine dimer
CS:	Cockayne's syndrome
GGR:	global genome repair
ICAM-1:	intercellular adhesion molecule 1
NADPH:	reduced nicotinamide adenine dinucleotide phosphate
NER:	nucleotide excision repair
NK:	natural killer
6-4 PP:	pyrimidine (6-4) pyrimidone photo-product
TCR:	transcription coupled repair
TTD:	trichothiodystrophy
UDS:	unscheduled DNA synthesis
XP:	xeroderma pigmentosum

relationship and classification scheme within the spectrum of the ectodermal dysplasias.⁶ Within the past 10 years the clinical expressions of TTD have further expanded, and our understanding of the cellular,

genetic, and molecular mechanisms associated with this symptom complex have evolved substantially.⁷⁻⁹

TTD, the encompassing term for the sulfur-deficient, brittle hair syndromes, is a rare disorder, inherited as an autosomal recessive trait. To date only one case with possible X-linked inheritance has been reported.¹⁰ The diagnostic findings are short, unruly, and brittle hair with low-sulfur content, alternating dark and light bands of the hair shaft under polarizing microscopy, trichoschisis, and absent or defective cuticle visualized by scanning electron microscopy¹¹ (Fig 2). Although dark and light banding of hair shafts under polarizing light microscopy is highly suggestive for TTD, this finding is not diagnostic.

Recently, Goerz et al¹² reported an 8-year-old girl with the clinical features of TTD including the "tiger-tail" pattern, visualized on polarizing microscopy and severe cuticular defects detected on scanning microscopy, but the cyst(e)ine content of the hair was normal. However, a deficiency of the sulfur-containing amino acid, methionine in the hair was documented. This case emphasizes the fact that the

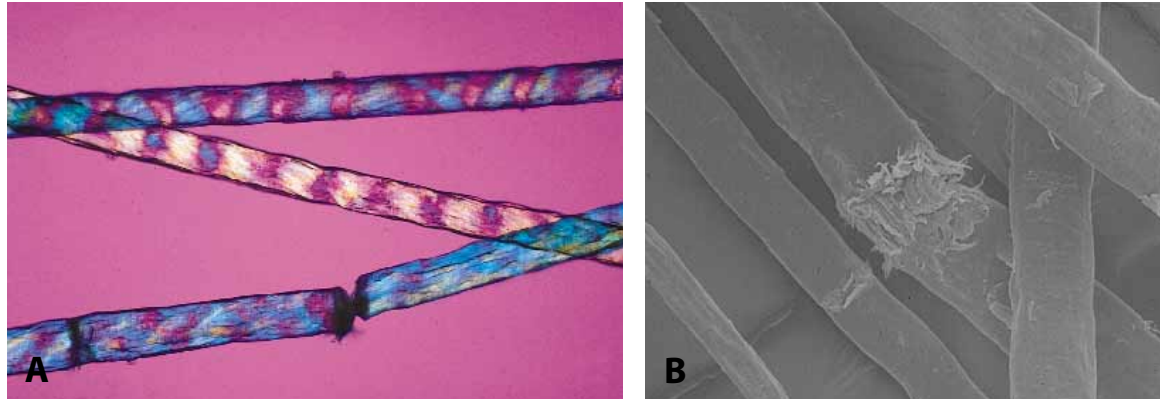


Fig 2. Microscopy of TTD hair. **A**, Polarizing microscopy of hair shafts showing banded or “tiger-tail” pattern and fracture. **B**, Scanning electron microscopy demonstrates trichoschisis and absent or damaged cuticle. (Original magnification $\times 250$.)

morphologic abnormalities of TTD are not restricted to cyst(e)ine deficiency but also methionine and possibly other amino acid deficiencies in the hair shaft that produce a similar clinical picture.

The report of Kvedar et al¹³ supports this contention. They observed fragile hair in two untreated patients with argininosuccinic aciduria, who showed an abnormal alternating banding pattern of the hair shafts, using polarizing microscopy. The half-cystine content was only slightly lower than in normal hair. With the institution of dietary treatment, the “tiger-tail” pattern disappeared. They coined this entity “pseudo-trichothiodystrophy” in a patient with arginosuccinic aciduria.¹⁴

Other inherited metabolic disorders may induce a similar phenotype. Acrodermatitis enteropathica may lead to an irregular morphologic pattern observed in the hair shaft that is characterized by alternating dark and bright bands under polarizing microscopy.¹⁵ After 2 years of zinc supplementation the anomaly could no longer be detected. Moreover, nonheritable alterations of hair protein composition may be seen. Amino acid content of hair may vary with season and nutrition.

A simple decrease in hair sulfur content is not diagnostic for TTD, and this entity must be recognized as a complex disease in which clinical manifestations, structural alterations of the hair shaft, and biochemical abnormalities require correlation and interpretation. Untreated kwashiorkor has been found to manifest subnormal sulfur content of hair.¹⁶ With treatment, the sulfur content normalized. Morganti et al¹⁷ found a marked decrease in cyst(e)ine and other amino acids in the hair of several patients with different types of ichthyosis, but they did not otherwise qualify for the diagnosis of TTD. Three patients with Clouston’s ectodermal dysplasia were found to have normal hair sul-

fur content, but the cyst(e)ine content of hydrolyzed hair was approximately 25% to 30% lower than that of control subjects.¹⁸ In addition, exogenously induced and acquired types of low-sulfur hair exist. Cyst(e)ine content in hair may decrease remarkably after treatment with cold-waving lotions, depilatories, bleaching solutions, and synthetic-organic dyes.^{19,20}

It must be emphasized that a single, isolated morphologic abnormality of the hair shaft is not sufficient to establish the diagnosis of TTD. Although trichoschisis and alternating light and dark banding by polarizing microscopy are typical findings in TTD, they may occasionally occur in patients without this disorder.²¹⁻²⁸

TTD syndromes: Delineation and spectrum of expression

In 1968, Pollitt, Jenner, and Davies⁴ reported the first cases of “trichorrhaxis nodosa,” low-sulfur content of hairs combined with mental and physical retardation. Two years later, Brown et al⁵ described a case of trichoschisis with alternating “birefringence” (ie, light-dark banding along the hair shaft visualized by polarizing microscopy) and low-sulfur content of the hair. Trichoschisis is characterized by a sharp fracture, transversely through the entire hair shaft that is especially well detected by means of the polarizing microscope. This finding is quite typical for TTD. These investigators also discovered the marked decrease in hair sulfur content of a patient with hidrotic ectodermal dysplasia, and scanning electron microscopy revealed defective cuticle.²⁹ The cuticle deformity is an additional key finding in TTD. In 1971, Tay³⁰ studied 3 patients with ichthyosiform erythroderma, hair shaft abnormalities, mental and somatic growth retardation. Microscopy of hairs showed the typical findings of TTD. Several observations relating Tay syn-

Table I. TTD subtype classification⁶⁶

Type	Findings	Eponym/Acronym	OMIM ¹⁹⁹
A	Hair +/- nails		
B	Hair +/- nails + mental retardation	Sabinas	211390
C	Hair +/- nails + mental retardation + folliculitis + retarded bone age +/- caries	Pollitt	275550
D	Brittle hair +/- nails + infertility + developmental delay + short stature	BIDS	234050
E	Ichthyosis + BIDS. Hair +/- nails + mental retardation + short stature +/- decreased gonadal function +/- lenticular opacities/cataracts + failure to thrive/"progeria" + microcephaly +/- ataxia +/- calcifications of the basal ganglia + erythroderma and scale	Tay + BIDS	242170
F	Photosensitivity + IBIDS	PIBIDS	278730
G	TTD with immune defects. Hair +/- mental retardation + chronic neutropenia or immunoglobulin deficiency	Itin	258360
H	Trichothiodystrophy with severe intrauterine growth retardation (IUGR). Hair + severe IUGR and failure to thrive + developmental delay + recurrent infections + cataracts + hepatic angioendotheliomas		

drome to low-sulfur content of hair followed.³¹⁻³⁵ At birth, children present with ichthyosiform erythroderma, and they may be encased in a collodion-like membrane.³⁶ After some weeks, the erythema fades.³⁷ Happle et al³⁸ described translucent scaling, whereas others have observed large, dark, alligator-like hyperkeratoses.^{39,40} Flexures may be spared, and distinction from ichthyosis vulgaris is sometimes difficult. Histologic examination of the skin may show a thin epidermis with hyperkeratosis and absence of the granular layer,⁴¹⁻⁴³ but parakeratosis or a normal granular layer with spongiosis has also been described.^{33,42,44} In 1974, Jackson, Weiss, and Watson⁴⁵ identified a pedigree of 25 persons among an Amish kindred with brittle hair, short stature, intellectual impairment, decreased fertility, and low-sulfur content of hair. The inheritance pattern was consistent with an autosomal recessive disorder.

Cantu et al⁴⁶ in 1975 reported an apparently unrelated condition with a constellation of onychotrichodysplasia and chronic neutropenia. In 1979, three similar cases were reported.⁴⁷ An additional patient with onychotrichodysplasia, chronic neutropenia, and mild mental retardation was subsequently described; this condition was called the ONMR syndrome.⁴⁸ Another patient with onychotrichodysplasia, neutropenia, and normal intelligence was described.⁴⁹ We subsequently examined a patient with chronic neutropenia, mild mental retardation, and "onychotrichodysplasia." We further characterized the disorder as sulfur-deficient, brittle hair with trichoschisis, dark and light banding by polarizing light microscopy, and absent cuticle on electron microscopy.⁵⁰ This observation expanded the spectrum of TTD syndromes, and Camacho⁵¹ designated the symptom complex as "Itin syndrome". Over these years additional cases have been described.^{43,44,52-58}

Key observations along yet other seemingly separate directions had been made in the 1970s. Arbisser et al⁵⁹ in 1976 described the Sabinas syndrome, named after a town in Mexico where most of the patients resided. They were found to have brittle hair, neuroectodermal dysplasia, and a low-sulfur content in hair. Baden et al⁶⁰ used the acronym BIDS syndrome for brittle hair, intellectual impairment, decreased fertility, and short stature in association with low-sulfur content in the hair. Their report described hairs with an "alternating birefringent pattern" when examined by polarizing microscopy. Jorizzo et al⁴⁰ suggested the term IBIDS syndrome for ichthyosis-associated cases in conjunction with the low-sulfur content hair of BIDS.

Earlier studies had documented a patient with Marinesco-Sjögren syndrome with low-sulfur content of the hair.^{24,61} In 1971 Porter⁶² reported a case of Marinesco-Sjögren syndrome with trichoschisis and abnormal "birefringence" by polarized light microscopy.

The unifying term TTD was proposed in 1979 and 1980 by Price et al¹⁻³ to characterize the condition of patients with sulfur-deficient brittle hair and other neuroectodermal symptoms and signs. They recognized sulfur deficiency of hair as a possible marker for a special group of neuroectodermal diseases.

Chapman⁶³ detected osteosclerotic abnormalities in a patient with TTD and proposed the acronym SIBIDS for osteosclerosis, ichthyosis, brittle hair, impaired intelligence, decreased fertility, and short stature. Several patients with central osteosclerosis have subsequently been described.^{33,43,44,53,54,64,65} In 1998 Petrin, Meckler, and Sybert⁶⁶ observed a new variant of TTD with recurrent infections, failure to thrive, hepatic angioendotheliomatosis, and death. Possibly, the case described by Hersh et al⁴⁴ also represented this subgroup of TTD (Table I).

Photosensitive trichothiodystrophy, linkage to xeroderma pigmentosum, and a unifying classification

Systematic examination of brittle hair that was detected in patients with various other phenotypic abnormalities further expanded the spectrum of TTD syndromes and eventually provided a link to another distinct group of inherited dermatologic disorders with photosensitivity and variable neurocutaneous abnormalities.

In 1983 Crovato, Borrone, and Reborna⁶⁷ reported a low-sulfur hair syndrome with photosensitivity and IBIDS and suggested the acronym PIBIDS syndrome, although photosensitivity in patients with TTD had been reported earlier or concurrently.⁶⁸ Another genodermatosis, xeroderma pigmentosum (XP), had been well characterized as an autosomal recessive photosensitivity disorder in which exaggerated sun damage and a very high rate of both nonmelanoma skin cancer and melanoma were characteristic features. XP was known to be associated with defective DNA repair.

Lehmann⁶⁹ suggested a two-mutation hypothesis to explain the finding of defective DNA repair in TTD and to extend and relate the condition to XP. Nuzzo et al⁷⁰ identified a common ancestor among families of patients with TTD and XP, and they speculated that two mutations were responsible for the co-occurrence of TTD and XP type D (see later "Cellular and Molecular Genetic Characteristics of TTD: Genetic Classification of TTD" [page 900]). They concluded that if two mutations were responsible for the two diseases they are linked loci or affect the same gene.

Van Neste, Miller, and Bohnert^{71,72} have proposed a classification using letters alphabetically to denote the main symptoms and to separate each distinct subgroup. This classification has been updated based on recent additional findings reported in the literature and summarized in this review (Table I). This classification underscores the range as well as the overlapping consistency of features within the TTD syndromes.

Together, the TTD syndromes represent disorders within the larger spectrum of ectodermal dysplasias. Ectodermal dysplasias are a large group of heritable conditions characterized by a congenital dysplasia of one or more ectodermal structures and their accessory appendages. Although protean in expression, distinct combinations of abnormalities are observed in TTD syndromes and demonstrate consistency within the families that have been reported. The ectodermal dysplasias, as a rule, are not pure "one-layer diseases." Mesodermal and rarely endodermal dysplasias coexist. Embryogenesis exhibits distinct tissue organiza-

tional fields and specific interactions among the germ layers that may lead to the wide range of ectodermal dysplasias when genes are mutated or otherwise altered in expression.^{73,74}

Clinical manifestations and new findings in TTD

TTD is a classic differential diagnosis in congenital alopecias.⁷⁵ The hair of patients with TTD is dry and sparse and the hair shafts break easily with trauma.⁶ Other environmental factors and mechanical stress also play roles. Intermittent hair loss during infections was observed by Kleijer, Beemer, and Boom⁷⁶ and Foulc et al.⁷⁷ In addition, hair loss may occur with periodic cyclicity, especially in patients with a concomitant DNA repair defect.⁵⁴ Fractures of the hair shaft develop, and the viscoelastic parameters of hair are compromised compared with the hair of controls.^{78,79}

No effective treatment has been found for the brittle hair. In this regard Przedborski et al⁸⁰ attempted treatment with oral biotin (0.75 mg/kg per day) without improvement. However, trauma and mechanical/environmental stresses should be minimized. Future treatment options include application of agents or enzymes that induce chemical modification and cross-linking of hair proteins to bridge fragile sites within the shaft and protect the cuticle from excessive damage and breakdown.

Forty percent to 50% of patients with TTD exhibit marked photosensitivity. Photosensitive patients with TTD have a deficiency in DNA excision repair, which, in most cases, is indistinguishable from that observed in XP type D.^{77,81-86} There is no evidence for exaggerated development of skin cancers in patients with TTD, whereas there is for patients with XP type D. Severe neuroectodermal disorders frequently occur in photosensitive TTD, but none is a constant feature. Sulfur-deficient, brittle hair remains the key finding and the objective marker for a broadening range of associated autosomal recessive ectodermal and neuroectodermal diseases, although isolated cases of TTD without other defects have been reported in recent years.⁸⁷⁻⁸⁹

The clinical spectrum of associated signs and symptoms that constitute the TTD syndromes is extensive (Table II). Since our last review in 1990, the following additional clinical associations have been observed: expansion of neurologic abnormalities, including autism⁴¹ and partial agenesis of corpus callosum.⁹⁰ Central nervous system dysmyelination occurs quite commonly, and this feature bears a similarity to Cockayne syndrome (CS).^{32,34,35,52,64,65,91-94} Wetzburger et al⁵⁶ documented gray matter heterotopia and acute necrotizing encephalopathy in a 3-

Table II. Trichothiodystrophy syndromes: Associated signs and symptoms

<i>Hair*</i>	<i>Nervous system (cont'd)</i>
Sparse or absent eyelashes, eyebrows	Lethargy
Sparse or absent axillary, pubic, body hair	Perimedullary fibrosis of spinal cord
Few vibrissae and otic hair	<i>Dysmorphology and miscellaneous abnormalities^{ll}</i>
<i>Nails[†]</i>	Growth retardation
Dysplasia (onychodystrophy)	Cranial dysplasia
Splitting (onychoschezia)	Microdolichocephaly/microcephaly
Koilonychia	Protruding ears
Ridging	Hypoplastic ears
Thickening (onychogryphosis)	Preauricular pits
Yellow discoloration	Cleft ear lobes
Unguis inflexus	Ear deformation not specified
<i>Cutaneous[‡]</i>	Thin-beaked nose
Ichthyosis	Obstruction of the nose
Follicular keratosis	Receding chin
Collodion baby	Maxillary hypoplasia
Erythroderma	Dental abnormalities
Photosensitivity (defective DNA repair)	Caries
Erythema	Enamel hypoplasia
Eczema	Gastrointestinal malabsorption by jejunal atrophy
Hypohidrosis	White plaques on tongue
Pruritus	Gingival hyperplasia
Freckles	Bifid uvula
Telangiectasia	Small mouth
Hemangioma	Cleft lips
Lipoatrophy	Macrocheilia
Parchment-like skin	Raspy high-pitched voice
Poikiloderma	Frontal bossing
Folliculitis	Facial hemiatrophy
Cheilitis	Trunk-limb disproportion
Hyperpigmented eyelids	Polythelia
Hypopigmented macules	Short neck
Pyoderma	Goiter
Palmar pustules	Excessive palmar crease
<i>Nervous system[§]</i>	Single palmar creases
Mental retardation	Progeria
Autism	<i>Ocular^{ll}</i>
Dysmyelinization	Cataract
Spasticity/paralysis	Conjunctivitis
Ataxia	Nystagmus
Cerebellar deficiency	Photophobia
Intention tremor	Epicanthal folds
Motor control impaired	Retinal dystrophy
Pyramidal signs	Entropion
Muscle tone diminished	Ectropion
Peripheral neuropathy	Hypotelorism
Hyperreflexia	Exophthalmus/enophthalmus
Absent deep tendon reflexes	Esotropia
Hemiparesis	Myopia
Tetraparesis	Astigmatism
Intracranial calcifications	Retrobulbar hemangioma
Partial agenesis of corpus callosum	Chorioretinal atrophy
Gray matter heterotopia and necrotizing encephalopathy	Retinal pigmentation
Jerky eye movements	Antimongoloid eye slant
Seizures	Tortuosity of retinal vessels
Neurosensory hearing impairment	Diminished red-green discrimination
Dysarthria	Strabismus
Irritability	Hypertelorism

Table II. Cont'd

<i>Ocular</i> (cont'd)	<i>Skeletal</i> (cont'd)
Bacterial keratitis	Contracture
Meibomian gland inflammation	Zygodactyly
Blepharitis	Clinodactyly
Pale optic disc	Limited range of motion
Microcornea	Pectus excavatum
<i>Genital/urologic</i> [#]	Scoliosis
Hypoplasia	Thoracic kyphosis
Cryptorchism	Lumbosacral lordosis
Hypospadias	Metacarpal bones of the thumb reduced in size
Hydronephrosis	<i>Cardiovascular</i> ^{**}
Ureteral duplication	Hemangioma
Pyelocalyceal ectasia	Telangiectasia
<i>Pulmonary</i> ^{**}	Impairment of peripheral circulation
Pulmonary adenomatosis	Angioepitheliomas of the liver
Asthma	Pulmonic stenosis
Bronchiectasis	Ventricular septal defect
<i>Skeletal</i> ^{††}	<i>Immunologic/hematologic</i> ^{§§}
Genu valgum	Recurrent infections
Coxa valga	Neutropenia
Valgus deformity of the great toe	Anemia
Pes valgus	Hyper eosinophilia
Cubital and tibial valgus deformity	Impaired NK cell activity
Ulnar deviation of fingers	

*References 1, 5, 32, 42, 47, 48, 52, 64, 66, 80, 97, 99, 105, 204-208.

†References 1, 4, 32, 33, 36, 38-40, 42-44, 46-50, 52, 57, 77, 96, 97, 130, 203, 204, 208-214.

‡References 1, 4, 10, 30, 32-36, 38-44, 47, 49, 50, 52, 53, 57, 63, 65-68, 76, 77, 84, 86, 90-92, 96, 97, 100, 102, 105, 106, 109, 120, 130, 136, 137, 185, 206-210, 212, 214-237.

§References 1, 4, 10, 30, 32-36, 38-48, 50, 52-54, 56, 59, 63-65, 67, 68, 76, 77, 80, 84, 86, 90-92, 97, 99, 120, 130, 136, 137, 185, 204, 206-214, 216-220, 224, 225, 227, 228, 235, 237, 239-241.

||References 1, 4, 30, 32-34, 36, 38-46, 48-50, 52-54, 57, 63-68, 76, 77, 80, 84, 86, 91, 92, 95-97, 100, 106, 185, 204, 206, 207, 209-216, 218, 223-225, 235, 239-242.

¶References 1, 32, 33, 36, 39, 40, 42-47, 49, 50, 52-54, 57, 59, 63, 64, 66, 67, 77, 91, 92, 99, 102, 120, 130, 185, 204, 206, 207, 209, 211, 213, 214, 218, 220, 221, 224-226, 230, 240, 241, 243.

#References 33, 38-41, 43-45, 63, 97, 130, 204, 207, 212, 214, 219, 239.

**References 1, 40, 77, 209, 215, 216.

††References 32, 36, 39, 42, 43, 48, 53, 80, 96, 102, 207, 209, 212, 218, 225.

‡‡References 1, 4, 46, 66, 102, 206, 211, 212.

§§References 5, 30, 38, 46-50, 63, 95-97, 99, 185, 194, 205, 209, 211, 216, 225, 240.

year-old boy with TTD. Extreme failure to thrive and death have been observed by Petrin, Meckler, and Sybert⁶⁶ and has led to the addition of the new "H" subgroup in the classification of TTD (Table I).

Hematologic changes such as sideroblastic anemia⁹⁵ and eosinophilia⁹⁶ have been reported. TTD associated with right-sided hydronephrosis, ureteral duplication and left pyelocaliceal ectasia, as well as primary hypercalciuria is an additional clinical subset described recently.^{97,98} Gastrointestinal malabsorption with atrophic villi noted on jejunal biopsy findings and multiple food intolerance without celiac disease, requiring prolonged parenteral and enteral nutrition, has recently been observed.⁵⁷ Abnormal results of gonadal function tests in response to luteinizing hormone-releasing hormone have been

documented in patients with TTD by Przedborski et al.⁸⁰ A practical clinical observation by O'Brien and Wilhelmus⁹⁹ highlights ophthalmologic intervention to prevent bacterial keratitis induced by brittle, mis-oriented eyelashes.

Angioendotheliomas of the liver have been incorporated into the list of associated systemic developmental abnormalities recently described in TTD.⁶⁶ Cleft lip,⁴¹ meibomian gland inflammation, and blepharitis as well as poikiloderma and progeroid facies have also been observed.^{41,100} Bodemer et al¹⁰¹ recently described a patient with mitochondrial disease and TTD. Initially, collodion baby was believed to occur only in patients with TTD without *XPD* mutation, but Marinoni et al¹⁰² described a case of TTD with collodion baby and mutation in the *XP* group D.

Table III. Hair analysis in TTD

Microscopy	Sulfur analysis
Light: Trichoschisis, trichorrhexis nodosa	Semiquantitative: Scanning electron microscopy with electron-probe microanalysis
Polarizing: Light and dark banding—tiger-tail pattern, trichoschisis	Quantitative: Amino acid analysis of hydrolyzed hair
Scanning electron: Transverse fracture through the hair shaft, poor or absent cuticle	

Poor prognosis in TTD has been linked to severe, recurrent infectious disease with most pediatric deaths due to overwhelming bacterial infections.⁵⁷

HAIR AND SKIN ABNORMALITIES IN TTD New findings in light microscopy and scanning electron microscopy of hair

In patients with TTD, hair abnormalities are the only obligatory and diagnostic findings that identify the sulfur-deficient neuroectodermal dysplasias. Scalp hairs, eyebrows, and eyelashes are brittle, unruly, of variable lengths, easily broken, and generally feel dry. It is important to investigate the proximal parts of hair shafts because the distal portions often show marked weathering that may produce findings similar to TTD.¹⁰³ Macroscopic alterations are observed especially in the frontal and occipital hair, with only microscopic abnormalities detected in the occipital hair.⁴¹ For adequate diagnosis, hairs should be collected from different areas of the scalp and subjected to further light and electron microscopic examination^{27,104} (Table III).

Light microscopy reveals clean transverse fractures through the hair shafts (trichoschisis), and there is an irregular hair surface and diameter.⁶⁸ In addition, a decreased cuticular layer with twisting and a nodal appearance may mimic trichorrhexis nodosa.^{1,64,71,103-105} The distal hair shaft often terminates in “brush breaks.”¹⁰³ The flattened hair shafts tend to fold over like a ribbon or shoelace during microscopic mounting. An abrupt 180° twist of the hair shaft is sometimes observed, mimicking pili torti. Polarizing microscopy with crossed polarizers shows the typical appearance of alternating light and dark bands, giving a “zig-zag” or “tiger-tail” pattern.^{5,6,43,106-108} The term *alternating birefringence* incorrectly describes the phenomenon and has therefore been abandoned. Brusasco and Restano¹⁰⁹ reported the interesting finding that the typical “tiger-tail” pattern of the hair shaft in TTD may not be present at birth. This classical pattern was clearly evident only at 3 months of age in their case. However, hair examination from a 21-week gestation, aborted fetus showed the alternating light and dark banding pattern under polarized light micros-

copy.¹⁰⁵ Within the past few years, it has been shown that “tiger-tail” pattern on polarized hair microscopic examination also may be found in healthy infants, and therefore amino acid analysis that quantitates sulfur, specifically cyst(e)ine levels, remains the definitive test for TTD^{110,111} (Table III). In this regard Garcia-Hernandez and Moreno-Giménez¹¹² have documented alternating dark and white zones within the hair shaft of a young patient who scratched his scalp intensely. Cessation of scratching, topical application of minoxidil 2% solution, and cysteine supplementation resulted in marked improvement within a year. The condition appears sufficiently different by polarizing light microscopy, and this sulfur-deficient hair alteration is referred to as “pseudo tiger-tailing.”

The structural abnormality that causes the interrupted transverse bright lines along the hair shaft is not completely understood. However, Calvieri et al¹¹³ and Rossi et al¹¹⁴ found by x-ray microanalysis an alternating content of sulfur along the long axis of the trichothiodystrophic hair. Image analysis was also used to match the same regions that were examined by polarized microscopy and scanning electron microscopy. The x-ray analysis results also showed that calcium was absent in tracts corresponding to dark bands, whereas it was normally present in light bands.¹¹⁵ Definitive confirmation of these findings is awaited.

Scanning electron microscopy also shows incomplete or absent cuticle and longitudinal grooving.⁶ Transmission electron microscopy from hairs of patients with TTD shows material that resists extraction throughout the cortex.¹¹⁶ Cross-sectional examination of the cuticle in hair shows lack of the exocuticle and A layer. Transmission electron microscopy demonstrates an abnormal arrangement of microfibrils.⁶⁰ Absence of the exocuticle and the sulfur-rich, A layer (outer aspect of the cuticle cell) causes cuticular weathering and weakness of the hair shaft¹¹⁷⁻¹¹⁹ (Table III).

Transmission electron microscopy and gene alterations of skin

Only a few studies on the ultrastructural aspects of the skin in TTD have been undertaken.^{42,120}

These observations focused on a peculiar feature of ichthyotic skin in patients with TTD. In both patients, notable findings were similar and showed perinuclear vacuoles within unit membranes of keratinocytes and dispersed, irregularly arranged bundles of tonofilaments, particularly at the desmosome junction. The authors concluded that the abnormalities of tonofilaments could be explained by the generalized abnormality in sulfur-containing proteins, including disruption in the synthesis of keratins.

Analysis of gene expression in the TTD mouse model (see "Transgenic and Knockout Mice," page 910) has demonstrated that at least the cutaneous changes, such as acanthosis and hyperkeratosis, are associated with reduced transcription of the skin-specific, differentiation-related gene *SPRR2*, a member of the small *proline-rich* protein (SPRR) family expressed in epidermis.¹²¹ The *SPRR2* gene encodes a structural component of the cornified envelope and is expressed in the final stage of terminal differentiation.^{122,123} Reduced *SPRR2* expression in TTD skin reflects defective gene transcription in late stages of terminally differentiating epidermal keratinocytes.¹²⁴

Biochemical changes of hair shaft

The mammalian hair follicle develops embryologically from the surface ectoderm and epidermis.¹²⁵ The hair shaft is composed anatomically of the cuticle, cortex, and medulla. Hair is composed of two major structural protein families contained within the cortex predominantly, the keratins and keratin-associated proteins (KAPs), which are further classified into multiple (at least 11) subfamilies¹²⁶ (Table IV). The keratin intermediate filament proteins and KAPs form the cuticle and cortex of the hair shaft.¹²⁷ Keratin intermediate filaments belong to the superfamily of proteins that form 8- to 10-nm filaments in the cytoplasm of many epithelial cell types. Based on the amino acid composition, keratin intermediate filament proteins are classified as acidic or basic-neutral types.¹²⁶ KAPs are divided into two groups, cyst(e)ine-rich and glycine-tyrosine-rich polypeptides, according to the amino acid composition of these proteins. Cyst(e)ine-rich KAPs contain high-sulfur (15%-30%) proteins (KAP1-3 or HSps), and ultra-high-sulfur proteins (KAPs 4 and 5 or UHSp) are composed of more than 30% cyst(e)ine residues.¹²⁸ Other members of the KAP family as well as trichohyalin and other proteins of the hair shaft are continuing to be identified and characterized. Powell and Rogers¹²⁶ have proposed a comprehensive classification scheme for hair proteins.

Total hair sulfur values were reported as early as 1806 by Vauquelin. Kutner, Miller, and Brown²⁹ per-

Table IV. Constituent proteins of the hair shaft

Keratin or intermediate filament (KRT or IF)
KRT 1.1-1.9, type I-(acidic)—human hair "acidic" (hHa) types
KRT 2.9-2.17, type II-(basic)—human hair "basic-neutral" (hHb) types
Keratin- or IF-associated proteins (KRTAP/KAP or IFAPs)
Cysteine-rich group (cys-KAPs)
High sulfur
KAP 1 (B2) family
KAP 2 (BIIIA) family
KAP 3 (BIIIB) family
Ultra-high sulfur
KAP 4 family
KAP 5 family
Cuticle
KAP 10 family
Glycine/tyrosine-rich group (gly/tyr-KAPs)
KAP 6 (type II) family
KAP 7 (type I C2) family
KAP 8 (type I F) family
Other proteins
KAP 9 (mouse ultra-high sulfur) family
KAP 11.1 (novel mouse hair protein)
Medulla proteins
Trichohyalin
Calcyclin
Involucrin

Modified from Powell and Rogers¹²⁶ and Bertolino and O'Guin.²⁴³

formed a systematic analysis of hair sulfur content in numerous hair shaft disorders, and they compared the results with many controls. To date, TTD is the only disease entity in which a marked decrease of sulfur content of hair composes part of the diagnostic criteria.

Amino acid analysis of hair shows a cyst(e)ine and high-sulfur protein content that is much lower than normal. In particular, the cyst(e)ine-rich proteins of TTD have lost the large heterogeneous KAP4-5 or UHSp group and at least 8 major KAP 1-3/HSps components.¹²⁸ As a rule, hair of patients with TTD shows at least a 50% decrease in cyst(e)ine and sulfur content. Often, more marked decrease to less than 10% of the normal value is found. Urine and serum levels of these amino acid constituents usually are normal, but the nails may also show a decrease in cyst(e)ine and sulfur content.¹ Frequently, serine, threonine, and proline are also reduced; these amino acids are components of the KAP 1,2,3.^{41,44,95} A concomitant, related increase in aspartic acid, methionine, phenylalanine, alanine, leucine, and lysine may be found.¹²⁹ The low-sulfur protein components of hair in patients with TTD appear to be almost identical to that of normal control subjects,

but occasionally they are higher than normal.¹³⁰ The KAP 1-3/HSps are altered qualitatively, and, moreover, the KAP4-5/UHSps are severely decreased.¹³¹ One-dimensional electrophoresis analysis by sodium dodecyl sulfate–polyacrylamide gel electrophoresis followed by fluorography shows that levels of high-molecular-weight basic-neutral keratins are generally preserved among hair diseases when compared with their acidic keratin partners and to KAP 1-3/HSps and KAP 4-5/UHSps.

Hairs in TTD are characterized by loss of the large heterogeneous KAP 4-5/UHSp group including the 33- and 42-kd proteins and at least 8 major KAP 1-3/HSp components. The expression of the 54-kd type 1 keratin and the 38-kd KAP 1-3/HSp varies among patients with TTD.¹³² These findings provide evidence for the concept of heterogeneity of TTD. Gillespie, Marshall, and Rogers¹³³ observed in their analysis of hair by two-dimensional protein electrophoresis that the pattern of KAP 1-3/HSp and KAP 4-5/UHSp in TTD differed from normal controls but also among individual patients.

The typical brittleness of TTD hair likely results from a reduction in the content of the hair-specific cyst(e)ine-rich proteins, KAP 1-3/HSps, and KAP 4-5/UHSps that fill the spaces within the matrix. The assembling keratin filaments form the microfibrils, and the high proportion of cysteine residues, ranging from 15 to 70 or more, in the KAPs likely promote formation of multiple covalent disulfide bonds within and between these proteins. De Berker, Tolmie, and Dawber¹¹⁰ concluded that the intrinsic defect is due to failure of incorporation of sulfur-rich protein into the cuticle and matrix of the hair cortex. KAP 1-3/HSps and KAP 4-5/UHSps can be modified quantitatively or qualitatively as in a TTD variant defined by Van Neste et al.¹³⁰ This contrasts with the qualitative *and* quantitative alterations observed in classic TTD. Van Neste et al.¹²⁹ and De Brouwer et al.¹³⁴ showed that the amino acid composition of hairs collected from a patient with a TTD variant was preserved when follicles had been grafted and maintained up to 6 months on nude mice. The persistence of disease-specific abnormalities within the hair shaft indicates that the TTD-variant mutation is constitutively expressed within the hair follicle unit and is independent of host-related factors.

Deficiency in cyst(e)ine residues and decrease in the fraction of KAP 4-5/UHSp of the matrix are consistent abnormalities within the hair shaft of TTD. In addition to the abnormal low-sulfur distribution in the cortex, sulfur deficiency has also been localized to the cuticle cells. In cuticle cells from TTD hair, the exocuticle appears less dense and the A layer is absent or greatly reduced in thickness.¹¹⁶ These

changes seem to reduce the mechanical strength of the cuticle cells. Cuticle is lost, and the cortex becomes vulnerable to weathering. Hair color, however, appears to be unaffected. In the future it would be worthwhile to analyze sulfur content in the hair of patients with XP and CS, although clinically they do not feature marked brittleness of hair shafts.

PRENATAL DIAGNOSIS

Selected types of TTD manifest significantly more severe and potentially lethal phenotypes. In these cases, prenatal diagnosis and therapeutic abortion or other interventions have been considered. Approximately 50% of patients with TTD show photosensitivity and reduced DNA repair levels similar to those found in XP.¹³⁵ Under these circumstances, prenatal diagnosis based on measurement of DNA repair in trophoblasts or amniotic cells and subsequent confirmation by microscopic analysis of fetal hairs has been performed.^{76,105,136,137} Examination of hair by polarized light microscopy of an aborted fetus demonstrated the alternating light and dark bands typically seen in TTD.¹⁰⁵ The conventional procedure to assay unscheduled DNA synthesis requires 4 to 5 weeks and is labor intensive. Alapetite et al.¹³⁸ recently proposed the more rapid, yet sensitive comet assay as a DNA repair test for prenatal diagnosis of TTD. This examination can be performed as a single-cell gel electrophoresis assay that typically provides a result within 24 hours and avoids radioactive substances.

CELLULAR AND MOLECULAR GENETIC CHARACTERISTICS OF TTD

On treatment with DNA-damaging agents, it is possible to detect and further characterize cellular abnormalities linked to nucleotide excision repair (NER) defects with the use of end points such as reduced levels of DNA repair synthesis, decreased cell survival, decreased rates of DNA and RNA synthesis, and increased mutability.¹³⁹ Cells from patients with NER defects are usually assigned to a designated complementation group by means of the somatic cell fusion assay that measures the level of unscheduled (separate from the S phase of the cell cycle where DNA replication occurs) DNA synthesis (UDS) after UV irradiation of fused heterokaryons. Cell fusion studies or expressed, cloned excision repair genes after microinjection^{140,141} or retroviral infection¹⁴² have disclosed genetic heterogeneity among patients with defective NER. Although there is considerable molecular-genetic overlap among DNA repair-deficient patients (Fig 3), clinical features may differ dramatically.¹⁴³ A major discovery in advancing the understanding of the genetics of TTD

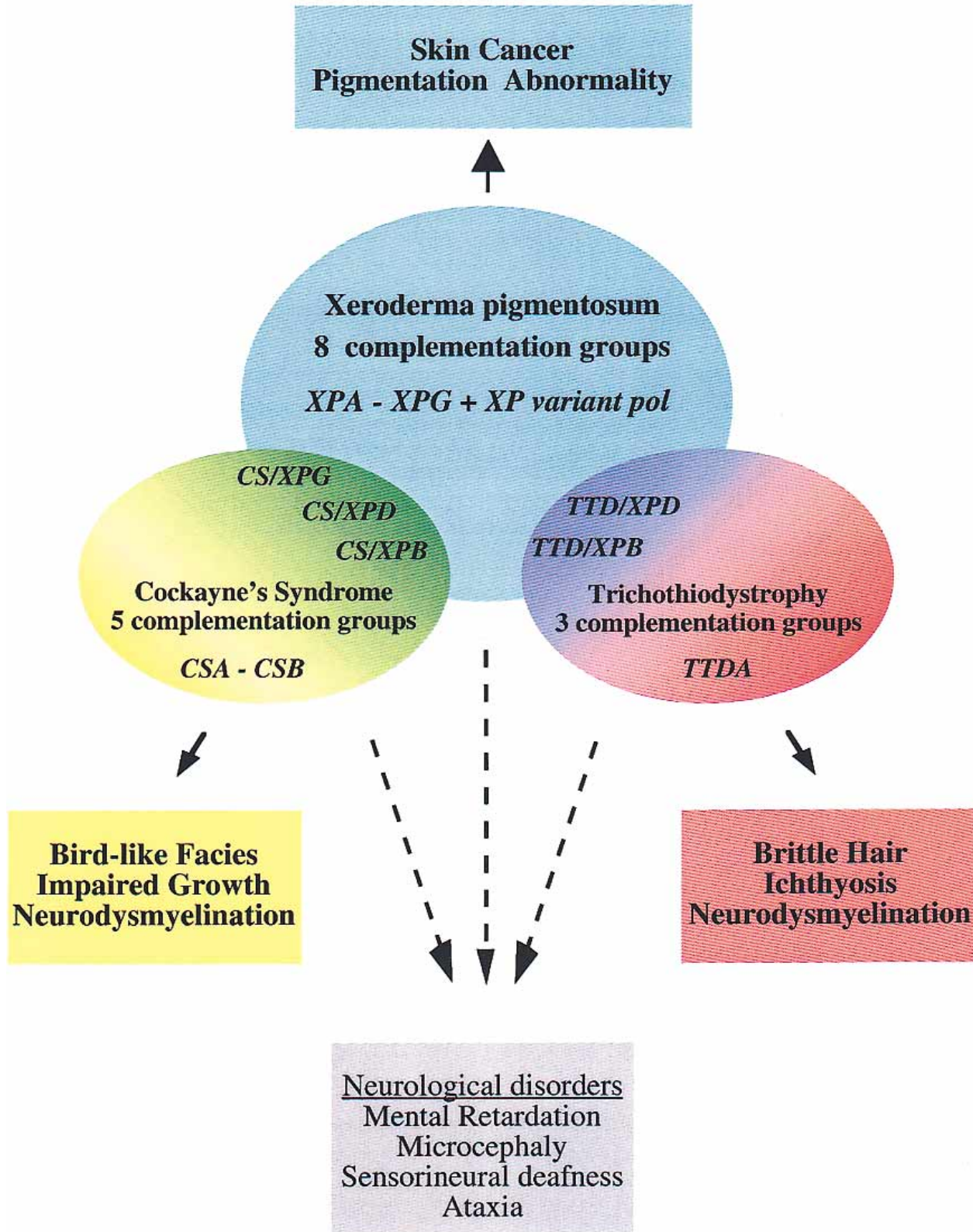


Fig 3. Clinical and genetic heterogeneity in patients with XP, CS, and TTD. The genetic heterogeneity between the 3 diseases is shown by the overlap between XP and XP/CS due to mutation on the *XPB*, *XPD*, or *XPG* genes and between XP and TTD due to mutation on the *XPB* or *XPD* genes.

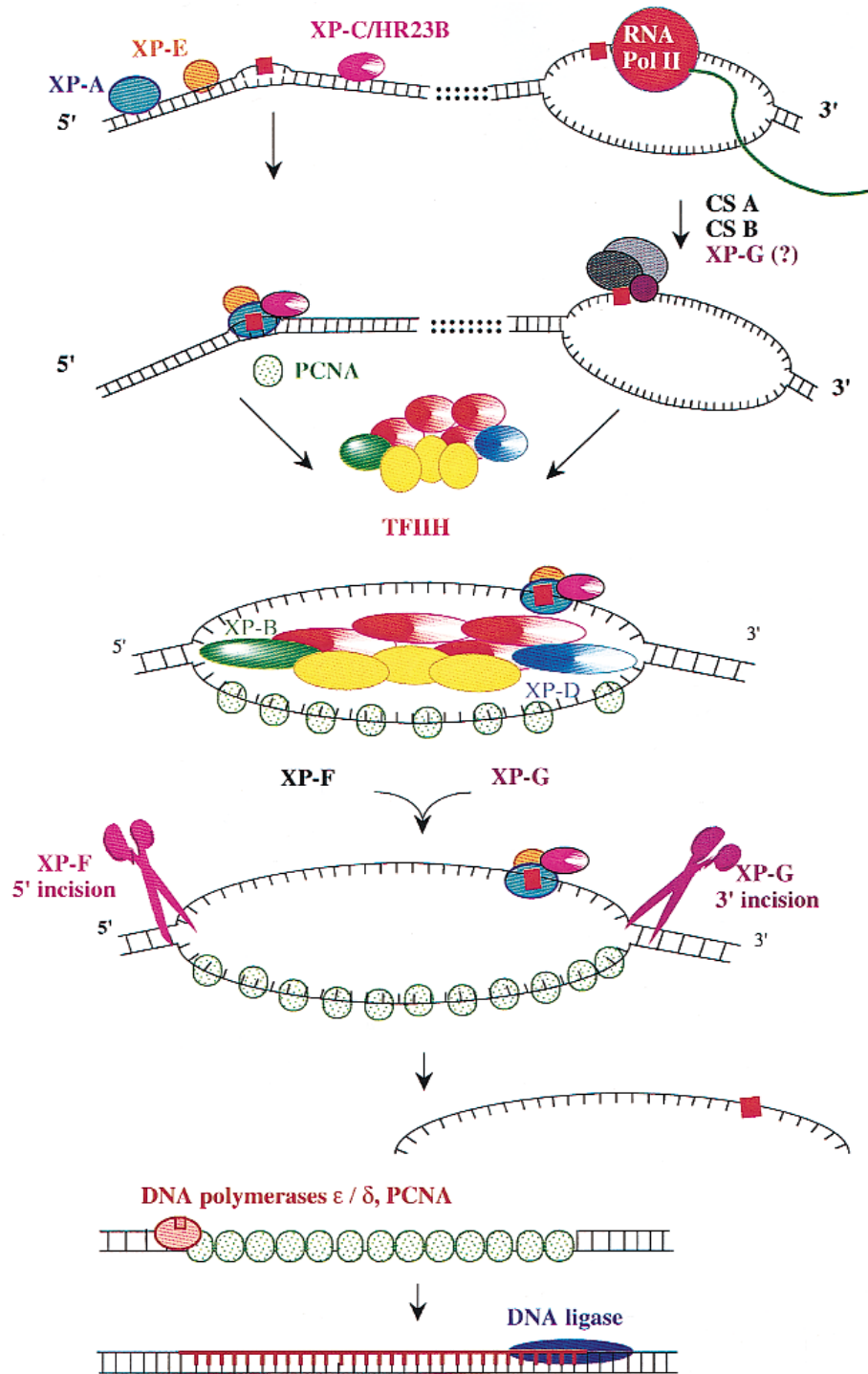


Fig 4. Model of the global genomic repair (GGR, *left part*) and transcription-coupled repair (TCR, *right part*) of UV-induced DNA lesions. The complex XP-C/HR23B is the first factor in GGR only to bind DNA lesions and to attract XPA, RPA (ssDNA binding protein) and then TFIIH. The XPE protein seems to facilitate the identification of lesions, which are poorly recognized by the XPC/H23R complex (such as the CPD). Demarcation of the lesions is carried out by the two helicase activities (XPB and XPD) of TFIIH followed by sequential cleavage by the two structure-specific nucleases XPG (on 3' side) and ERCC1-XPF (on 5' side). After removal of an oligonucleotide (27-30 nucleotides long) containing the lesion, DNA synthesis occurs using either polymerase δ or ϵ in presence of PCNA and RF-C complexes as processivity factors. The final NER step is ligation of the newly synthesized DNA patch to parental DNA probably by DNA ligase I. On damaged templates, RNA polymerase II is blocked by bulky lesions inducing a signal for TCR (*right part*). The proteins CSA, CSB, and possibly XPG and TFIIH displace the stalled RNA pol II from the lesion, which becomes accessible for further repair in the same way as for GGR.

Table V. Laboratory comparison of XP, CS, and TTD complementation groups

Complementation group	UV sensitivity	Residual UDS	TCR*	GGR*	Overlap with other nucleotide excision syndromes
TTD-A	+	15%	+(?) [†]	+	—
XP-A	++	<5%	+	+	—
XP-B	++	<10%	+	+	CS, [‡] PIBIDS
XP-C	+	15%-30%	—	+	—
XP-D	++	15%-50%	+	+	CS, [‡] PIBIDS
XP-E	+/-	>50%	?	?	—
XP-F	+	15%-30%	+	+	—
XP-G	++	<10%	+	+	CS [‡]
CS-A	+	WT	+	—	—
CS-B	+	WT	+	—	—

Adapted from Hoeijmakers JHJ. *Eur J Cancer* 1994;30A:1913.

WT, Wild type (control level).

*+, Wild type; -, defect; +/-, minimal; +, present; ++, marked.

[†]XP/CS complex.

[‡]Decreased intracellular TFIIH.

syndromes was the demonstration that fibroblasts of some patients with TTD were genetically similar to those isolated from patients with XP belonging to the D group.¹⁴⁴ Because patients with XP were known to be deficient in DNA repair, it was then hypothesized that the cells from patients with TTD were also DNA repair deficient.

General aspect of the NER pathway

NER is critical in all organisms to protect the genome against injury by numerous mutagenic and carcinogenic agents.^{145,146} A complex-overlapping network of enzymatic pathways for DNA repair has evolved to minimize genetic instability and initiation of carcinogenesis.¹⁴⁷ Approximately 30 gene products are involved in this intricate protective mechanism.¹⁴⁸ This NER system eliminates structural lesions that range from UV-induced photoproducts to chemical-produced adducts and intrastrand crosslinks. A series of steps is involved in the NER complex including recognition of the DNA lesion, removal of the damaged oligonucleotide, gap filling by DNA synthesis, and ligation (Fig 4). In addition, NER mechanisms can also recognize small oxidative adducts, as shown by Le Page et al^{149,150} and Leadon,¹⁵¹ that may be involved in the progressive neurologic deterioration of some patients (Tables V and VI).

The link between DNA repair and transcription

There is growing evidence that damage produced by UV is repaired more rapidly in transcriptionally active DNA than in the genome as a whole.¹⁵² This preferential repair mechanism has been shown to be

due to accelerated repair of damage in the transcribed strand versus the nontranscribed strand of DNA because of the blockage of the RNA polymerase II at the site of the lesion, giving rise to a signal for rapid removal. Indeed, for a subset of DNA lesions, two overlapping pathways have been identified in the NER process. One pathway is the more rapid transcription-coupled repair (TCR) of expressed genes, targeted to the transcribed strand of DNA, and the other is the slower, global genome repair (GGR) of DNA, which includes repair of the nontranscribed strand of potentially expressed genes, as well as the inactive chromatin (Fig 4).

The predominant types of UV-induced lesions are cyclobutane pyrimidine dimers (CPD) and pyrimidine (6-4) pyrimidone photoproducts (6-4 PP), both removed by NER. In all classic XP cells, repair of both lesions is defective in all parts of the genome, except the XP group C cells that are fully proficient in the TCR of these adducts. The XPC protein is therefore not necessary for TCR because the signal for the presence of lesions is probably given by the stalled polymerase. By contrast, cells from patients with CS are able to remove these lesions in all parts of the genome except those located on transcribed strands.¹⁵² The CSA and CSB proteins, which are mutated in most patients with CS, are thought to allow the removal of the stalled polymerase in such a way that the lesion becomes accessible to repair enzymes.¹⁴⁶ Eveno et al¹⁵³ have shown that repair of CPD was significantly reduced in all TTD cell lines (at a similar level as in XP cells), whereas almost normal repair of 6-4 PP was found in most TTD lines except for some specific patients in whom the efficiency was

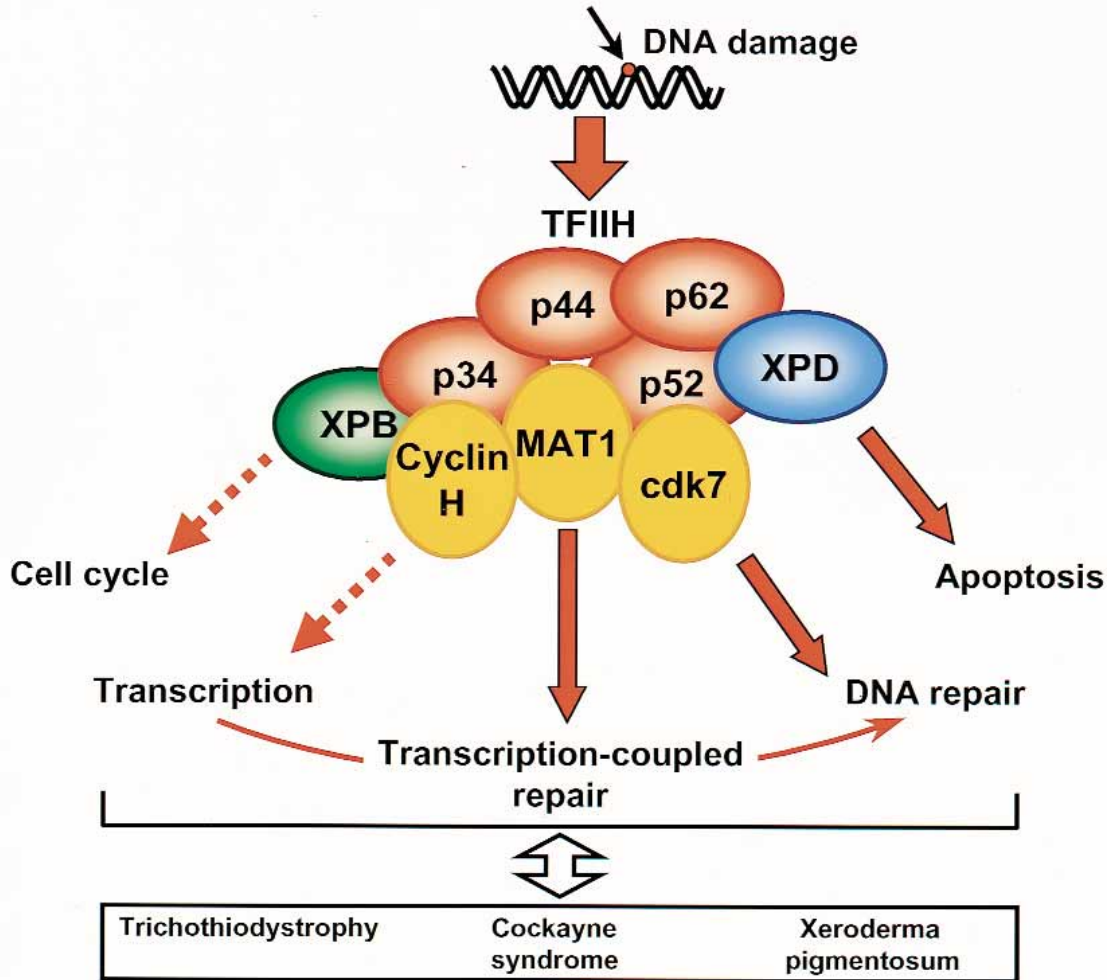


Fig 5. Diagram of TFIIH complex as it inhibits cell cycle progression and transcription but induces TCR, DNA repair, or apoptosis occurring after genome damage. TTD, CS, or XP are the consequence of TFIIH malfunction. (Adapted from Moustacchi E, coordinator. DNA repair. *Biochimie* 1999;81:1-181.)

less than normal (see "Cellular responses in TTD," page 908).

The relationship between DNA repair and transcription became obvious when Schaeffer et al^{154,155} studied the protein structure of one of the major transcription factors, TFIIH. TFIIH is a large complex of 9 proteins involved in the last step of the initiation of transcription, as well as in the regulation of the cell cycle through its cyclin kinase activity and in the NER pathway because of the presence of the XPB and XPD proteins with helicase activities. The multiprotein complex is composed of subunits ranging in size from 32- to 89-kd (Fig 5). Two main components, the core-TFIIH subcomplex containing the XPB-p89 subunit and the subcomplex containing the kinase activity (cdk7, MAT1, and cyclin H) are associated with the XPD

(80 kd) subunit. The TFIIH complex regulates transcription and the cell cycle under basal conditions, but also coordinates TCR, DNA repair, or apoptosis when DNA damage is induced by UV.

The XPB helicase is absolutely required for transcription initiation, whereas the XPD helicase is dispensable but stimulates transcription by helping XPB in promoter opening.^{156,157} Therefore TFIIH is thought to unwind the DNA to allow promoter clearance at the site of transcription initiation and at the damage site during NER. The binding of wild-type p53 protein to XPD or XPB proteins inhibits the helicase activities of purified TFIIH *in vitro*.¹⁵⁸

The dual role of TFIIH in transcription and repair has led to the hypothesis that some of the DNA repair-deficient patients could also be partially affected in their transcription efficiency.¹⁵⁹ The same gene

defect can result in apparently identical cellular phenotypes related to DNA repair deficiency, yet gives rise to completely different clinical features. Mutation in one of the two DNA repair genes in TFIIH may lead to 3 different human disorders: the skin cancer-prone syndrome, XP, and TTD- or CS-associated or not with XP in the same patient¹⁵² (Fig 3). In addition to sun sensitivity (for a fraction of patients with TTD or CS), all these syndromes include neurologic abnormalities associated with nerve dysmyelination and severe growth retardation. TTD and CS could well be part of an enlarging group of heterogeneous disorders classified as transcription diseases¹⁵⁹ (see "TTD as a Transcription Disease," page 911).

Genetic classification of trichothiodystrophy

Patients with TTD can be categorized in two major groups: (1) the nonphotosensitive and defect-free in excision repair of UV damage and (2) the photosensitive with NER defect. In the first group, no gene has been isolated yet, because of the lack of a screening assay to isolate the gene(s). In the second group, 3 complementation groups have been determined. The major one, representing about 95% of the photosensitive patients, is due to mutations within the *XPD* gene.¹⁴⁴ Two patients have mutations of the *XPB* gene^{106,160} and one patient has a mutation of a yet-unknown gene, called *TTD-A*.¹⁶¹ Furthermore, to date not all mutations have been identified in the photosensitive TTD group.

The *XPD* gene and TTD. The DNA repair gene, *ERCC2* (according to the former nomenclature), has been identified as the gene mutated in XPD. A set of rodent mutants has been valuable as a template for the isolation of human NER genes that correct DNA repair defects; one such gene is termed *ERCC2* for excision repair cross-complementing, with the numeral 2 referring to the rodent complementation group. The human *ERCC2* gene homologue (*XPD*) maps to the long arm of human chromosome 19 within a region containing several other genes involved in DNA repair and metabolism. *XPD* is located on 19q13.2-q13.3 and within 2 megabases of the *XRCC1* locus. In the human, the *XPD* gene is transcribed from centromere to telomere, in the same orientation as the nearby *ERCC1* gene.¹⁶² The *XPD* gene is composed of 23 exons with a genomic distance of 18.9 kb and encodes a 760 amino acid protein with adenosine triphosphate-dependent DNA 5'-3' helicase activity.¹⁶³ The *XPD* gene is highly conserved over evolution, with the order and orientation of at least 3 genes preserved within the mammalian lineage of this linkage group. After transfer by microinjection or retroviral transduction into

cells from patients with XPD or with photosensitive TTD, respectively, wild-type *XPD* gene was found to restore normal UV sensitivity and DNA repair to cells as well as provide partial resistance to UV-induced mutagenesis.^{141,164}

Weeda et al¹⁶⁵ proposed that the *XPD* helicase unwinds the DNA in the vicinity of a lesion in the opposite direction to the *XPB* helicase. As already described, this protein is involved in TCR, being an integral member of the basal transcription factor TFIIH complex.^{154,155} Two patients with specific mutations on the *XPD* gene also exhibit CS, reinforcing the relationship between repair and transcription deficiencies.^{166,167}

Nucleotide sequence analysis of the *XPD* complementary DNA (cDNA) from TTD cell strains revealed mutations within the coding sequence, and particularly in highly conserved regions within previously identified helicase functional domains. To date, 47 mutations have been characterized in patients with XPD or XPD/CS and 45 mutations in patients with TTD (see Fig 6, A).^{57,143,168-171} These mutations are mostly point mutations leading to a single amino acid change located mainly in the C-terminal part of the protein. The various clinical presentations and DNA repair characteristics of the cell strains should be, in theory, correlated with the particular mutations found in the *XPD* locus. However, because these repair-deficient diseases are transmitted as a recessive trait, the two alleles of the same gene have to be mutated. In approximately 50% of cases, the sequenced *XPD* genes in patients with TTD revealed compound heterozygotes (Fig 6, A). In such cases, it is plausible that the phenotype is defined by the residual activity of the less severe of the two alleles. Therefore it was essential to determine which mutated allele was responsible for the clinical presentation. Taylor et al¹⁷² examined the phenotype in the haploid state using the eukaryotic yeast model *Schizosaccharomyces pombe rad 15* for most of the homologues of *XPD* mutations found in patients with TTD and in those with XP to determine the null and the functional alleles. By extrapolation, they could deduce the human mutations directly responsible for a given phenotype and exclude the mutations that were nonviable in the yeast system (Fig 6). Analysis of Fig 6, B reveals that most causative mutations are clustered in the C-terminal fourth of the protein with the exception of a TTD hotspot close to the N-terminus. All the mutations are specific for either TTD or XP (in contrast to the mutations presented in Fig 6, A where null alleles were found in common between TTD and XP cells). Sixty percent of causative mutations for XP are located at the Arg683 hotspot, whereas 50% of TTD mutations are

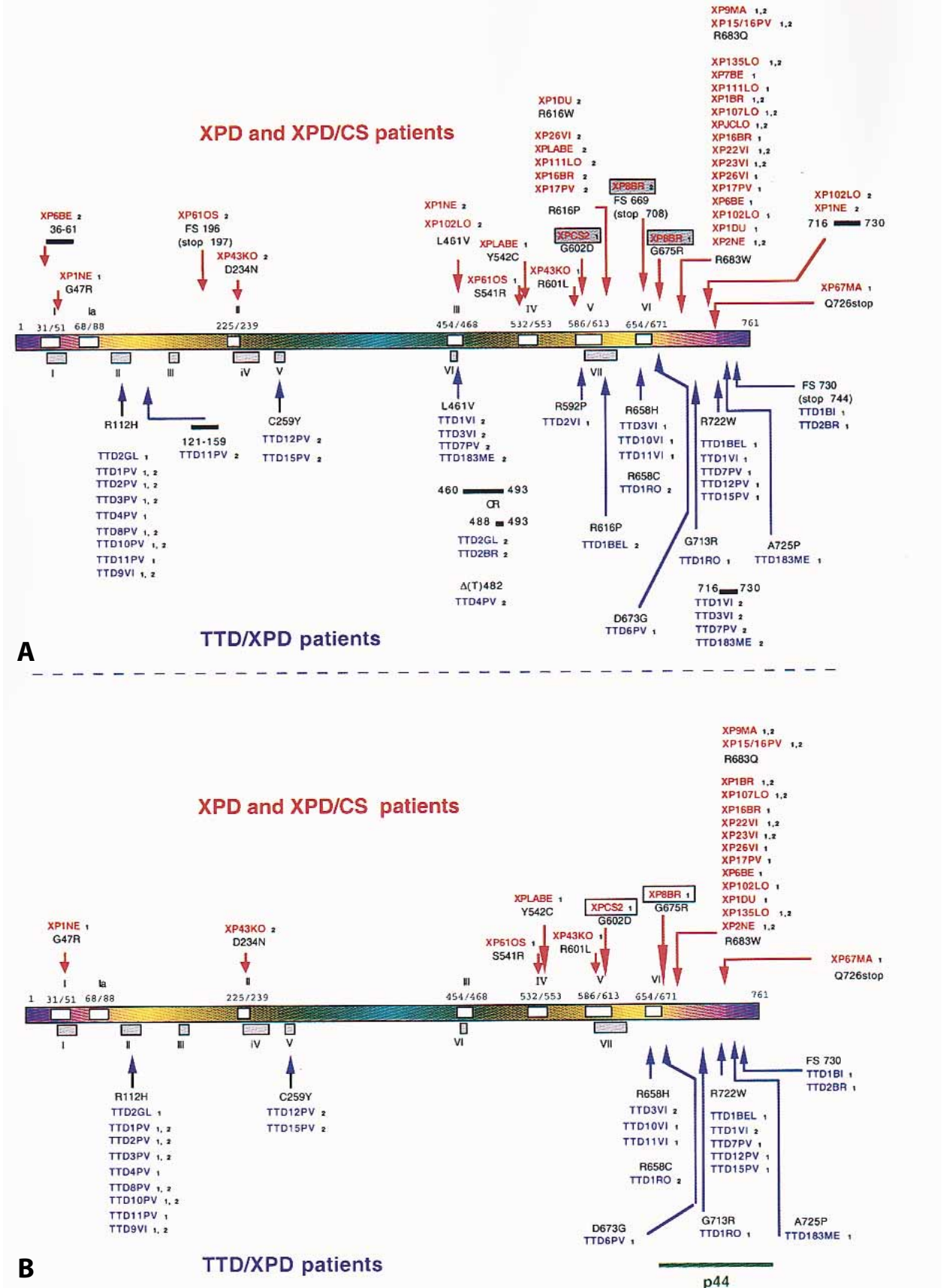


Fig 6. See legend on facing page.

Table VI. Main clinical findings of NER syndromes

Clinical symptoms	XP	XP/CS	CS	TTD
Photosensitivity	++	++	+	+
Skin cancer	++	+	-	-
Progressive mental degeneration	+/- [†]	+	+	+
Neuronal loss	+/- [†]	-	-	-
Neurodysmyelination	-	++	+	+
Thin facies	-	+	+	+
Growth defect	+/- [†]	+	+	+
Hypogonadism	+/-	+	+	+
Brittle hair and nails	-	-	-	+
Ichthyosis	-	-	-	+

Modified from The Metabolic and Molecular Bases of Inherited Diseases, CD-ROM version. New York: McGraw-Hill; 1996.

-, Absent; +/-, minimal; +, present; ++, marked.

*Patients with TTD and CS may have no photosensitivity and NER defect.

[†]Neurologic and growth defects characteristic of XP patients with DeSanctis-Cacchione syndrome.

located at the Arg112 hotspot. The other TTD mutations are localized in the C-terminal region at 6 different, but closely linked, positions (Fig 6, B).

By reconstituting a functionally active TFIIH with recombinant polypeptides, Coin et al¹⁷³ showed that the XPD helicase activity was strongly stimulated by the interaction with the p44 subunit, inside the transcription complex. This interaction occurs within the C-terminal domain of XPD and the mutations found in this part in patients with TTD or XPD do not abolish the helicase activity per se but prevent the interaction and therefore the stimulation by p44 of the helicase activity. This low helicase activity is responsible for the NER defect in these patients.^{173,174}

The XPB gene and TTD. The *ERCC3* gene has been isolated as the gene mutated in group 3 of DNA repair-deficient rodent cells. The human homologue, *XPB*, was able to complement the cells isolated from patients with XP group B.¹⁷⁵ This gene is located on chromosome 2q21 and encodes 782 amino acids with a 3'-5' helicase activity. The helicase unwinds the DNA at the lesion in parallel with the XPD protein, both present in the TFIIH complex.^{154,176}

Only 5 patients are known to harbor mutations within this gene (Fig 7), indicating clearly that the protein is absolutely necessary for viability, as confirmed by knock-out animals which are nonviable.^{121,124} Any mutation that destroys the transcrip-

tional activity of TFIIH will be lethal because, in contrast to XPD, XPB plays a crucial role in TFIIH activity. Among these patients, 3 have both XP and CS. Coin et al¹⁷⁴ demonstrated that mutations in these patients had decreased transcriptional activity of the corresponding purified TFIIH because of promoter opening blockade. One patient, initially described in 1980 and now in his twenties, has the typical signs and symptoms of TTD, with sensitivity to sunlight since early childhood.¹⁰⁶ His clinical features are quite distinct from those associated with XP. There is no significant freckling or other pigmentary changes and no development of malignant skin tumors.¹⁴³ A new NER gene associated with this TTD patient has been identified and shown to be the gene involved in XP group B.¹⁶⁰ Another sibling showed the same defect (Fig 7).

Riou et al¹⁷⁷ examined the relative expression of mutated *XPB* genes that are associated with either the XP/CS or TTD cellular phenotypes. They isolated 3 cDNA clones that specifically express the *XPB-A355C* (TTD) allele or the *XPB-T296C* (XP/CS) allele or both. Expression of the TTD mutated allele in XP/CS cells gives rise to a cellular phenotype of increased excision repair and cell survival, whereas equivalent coexpression of the two mutated genes leads to an intermediate cellular phenotype between XP/CS and TTD. This result demonstrates clearly the

Fig 6. Mutations in the *XPD* gene found in patients with TTD, XP, and XP/CS. The XPD protein (761 amino acids) contains 7 domains DNA/DNA helicase (indicated by the number of amino acids involved) and 7 domains of DNA/RNA helicase (indicated in *gray-shaded boxes* below the protein). The mutations are indicated as the number and the type of the amino acid change. Mutations above the XPD protein correspond to XP patients (the XP/CS mutations are boxed) and below the XPD protein correspond to TTD patients. *FS* = frameshift and *dotted line* indicates deletion. The different mutated alleles in the same patient are indicated with numbers 1 and 2. **A**, All the XPD mutations found in the two classes of patients are indicated. **B**, Only causative mutations are indicated according to Taylor et al¹⁷² and Botta et al.⁵⁷ The interaction domain between the XPD helicase and the p44 protein inside the TFIIH factor is indicated according to Coin et al.^{173,174}

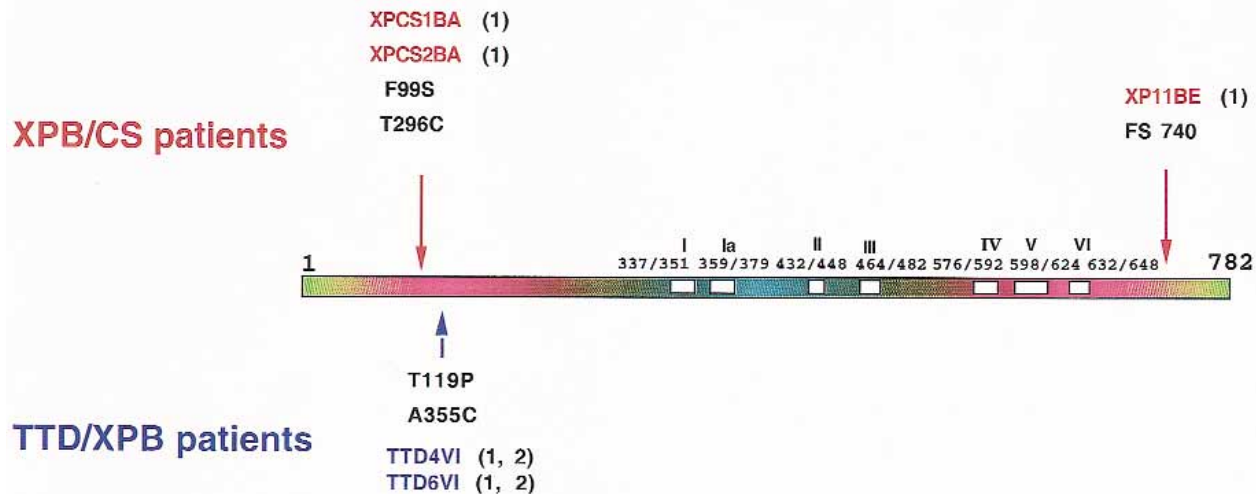


Fig 7. Mutations in the *XPB* gene found in patients with TTD and XP/CS. The *XPB* protein (782 amino acids) contains 7 domains of DNA/DNA helicases. Mutations in 3 different XPB/CS and 2 TTD patients are indicated by the numbers of the modified nucleotide as well as the modified amino acids. *FS* corresponds to frameshift.

essential role of gene dosage in the clinical and cellular expression of these syndromes, as also suggested with the *XPD* mutations.

TTD-A and TTD.¹⁶¹ A new patient was described in 1982⁴⁰ with characteristic hair shaft abnormalities, ichthyosis, sun sensitivity, and severe growth retardation. Fibroblasts from this TTD1BR patient exhibit low survival and low UDS after UV irradiation. These cells were able to complement all known XP complementation groups, thereby indicating that it represented a new excision repair group.¹⁶¹ Micro-needle injection of purified wild-type TFIIH factor in these cells was able to complement the repair defect. Surprisingly, none of the TFIIH subunits carried a mutation, and the TFIIH factor from TTD-A cells was normally active. Immunoblot and immunofluorescence analysis has revealed a strong reduction in the intracellular TFIIH concentration. The sublimiting amounts of TFIIH mainly affect its repair function but essentially spare general transcription.¹⁷⁸

An additional patient (XP38BR) has been described recently by the group of Lehmann (manuscript submitted for publication to *Am J Hum Genet*) manifesting XP associated with some TTD features. According to the types of mutations within the *XPD* gene that possess specificity for either XP or TTD, a "TTD mutation" in one allele and an "XPD mutation" in the other allele could be envisioned. In this case, the clinical symptoms will depend on the gene dosage between the two alleles. XP38BR may represent this possibility.

Cellular responses in TTD. All cultured cells isolated from photosensitive patients with TTD are sen-

sitive to the cidal effects of UVC or UVB irradiation and present a reduced level of DNA repair synthesis compared with the heterozygote parent or normal cells. These two cellular characteristics allowed us to propose prenatal diagnosis of these syndromes.¹⁰⁵ The cellular responses to UV irradiation are remarkably heterogeneous among the various TTD cell lines. Some TTD lines mutated on the *XPD* or *TTD-A* genes exhibit a very low survival and UDS level after irradiation, whereas other *XPD*- or *XPB*-mutated TTD cells presented a smaller reduction in UDS level and a better cell survival after UV.¹⁷⁹ These variations are presumably linked to the extent of repair of CPD and 6-4 PP in these various cells.^{153,180}

The cellular sensitivity to UV irradiation is largely dependent on the position of the functional mutation^{181,182} (Fig 6, A). There is no correlation between the severity of DNA repair deficiency and the clinical symptoms. The R112H hotspot, found in almost 30% of patients with TTD, is associated with a drastic reduced level of DNA repair but with moderate clinical features and no cancer sensitivity.⁵⁷ Botta et al⁵⁷ concluded that the severity of the clinical features might be linked to the gene dosage between the two different mutated *XPD* alleles. The most severe clinical features are observed in patients with TTD who appear to be hemizygous for the mutated allele. This result implies that the transcriptional efficiency of the mutated TFIIH in TTD could be more important for the clinical features than the DNA repair level itself.

Cultured TTD fibroblasts exhibit a high mutation frequency after UV irradiation.¹⁸³⁻¹⁸⁵ Madzak et al¹⁸³ and Marionnet et al¹⁸⁴ documented that the fre-

Table VII. Similarities and differences between XPD and TTD/XPD cells after UV irradiation

Cellular response	XPD cells	TTD/XPD cells*
UV survival	Very low	Low
UDS	20%-40%	15%-30%
Mutation frequency	High	High
Spectrum of base substitutions	Different from WT	WT
Repair of CPD	Low	Low
Repair of 6-4 PP	Low	WT [†]
p53 Responses	Low UV dose	Low UV dose
UV-apoptosis induction	Low UV dose	Medium UV dose
Catalase activity	Low	WT
Induction of ICAM-1	Low	WT [†]

WT, Wild type.

*For photosensitive patients.

[†]The TTD cells mutated at the site R112H are closer to the XPD cell responses than the other TTD cells.

quency of mutations in TTD and XP cells are similar and therefore high levels of UV-induced mutations are not always directly related to a predisposition to cancer. In TTD cells, there are more rearrangements than in either repair-proficient or XP-D cell lines. It has been speculated that the consequences of UV-induced mutations in TTD cells could be deleterious for essential genes, resulting in cell death rather than mutation propagation and tumorigenesis.¹⁸⁴ Outside the frequency of gene rearrangements, the types of substitutions are closer to that observed in normal cells than that of XPD cells, indicating that the mutagenesis pathway in TTD is similar to normal cells. However, the absence of repair of CPD (at least) produced a higher rate of mutations.

Otto et al¹⁸⁶ have recently shown differential responses of primary (nontransformed) fibroblasts and keratinocytes from normal and DNA repair-deficient patients toward UVA and UVB. The same dose of UVB (1000 J/m²) induced twice as many DNA lesions in normal fibroblasts compared with normal keratinocytes. UV survival, determined by clonal analysis, was consistently higher in keratinocytes than in fibroblasts. Normal and TTD keratinocytes survived better after UVA and UVB irradiation than keratinocyte cells from patients with XP type C or D. Furthermore, the authors showed that UV irradiation resulted in a transition from proliferative to abortive colonies. This transition, which varied between donors, could reflect a natural protection against UV-induced tumorigenesis. This process was, in part, inversely correlated to the patient's predisposition to cancer.¹⁸⁶

Variable results have been reported for the efficiency of repair of specific UV-induced DNA lesions in TTD versus XP and normal cells.^{153,168,180,185} Basically, however, TTD cells are able to repair almost normally the 6-4 PP but are deficient in the repair of CPD,

whereas the XPD cells are deficient in both repair mechanisms. The level of repair varies according to the site of mutations in the *XPD* gene. For example, cells mutated at the R722W position are virtually "wild type" for the 6-4 PP repair, whereas cells homozygous at the hotspot R112H have a repair deficiency approximating the XPD cells.¹⁶⁸ This finding explains why cells from patients with TTD have only a mild defect in survival after UV irradiation, whereas the XPD lines are very UV sensitive. CPD and 6-4 PP are repaired in a rapid and complete fashion by the TCR machinery in the transcribed strand of active genes. Elsewhere in the genome, repair by GGR is slower and less efficient.¹⁵² Dumaz et al¹⁸⁷ have shown that accumulation of the p53 tumor suppressor gene product is markedly enhanced after UV radiation in cells of XP as well as in TTD and CS. p53 is stabilized with a much lower amount of UV in TTD, CS, and XPD cells versus normal cells and for a much longer time (3-4 days instead of 16 hours), thereby indicating that the stabilization of the p53 protein and the blockage of the cell cycle is due to the presence of DNA lesions on the transcribed strands of active genes and probably to the presence of unrepaired CPD, which inhibits RNA polymerase II progression. In addition, the same authors documented recovery of the normal p53 response after UV treatment in DNA repair-deficient fibroblasts by retrovirally mediated correction with the *XPD* gene.¹⁸⁷ These results were confirmed by a study by Abrahams et al¹⁸⁸ showing differences in the regulation of p53 stability in UV-irradiated normal versus DNA repair-deficient human cells. The authors showed that normal fibroblasts exhibit a transient and UV dose-dependent stabilization of p53, but fibroblasts from repair-deficient syndromes show abnormalities in p53 protein stability.

Although it has been shown that XPD and XPB cells are deficient in p53-induced apoptosis,¹⁵⁸ we

Table VIII. Characteristics between NER mouse models and corresponding human syndromes

Gene	Mouse mutation	UV sensitivity		UDS (%)		Skin cancer	
		Man	Mouse	Man	Mouse	Man	Mouse
XPA	KO	+++	+++	<5	<5	++	++
XPB	KO*	N/A	N/A	N/A	N/A	N/A	N/A
XPC	KO	+	+	15-30	30	++	++
XPD	KO*	N/A	N/A	N/A	N/A	N/A	N/A
XPD	TTD point mutation	+/-	+/-	25	25	-	+
CSB	Truncation	++	++	Normal	Normal	-	+
CSA	KO	++	++	Normal	Normal	-	ND
ERCC1	KO truncation [†]	N/A	+++	N/A	<5	N/A	ND
mHR23a	KO	N/A	Normal	Normal		ND	
mHR23b	KO	N/A	-	Normal		N/A	ND

Adapted from de Boer J, Hoeijmakers JH. *Biochimie* 1999;81:127-37.

KO, Knockout; N/A, not applicable; ND, not done.

*Early embryonic lethality.

[†]Die before weaning.

found that low doses of UVC or UVB induced much more apoptosis in XPD fibroblasts than in TTD (Queille S et al, *J Invest Dermatol*; in press). If keratinocytes behave as fibroblasts do, this suggests that the absence of skin cancer in TTD is not due to enhanced levels of apoptosis in damaged cells. The high level of apoptosis in XPD cells irradiated with low UV doses stimulates cell-cycle turnover in the irradiated epidermis, compensating for the decrease in total cell number and leads to DNA replication in stem cells containing DNA lesions. This process is mutagenic in itself and may be carcinogenic as well, which explains the predisposition to cancer in patients with XPD.

Similarities and differences between XP type D and TTD cells after UV exposure are summarized in Table VII.

TRANSGENIC AND KNOCKOUT MICE

Because no animal model had been available to mimic human DNA repair-deficient diseases, transgenic mice and, subsequently, knockout animals have been produced to study the biologic consequences of repair deficiency in animals. NER-deficient mice have recently been generated, giving rise to phenotypes close to XP, CS, and TTD.¹²⁴ As expected, XPA and XPC knockout or null animals were very close to the human phenotypes, showing UV sensitivity and predisposition to cancer, whereas XPD and XPB null animals were nonviable, resulting in very early embryonic lethality and showing clearly the indispensable role of these two helicases for normal life.^{121,124} A mouse model for CS, with selective impairment of TCR, has been produced. These animals mimic very well the human phenotype, except

they are prone to skin cancers whereas the human counterparts are not (Table VIII).

A transgenic mutant with a partial repair defect and associated clinical symptoms similar to TTD was created by mimicking a point mutation, identified as one of the hotspots in the *XPD* gene, of a photosensitive patient with TTD (mutation R722W, see Fig 6, A) and using a novel gene cDNA fusion targeting strategy.¹²¹ TTD mice reflect, to a remarkable degree, the human disorder, including growth retardation, developmental abnormalities, reduced life span, skin abnormalities, and prematurely aged appearance.¹⁹⁰ Low cysteine content in hair, hair loss, and brittle hair were similar to that found in patients with TTD. Cellular and skin UV sensitivity and low UDS level are similar to that observed with the corresponding human TTD cells. The reduced transcription of the specific *SPRR2* gene, involved with the cross-linking process of the cornified envelope and expressed in the final stage of terminal differentiation, strongly supports the concept of TTD as a human disease due to inborn defects of basal gene transcription and DNA repair. However, De Boer et al^{190,191} recently found that, in striking contrast to human TTD, the TTD mouse is clearly susceptible to UV- and 7,12-dimethylbenz[a]anthracene-induced skin carcinogenesis, although at a lower level than the XPA or XPC mouse. These findings suggest that patients with TTD could harbor a predisposition to skin cancer, though this is not in agreement with the human clinical experience. Long-term clinical surveillance will be necessary to more clearly delineate this possible risk. However, it might well be that the human genome and/or cells have developed inherent protective mechanisms not

present in lower order species, such as the mouse. Nonetheless, these animal models provide helpful tools to understand the complex relationships between DNA repair defects, transcription function, and clinical manifestations.

LACK OF PREDISPOSITION TO CANCER IN TTD

It is clear that during their lifetimes, patients with TTD with DNA repair deficiency as well as those with CS do not develop excess malignancies, whereas patients with classic or variant XP with similar DNA repair defects are predisposed to numerous malignancies.^{166,167,179}

Vuillaume et al¹⁹² reported striking differences in cellular catalase activity between XP and TTD. In XP fibroblasts, catalase activity was 5-fold less than that in controls. Fibroblasts of patients with TTD showed a high level of catalase activity. However, molecular analysis of catalase gene or messenger RNA accumulation showed no difference between normal, XP, and TTD cells. The low catalase activity has been shown to be due to an intrinsic low level of the intracellular concentration of reduced nicotinamide adenine dinucleotide phosphate (NADPH), for yet unknown reasons, which is an obligatory cofactor of catalase. Therefore this low level of NADPH is directly responsible for the low catalase activity and is specific for XP cells versus TTD or normal cells. Growth of XP cells in the presence of 0.1 mmol/L of NADPH fully complements the catalase deficiency in XP cells.¹⁹³ UV irradiation induced 3 to 5 times more intracellular hydrogen peroxide production in XP cells compared with TTD cells or controls. These striking differences were interpreted by the authors as showing that UV radiation, directly or indirectly, together with defective oxidative metabolism may increase the initiation and/or the progression steps in the XP cellular environment compared with TTD.¹⁹²

Terleth et al¹⁹⁴ attempted to explain the absence of cancer predisposition in patients with TTD as well as in patients with XP by the lack of induction of the ornithine decarboxylase gene, a putative proto-oncogene, and the absence of the induction of mammalian SOS-like response, after irradiation: these two events seem to be necessary for a cell response leading to cancer. However, the molecular reason for this lack of induction is not yet understood.¹⁹³

One of the major processes involved in cancer development and progression is the efficiency of host immune surveillance. It is known that immunodeficient patients are predisposed to skin cancers on sun-exposed body parts. Similarly, an impairment of cell-mediated immunity has been proposed as a cofactor

in the predisposition to cancer of patients with XP. For example, Mariani et al¹⁹⁵ documented that the relative proportion of CD3⁺ and CD4⁺ circulating lymphocytes was reduced in patients with XP but not in those with TTD. In this study, low natural killer (NK) activity was found in both syndromes. However, Norris et al¹⁹⁶ found reduced NK activity in patients with XP, whereas patients with TTD and CS showed normal NK activity. The authors concluded that increased susceptibility to skin cancers in XP may also be determined by reduced NK cell activity. Gaspari, Fleisher, and Kraemer¹⁹⁷ documented that lymphocytes from patients with XP have defective interferon production and may play an important role in the susceptibility to skin cancer, in addition to DNA repair defects, because NK cell function was not stimulated by interferon in patients with XP.

Ahrens et al¹⁹⁸ have documented that cells from XPD exhibit a marked UVB-induced inhibition of intercellular adhesion molecule type 1 (ICAM-1) expression after stimulation with interferon gamma. Patients with TTD showed no alteration in ICAM-1 expression, except for the TTD cells mutated at the R112H hotspot, which behave almost like XPD cells.¹⁶⁸ The absence of ICAM-1 expression after irradiation inhibits skin cell interactions with lymphocytes, a process necessary for most cell-mediated immune responses and for an efficient immune surveillance in the skin, thereby further contributing to the predisposition to cancer found in patients with XP.

To explain the limited skin abnormalities of TTD, it has been speculated that scaling and thickening of ichthyotic skin in patients might shield replicative keratinocytes from UV damage.¹²⁴ However, we are not convinced that this mechanism has a relevant impact for cancer protection. Reduced lifespan of patients with TTD and frequent illness and lifestyle limitations in such patients may prevent them from acquiring a sufficient burden of UV radiation over time.

TTD AS A TRANSCRIPTION DISEASE

Clinically, it is increasingly evident that TTD with photosensitivity and CS resemble each other. Overlap in neurologic, developmental, and cutaneous abnormalities and the lack of cancer predisposition are observed. NER defects can easily explain photosensitivity and a predisposition to cancer but not growth retardation, brittle hair and nails, and neurodysmyelination as found in CS and TTD. Because for some patients the cellular responses to UV in TTD and XP are very close, it can be concluded that a pathway not involved in repair and lesion processing may be different between the two diseases. Therefore it was hypothesized that these non-XP features could be due to an impairment of basal

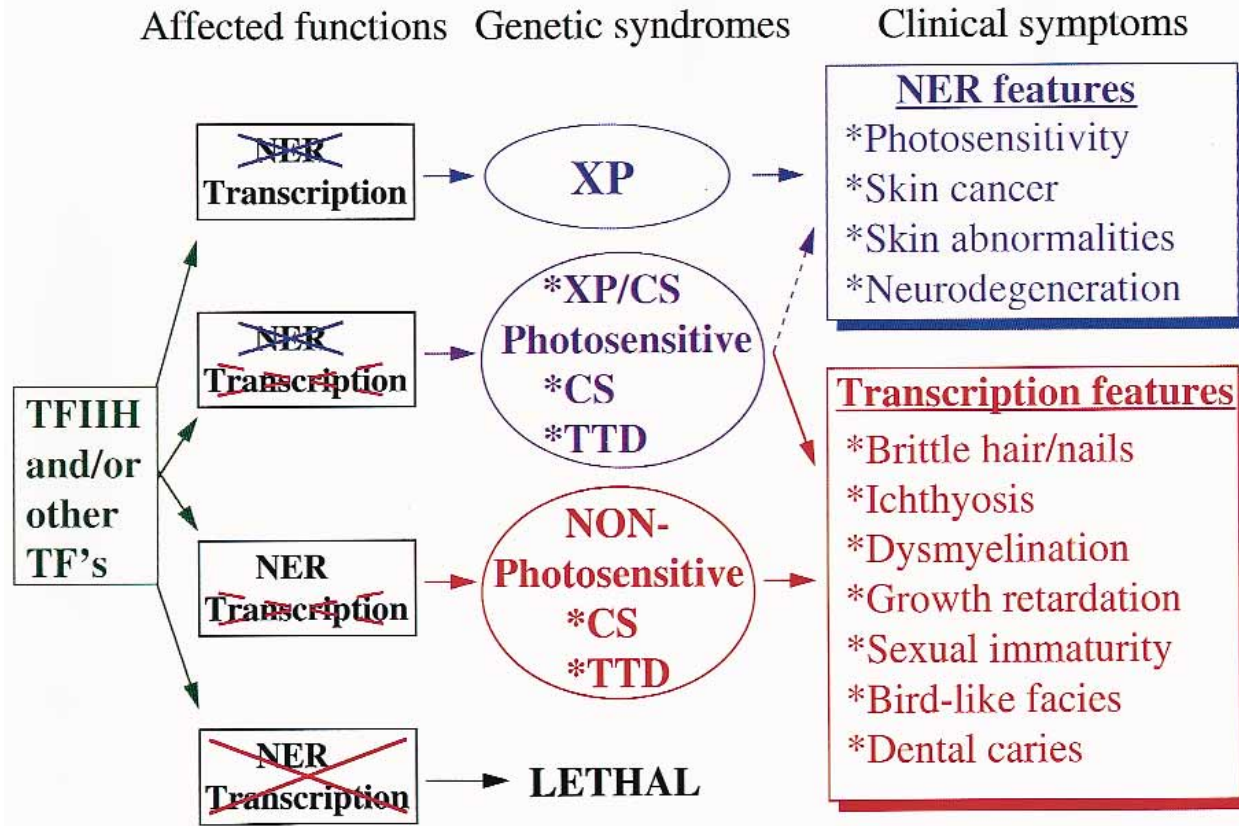


Fig 8. Model for the overlap between DNA repair diseases and transcription syndromes (see text for explanation). (Adapted from Vermeulen W, Scott RJ, Rodgers S, Müller HJ, Cole J, Arlett J, et al. *Am J Hum Genet* 1994;54:191-200.)

transcription of some specific genes because of the dual role of the XPD and XPB helicases.¹⁵⁹ In such case, nonphotosensitive patients with CS or TTD will exhibit the transcription defects, but with normal NER activity¹⁹⁸ (Fig 8).

TFIIH is a high-molecular-weight protein complex with remarkable dual function in NER and initiation of RNA polymerase II transcription. TFIIH is composed of 9 subunits, in which the XPB and XPD helicases as well as the p44 protein are necessary for a normal unwinding activity at the site of transcription initiation and at the site of lesion repair (see Fig 5). All TTD lines tested appear to have smaller amounts of the TFIIH complex,¹⁷⁸ which may represent the limiting factor when cells require enhanced TFIIH levels for transcription or repair, or when differentiated cells do not synthesize TFIIH de novo and amounts of this complex become suboptimal. This could explain the brittle hair/nail phenotype.

A remarkable recent finding has been the characterization of 4 unusual cases of TTD that exhibited fever-dependent, reversible deterioration of typical TTD-related features, including loss of brittle hair

and worsening of ichthyosis and ataxia. One patient was a compound heterozygote in *XPD* with a R658C amino acid substitution in one allele and a G713R change in the other. The mutant alleles induced markedly decreased basal transcription rates in the TTD fibroblasts when subjected to elevated incubation temperatures oscillating around 41°C. Moreover, overall NER activity dropped to less than 10% of the already reduced levels seen at 37°C. This was associated with thermal instability of TFIIH. The investigators suggest that continued de novo synthesis of the complex partly compensates for the TFIIH instability until terminal differentiation is initiated (eg, in epidermis and hair follicle cells). Under these conditions with thermolabile, destabilizing TTD mutations, TFIIH is depleted more rapidly, leading to worsening of hair and skin findings with fever.²⁰⁰ This is one of the few examples of a temperature-sensitive, heritable disorder observed in humans and characterized at the molecular level.

The dysmyelination process observed in patients with TTD may also result from insufficient transcription of abundant genes coding the structural com-

ponents of the myelin sheath. *CSA* and *CSB* genes, unlike *XPB* and *XPD* genes, are not essential for viability. Their products also interact with the RNA polymerase II, likely allowing some form of transcription regulation during RNA synthesis on the normal template and/or damaged template. This effect on transcriptional regulation may explain the resemblance of TTD with CS, but the different modes of action of these gene products on transcription may also explain the dissimilarities between the two syndromes.

This model of attenuated transcription in terminally differentiating cells in TTD has received support from studies with the fruit fly *Drosophila melanogaster* (*Dm*). The viable mutated alleles of the *Dm haywire* gene (the equivalent of the *XPB* gene product that is also part of the TFIIF complex) can cause defects in the central nervous system and growth retardation that may be akin to abnormalities in patients with CS/XP-B.²⁰¹ Spermatogenesis in *Drosophila* is very sensitive to the level of the tubule protein, β 2-tubulin.²⁰² Mutations within the *Drosophila XPB* gene affect β 2-tubulin expression, causing male sterility, and possibly may lower the expression of other crucial genes.²⁰¹ It is therefore likely that expression of this gene in *Drosophila*, and possibly in humans, is particularly sensitive to the level of transcription at particular stages of development and sensitive to subtle mutations in protein subunits of TFIIF. This may explain the immature sexual development observed in patients with TTD and CS.

Similarly, reduced transcription of genes encoding the class of KAP 4-5 of the hair shaft may account for the reduced cysteine content in the brittle hair of patients with TTD. The typical brittle hair in TTD is, indeed, due to a reduction in the content of hair-specific cysteine-rich matrix proteins that cross-link the keratin fibers and leads to the fragile hair found in patients with TTD.¹²⁴

CONCLUSION

In recent years, enormous progress has been made in our understanding of the NER processes and transcription factor complexes in humans and in the molecular mechanisms underlying UV-sensitive diseases such as TTD. The constellation of growth retardation, brittle hair, and neurodysmyelination has been difficult to explain by NER defects alone. There is now strong evidence that these non-XP features of TTD are due to an impairment of the transcription function of *XPD* and *XPB* gene products, whereas the photosensitivity is a consequence of the disruption of the DNA repair function. Nonphotosensitive subtypes of TTD may be reconciled by the "repair/transcription" syndrome model in which a

mutation impairs the transcription function of TFIIF but leaves the repair function intact.¹²¹ In normal dividing TTD cells, the abnormal TFIIF factor will be renewed sufficiently rapidly to compensate for its reduced stability. In terminally differentiated cells, however, the synthesis of de novo TFIIF may not be adequate and accumulation of inactive transcription factor and depletion may occur, giving rise to depressed basal transcription of some genes. In particular, those genes highly expressed in differentiated cells such as those involved in hair structure or in the neuromyelination process may be the targets of this disorder.²⁰³ Moreover, the low repair level found in cells from the photosensitive patient with TTD renders the transcription machinery even more vulnerable since RNA polymerases are blocked by DNA lesions and therefore are even less active after UV sun exposure.

The absence of skin cancers in patients with TTD may well be due to more efficient immunosurveillance than in those with XP since any premalignant or malignant cells might be targeted in TTD and, therefore, eliminated. However, taking into account results showing some predisposition to cancer in the experimental TTD mouse models, it is plausible to speculate that increased life expectancy of TTD could be accompanied by an increased risk in skin cancer. Therefore it is reasonable to recommend sun protective measures and periodic skin examinations to observe for any signs of premalignant or cancerous lesions in patients with photosensitive TTD.

We thank Drs A. Stary and T. Magnaldo for critical reading of the manuscript and Drs A. Lehmann and J. M. Egly for providing unpublished data.

REFERENCES

1. Price VH, Odom RB, Ward WH, Jones FT. Trichothiodystrophy: sulfur-deficient brittle hair as a marker for a neuroectodermal symptom complex. *Arch Dermatol* 1980;116:1375-84.
2. Price VH. Brüchiges Schwefelmangelhaar: Trichothiodystrophie. In: Orfanos CE, editor. *Haar und Haarkrankheiten*. Stuttgart: Gustav Fischer Verlag; 1979. p. 413-21.
3. Price VH, Odom RB, Jones FT, Ward WH. Trichothiodystrophy: sulfur-deficient brittle hair. In: Brown AC, Crouse RG, editors. *Hair, trace elements, and human illness*. New York: Praeger; 1980. p. 220-7.
4. Pollitt RJ, Jenner FA, Davies M. Sibs with mental and physical retardation and trichorrhexis nodosa with abnormal amino acid composition of the hair. *Arch Dis Child* 1968;43:211-6.
5. Brown AC, Belsler RB, Crouse RG, Wehr RF. A congenital hair defect: trichoschisis with alternating birefringence and low sulfur content. *J Invest Dermatol* 1970;54:496-509.
6. Itin PH, Pittelkow MR. Trichothiodystrophy: review of sulfur-deficient brittle hair syndromes and association with the ectodermal dysplasias. *J Am Acad Dermatol* 1990;22:705-17.
7. Price VH. Trichothiodystrophy: a defect in transcription. In: Camacho F, Montagna W, editors. *Trichology: diseases of the*

- pilosebaceous follicle. Madrid: Aula Medica Group; 1997. p. 237-42.
8. Price VH. Trichothiodystrophy: current concepts. *J Cutan Med Surg* 1996;1:45-9.
 9. Robert C, Sarasin A. Les trichothiodystrophies: anomalies de la réparation et de la transcription des gènes. *Ann Dermatol Venereol* 1999;126:669-71.
 10. Hordinsky MK, Briden B, Berry SA. Friable hair, urea cycle dysfunction, and trichothiodystrophy: a new X-linked genodermatosis. *Curr Probl Dermatol* 1987;17:52-60.
 11. Price VH. Trichothiodystrophy: update. *Pediatr Dermatol* 1992;9:369-70.
 12. Goerz G, Behrens W, Megahed M, Kuester W, Fohles J, Tsambaos D, et al. Brittle and sparse hair with normal cystine content caused by methionine deficiency? *Acta Derm Venereol (Stockh)* 1996;76:62-4.
 13. Kvedar JC, Baden HP, Baden LA, Shih VE, Kolodny EH. Dietary management reverses grooving and abnormal polarization of hair shafts in argininosuccinase deficiency. *Am J Med Genet* 1991;40:211-3.
 14. Baden L, Kolodny E, Baden HP. Pseudo-trichothiodystrophy in a patient with arginosuccinic aciduria: case report [abstract]. Presented at the 48th Annual Meeting of the American Academy of Dermatology, San Francisco, Calif, Dec 2-7, 1989.
 15. Traupe H, Happle R, Gröbe H, Bertram HP. Polarization microscopy of hair in acrodermatitis enteropathica. *Pediatr Dermatol* 1986;3:300-3.
 16. Gillespie JM. The dietary regulation of the synthesis of hair keratin. In: Crewther WG, editor. *Symposium on fibrous proteins*. Edinburgh: Butterworths; 1968. p. 362-3.
 17. Morganti P, Muscardin L, Avico U, Cristofolini M. Abnormal amino acid changes in human hair associated with rare congenital syndromes. In: Orfanos CE, Montagna W, Stüttgen G, eds. *Hair research: status and future aspects*. Berlin: Springer-Verlag; 1981. p. 442-5.
 18. Reynold JM, Gold RJM, Scriver CR. The characterization of hereditary abnormalities of keratin: Clouston's ectodermal dysplasia. *Birth Defects* 1971;7:91-5.
 19. Miyazawa F, Tamura T, Nozaki F. Alteration of amino acid composition and keratinolysis of hair due to chemical damage. In: Kobori T, Montagna W, editors. *Biology and disease of the hair*. Baltimore: University Park Press; 1976. p. 659-67.
 20. Leonard JN, Gummer CL, Dawber RPR. Generalized trichorrhexis nodosa. *Br J Dermatol* 1980;103:85-90.
 21. Leupold D. Ichthyosis congenita, Katarakt, Schwachsinn, Ataxie, Osteosklerose und Abwehrdefekt-ein eigenständiges Syndrom? *Monatsschr Kinderheilkd* 1979;127:307-8.
 22. Braun-Falco O, Ring J, Butenandt O, Selzle D, Landthaler M. Ichthyosis vulgaris, Minderwuchs, Haardysplasie, Zahnanomalie, Immundefekte, psychomotorische Retardation und Resorptionsstörungen. *Hautarzt* 1981;32:67-74.
 23. Salfeld K, Lindley MJ. Zur Frage der Merkmalskombination bei Ichthyosis vulgaris mit Bambushaarbildung und ekto-dermaler Dysplasie. *Dermatol Wochenschr* 1963;147:118-28.
 24. Brown AC. Congenital hair defects. *Birth Defects* 1971;7:52-68.
 25. Dupré A, Bonafé JL. Étude en lumière polarisée des dysplasies pilaires: essai d'actualisation de la nomenclature. *Ann Dermatol Venereol* 1978;105:921-30.
 26. Whiting DA. Structural abnormalities of the hair shaft. *J Am Acad Dermatol* 1987;16:1-25.
 27. Van Neste D. Dysplasies pilaires congénitales: conduite à tenir et intérêt de diverses méthodes de diagnostic. *Ann Dermatol Venereol* 1989;116:251-63.
 28. Adamski H, Chevrant-Breton J, Odent S, Patoux-Pibouin M, Le Marec B, Laudren A, et al. Dysplasie pilaire au cours du syndrome oculo-dento-digital: a propos d'un cas mère-fille. *Ann Dermatol Venereol* 1994;121:694-9.
 29. Kutner M, Miller K, Brown AC. A critique: hair sulfur analysis for evaluation of normal and abnormal hair. *The First Human Hair Symposium Proc* 1973;1:363-76.
 30. Tay CH. Ichthyosiform erythroderma, hair shaft abnormalities, and mental and growth retardation: a new recessive disorder. *Arch Dermatol* 1971;104:4-13.
 31. McCuaig C, Marcoux D. Tay syndrome [abstract]. *Pediatr Dermatol* 1992;9:221.
 32. Ostergaard JR, Christensen T. The central nervous system in Tay syndrome. *Neuropediatrics* 1996;27:326-30.
 33. Blomquist HKS, Bäck O, Fagerlund M, Holmgren G, Stecksens-Blicks C. Tay or IBIDS syndrome: a case with growth and mental retardation, congenital ichthyosis and brittle hair. *Acta Paediatr Scand* 1991;80:1241-5.
 34. Demir E, Aysun S. A case of Tay syndrome with cerebral hypomyelination [abstract]. *Eur J Pediatr Neurol* 1999;3:A58.
 35. Weis R, Schulz C, Porto L, Kieslich M, Gebhardt B, Zippel S, et al. Ichthyosis, Trichothiodystrophie, Entwicklungsverzögerung: die Beteiligung des zentralen Nervensystems beim Tay-Syndrom [abstract]. *Monatsschr Kinderheilkd* 1999;147:908.
 36. Koussseff BG. Collodion baby, sign of Tay syndrome. *Pediatrics* 1991;87:571-4.
 37. Traupe H. Ichthyosis and trichothiodystrophy: the Tay and PIBI(D)S syndromes. In: Traupe H, editor. *The ichthyoses*. Berlin: Springer Verlag; 1989. p. 162-7.
 38. Happle R, Traupe H, Gröbe H, Bonsmann G. The Tay syndrome (congenital ichthyosis with trichothiodystrophy). *Eur J Pediatr* 1984;141:147-52.
 39. Jorizzo JL, Crouse RG, Wheeler CEJ. Lamellar ichthyosis, dwarfism, mental retardation, and hair shaft abnormalities: a link between the ichthyosis-associated and BIDS syndromes. *J Am Acad Dermatol* 1980;2:309-17.
 40. Jorizzo JL, Atherton DJ, Crouse RG, Wells RS. Ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature (IBIDS syndrome). *Br J Dermatol* 1982;106:705-10.
 41. Schepis C, Elia M, Siragusa M, Barbareschi M. A new case of trichothiodystrophy associated with autism, seizures, and mental retardation. *Pediatr Dermatol* 1997;14:125-8.
 42. Calvieri S, Rossi A, Amorosi B, Giustini S, Innocenzi D, Micali G, et al. Trichothiodystrophy: ultrastructural studies of two patients. *Pediatr Dermatol* 1993;10:111-6.
 43. McCuaig C, Marcoux D, Rasmussen JE, Werner MM, Gentner NE. Trichothiodystrophy associated with photosensitivity, gonadal failure, and striking osteosclerosis. *J Am Acad Dermatol* 1993;28:820-6.
 44. Hersh JH, Klein LR, Joyce MR, Hordinsky MK, Tsai MY, Paller A, et al. Trichothiodystrophy and associated anomalies: a variant of SIBIDS or new symptom complex? *Pediatr Dermatol* 1993;10:117-22.
 45. Jackson CE, Weiss L, Watson JHL. "Brittle" hair with short stature, intellectual impairment and decreased fertility: an autosomal recessive syndrome in an Amish kindred. *Pediatrics* 1974;54:201-7.
 46. Cantú JM, Arias J, Foncerrada M, Hernández A, Podoswa G, Rostenberg I, et al. Syndrome of onychotrichodysplasia with chronic neutropenia in an infant from consanguineous parents. *Birth Defects* 1975;11:63-6.
 47. Hernández A, Olivares F, Cantú JM. Autosomal recessive onychotrichodysplasia, chronic neutropenia and mild mental retardation: delineation of the syndrome. *Clin Genet* 1979;15: 147-52.
 48. Corona-Rivera E, Hernández A, Padilla H, Perez-Garcia N, Aleman-Castaneda J, Rodriguez M, et al. Further delineation of the onychotrichodysplasia, chronic neutropenia and mild

- retardation syndrome (ONMRS) [abstract]. Sixth Int Cong Hum Genet Jerusalem 1981;267.
49. Verhage J, Habbema L, Vrensen GFJM, Roord JJ, Bleeker-Wagemakers EM. A patient with onychotrichodysplasia, neutropenia and normal intelligence. *Clin Genet* 1987;31:374-80.
 50. Itin PH, Pittelkow MR. Trichothiodystrophy with chronic neutropenia and mild mental retardation. *J Am Acad Dermatol* 1991;24:356-8.
 51. Camacho F. Genodermatosis with hypotrichosis. In: Camacho F, Montagna W, editors. *Trichology: diseases of the pilosebaceous follicle*. Madrid: Aula Medica Group; 1997. p. 219-36.
 52. Tolmie JL, De Berker D, Dawber R, Galloway C, Gregory DW, Lehmann AR, et al. Syndromes associated with trichothiodystrophy. *Clin Dysmorphol* 1994;3:1-14.
 53. Civitelli R, McAlister WH, Teitelbaum SL, Whyte MP. Central osteosclerosis with ectodermal dysplasia: clinical, laboratory, radiologic, and histopathologic characterization with review of the literature. *J Bone Miner Res* 1989;4:863-75.
 54. Bertoli P, Battistella PA, Peserico A. PIBI(D)S syndrome: a further case [abstract]. *Pediatr Dermatol* 1992;9:215.
 55. Bingol N, Leach J, Miraz L, Hahn C. Trichothiodystrophy with congenital ichthyosis associated with congenital neutropenia in two siblings [abstract]. *Am J Hum Genet* 1992;51:A91.
 56. Wetzburger CL, Van Regemorter N, Szliwowski HB, Abramowicz MJ, Van Bogaert P. Gray matter heterotopia and acute necrotizing encephalopathy in trichothiodystrophy. *Pediatr Neurol* 1998;19:392-4.
 57. Botta E, Nardo T, Broughton BC, Marinoni S, Lehmann AR, Stefanini M. Analysis of mutations in the XPD gene in Italian patients with trichothiodystrophy: site of mutation correlates with repair deficiency, but gene dosage appears to determine clinical severity. *Am J Hum Genet* 1998;63:1036-48.
 58. Dallapiccola B, Mingarelli R, Obregon G. Onychotrichodysplasia and chronic neutropenia without mental retardation (ONS): a second case report. *Clin Genet* 1994;45:200-2.
 59. Arbisser AI, Scott CIJ, Howell RR, Ong PS, Cox HLJ. A syndrome manifested by brittle hair with morphologic and biochemical abnormalities, developmental delay and normal stature. *Birth Defects* 1976;12:219-28.
 60. Baden HP, Jackson CE, Weiss L, Jimbow K, Lee L, Kubilus J, et al. The physicochemical properties of hair in the BIDS syndrome. *Am J Hum Genet* 1976;28:514-21.
 61. Goldsmith LA, Baden HP. The analysis of genetically determined hair defects. *Birth Defects* 1971;7:86-9.
 62. Porter PS. The genetics of human hair growth. *Birth Defects* 1971;7:69-85.
 63. Chapman S. The trichothiodystrophy syndrome of Pollitt. *Pediatr Radiol* 1988;18:154-6.
 64. Bracun R, Hemmer W, Wolf-Abdolvahab S, Focke M, Botzi C, Killian W, et al. Diagnosis of trichothiodystrophy in 2 siblings. *Dermatology* 1997;194:74-6.
 65. Battistella PA, Peserico A. Central nervous system dysmyelination in PIBI(D)S syndrome: a further case. *Childs Nerv Syst* 1996;12:110-3.
 66. Petrin JH, Meckler KA, Sybert VP. A new variant of trichothiodystrophy with recurrent infections, failure to thrive, and death. *Pediatr Dermatol* 1998;15:31-4.
 67. Crovato F, Borrone C, Rebora A. Trichothiodystrophy: BIDS, IBIDS and PIBIBS? *Br J Dermatol* 1983;108:247.
 68. Van Neste DJ, Boré PP, Thomas PM, Lachapelle JM. Trichoschisis: light sensitivity and growth retardation. XVI Congressus Internationalis Dermatologiae Tokyo 1982;79.
 69. Lehmann AR. Trichothiodystrophy and the relationship between DNA repair and cancer. *BioEssays* 1989;11:168-70.
 70. Nuzzo F, Zei G, Stefanini M, Colognola R, Santachiara AS, Lagomarsini P, et al. Search for consanguinity within and among families of patients with trichothiodystrophy associated with xeroderma pigmentosum. *J Med Genet* 1990;27:21-5.
 71. Van Neste D, Miller X, Bohnert E. Trichothiodystrophie: ein kutanes Merkmal für einen Symptomenkomplex von zunehmendem Schweregrad mit Beziehung zu Xeroderma pigmentosum. *Akt Dermatol* 1988;14:191-6.
 72. Van Neste D, Miller X, Bohnert E. Clinical symptoms associated with trichothiodystrophy: a review of the literature with special emphasis on light sensitivity and the association with xeroderma pigmentosum (complementation group D). In: Van Neste D, Lachapelle JM, Antoine JL, editors. *Trends in human hair growth and alopecia research*. Dordrecht: Kluwer Academic; 1989. p. 183-93.
 73. Spemann H. The embryonic field. In: Moore JA, editor. *Genes, cells and organisms. Great books in experimental biology*. New York: Garland Publishing; 1988. p. 297-317.
 74. Pinheiro M, Freire-Maia N. Ectodermal dysplasias: a clinical classification and a causal review. *Am J Med Genet* 1994;53:153-62.
 75. Prigent F. Alopecies et hypotrichoses néonatales. *Ann Dermatol Venereol* 1999;126:975-80.
 76. Kleijer WJ, Beemer FA, Boom BW. Intermittent hair loss in a child with PIBI(D)S syndrome and trichothiodystrophy with defective DNA repair—xeroderma pigmentosum group D. *Am J Med Genet* 1994;52:227-30.
 77. Foulc P, Jumbou O, David A, Sarasin A, Stalder JF. Trichothiodystrophies: manifestations évolutives. *Ann Dermatol Venereol* 1999;126:703-7.
 78. Tsambaos D, Nikiforidis G, Balas C, Sampalis F. Viscoelastic parameters of trichothiodystrophic hair: computerized analysis and quantitative determination [abstract]. *Clinical Dermatology 2000 London* 1990;8.
 79. Tsambaos D, Nikiforidis G, Balas C, Marinoni S. Trichothiodystrophic hair reveals an abnormal pattern of viscoelastic parameters. *Skin Pharmacol* 1994;7:257-61.
 80. Przedborski S, Ferster A, Goldman S, Wolter R, Song M, Tonnesen T, et al. Trichothiodystrophy, mental retardation, short stature, ataxia, and gonadal dysfunction in three Moroccan siblings. *Am J Med Genet* 1990;35:566-73.
 81. Stefanini M, Giliani S, Nardo T, Marinoni S, Nazzaro V, Rizzo R, et al. DNA repair investigations in nine Italian patients affected by trichothiodystrophy. *Mutat Res* 1992;273:119-25.
 82. Johnson RT, Squires S. The XPD complementation group. Insights into xeroderma pigmentosum, Cockayne's syndrome and trichothiodystrophy. *Mutat Res* 1992;273:97-118.
 83. Mondello C, Nardo T, Giliani S, Arrand JE, Weber CA, Lehmann AR, et al. Molecular analysis of the XP-D gene in Italian families with patients affected by trichothiodystrophy and xeroderma pigmentosum group D. *Mutat Res* 1994;314:159-65.
 84. Trevisan G, Marinoni S, Stefanini M. PIBIDS syndrome: trichothiodystrophy and photosensitivity with defective UV-repair of DNA [abstract]. 17th World Congress of Dermatology Berlin 1987;Case collection:61-2.
 85. Arlett CF, Lehmann AR, Mayne LV, King MB, Tolmie JL. Studies on fibroblasts from two trichothiodystrophy patients [abstract]. *Br J Dermatol* 1987;116:421-2.
 86. Takayama K, Danks DM, Salazar EP, Cleaver JE, Weber CA. DNA repair characteristics and mutations in the ERCC2 DNA repair and transcription gene in a trichothiodystrophy patient. *Hum Mutat* 1997;9:519-25.
 87. Peter C, Tomczok J, Hoting E, Behrendt H. Trichothiodystrophy without associated neuroectodermal defects. *Br J Dermatol* 1998;139:137-40.
 88. Milligan A, Fletcher A, Porter DI, Hutchinson PE. Trichothiodystrophy. *Clin Exp Dermatol* 1991;16:264-7.

89. Alfandari S, Delaporte E, Van Neste D, Lucidarme-Delespierre E, Piette F, Bergoend H. A new case of isolated trichothiodystrophy. *Dermatology* 1993;186:197-200.
90. Rizzo R, Pavone L, Micali G, Calvieri S, Diregorio L. Trichothiodystrophy: report of a new case with severe nervous system impairment. *J Child Neurol* 1992;7:300-3.
91. Peserico A, Battistella PA, Bertoli P. MRI of a very rare hereditary ectodermal dysplasia: PIB(D)S. *Neuroradiology* 1992;34:316-7.
92. Chen E, Cleaver JE, Weber CA, Williams ML, Packman S, Price VH. Trichothiodystrophy: biochemical and molecular characterization, and central nervous system imaging of two siblings [abstract]. *Am J Hum Genet* 1993;53:416.
93. Chen E, Cleaver JE, Weber CA, Packman S, Barkovich AJ, Koch TK, et al. Trichothiodystrophy: clinical spectrum, central nervous system imaging, and biochemical characterization of two siblings. *J Invest Dermatol* 1994;103(Suppl):154-8.
94. Toelle SP, Albisetti M, Itin PH, Trüeb R, Martin E, Boltshauser E. Neuroimaging findings in two sisters with SIB(D)S and progressive hearing loss [abstract]. *Brain Dev* 1998;20:442.
95. Lynch SA, De Berker D, Lehmann AR, Pollitt RJ, Reid MM, Lamb WH. Trichothiodystrophy with sideroblastic anaemia and development delay. *Arch Dis Child* 1995;73:249-51.
96. Feier V, Solovan C. Trichothiodystrophie et syndrome d'hyperéosinophilie, une association insolite. *Ann Dermatol Venereol* 1994;121:151-5.
97. Malvey J, Ferrando J, Soler J, Tuneu A, Ballesta F, Estrach T. Trichothiodystrophy associated with urologic malformation and primary hypercalciuria. *Pediatr Dermatol* 1997;14:441-5.
98. Malvey J, Ferrando J, Tuneu A, Ballesta F, Soler J, Estrach T. Trichothiodystrophy associated with urological malformation and primary hypercalciuria. In: Van Neste D, Randall VA, editors. *Hair research for the next millenium*. Amsterdam: Elsevier; 1996. p. 31-4.
99. O'Brien TP, Wilhelmus KR. Bacterial keratitis in trichothiodystrophy. *Can J Ophthalmol* 1995;30:270-1.
100. Ferrando J, Malvey J, Estrach T, Soler J, Ballesta F. Trichothiodystrophy. *Pediatr Dermatol* 1996;13:88.
101. Bodemer C, Rötig A, Rustin P, Cormier V, Niaudet P, Saudubray JM, et al. Hair and skin disorders as signs of mitochondrial disease. *Pediatrics* 1999;103:428-33.
102. Marinoni S, Gaeta G, Not T, Freschi P, Trevisan G, Briscic E, et al. Early recognition of trichothiodystrophy with xeroderma pigmentosum group D mutation in a collodion baby. In: Panconesi E, editor. *European Academy of Dermatology and Venereology. Congress: Florence, Italy; 1989*. Oxford: Blackwell Scientific Publications; 1991. p. 632-3.
103. Venning V, Dawber RPR, Ferguson DJP, Kanan MW. Weathering of hair in trichothiodystrophy. *Br J Dermatol* 1986;114:591-5.
104. Van Neste D, Houbion Y. Office diagnosis of pathological changes of hair cuticular cell pattern. In: Van Neste D, Lachapelle JM, Antoine JL, editors. *Trends in human hair growth and alopecia research*. Dordrecht: Kluwer Academic Publishers; 1989. p. 173-9.
105. Sarasin A, Blanchet-Bardon C, Renault G, Lehmann A, Arlett C, Dumez Y. Prenatal diagnosis in a subset of trichothiodystrophy patients defective in DNA repair. *Br J Dermatol* 1992;127:485-91.
106. Taieb A, Van Neste D, Lacombe D, Mezzina M, Sarasin A. Bébé collodion d'évolution favorable définissant un nouveau groupe génétique de trichothiodystrophie. *Ann Dermatol Venereol* 1994;121(Suppl I):S80.
107. Hansen LK, Wulff K, Brandrup F. Trichothiodystrophy: hair examination as a diagnostic tool. *Ugeskr Laeger* 1993;155:1949-52.
108. Pallotta R, Amerio PL, De Mattheis S. Trichothiodystrophy syndromes [abstract]. *Pediatr Dermatol* 1995;102:133.
109. Brusasco A, Restano L. The typical "tiger-tail" pattern of the hair shaft in trichothiodystrophy may not be evident at birth. *Arch Dermatol* 1997;133:249.
110. De Berker D, Tolmie J, Dawber RPR. Hair analysis in trichothiodystrophy to distinguish primary and secondary features [abstract]. *Br J Dermatol* 1991;125(Suppl 38):88.
111. De Berker D. "Tiger tail" pattern on polarized hair microscopic examination is found in healthy infants. *Arch Dermatol* 1997;133:1313-4.
112. García-Hernández MJ, Moreno-Giménez JC, Camacho F. Acquired, partial trichothiodystrophy. *Eur J Dermatol* 1996;6:579-80.
113. Calvieri S, Zampetti M, Corbo A. Preliminary results using a microanalysis system on the hair of patients affected by trichothiodystrophy [abstract]. *Clin Exp Dermatol* 1989;14:404.
114. Rossi A, Daniele L, Bonaccorsi P, Giustini S, Calvieri S. Microanalysis: applications in hair study. In: Van Neste D, Randall VA, editors. *Hair research for the next millenium*. Amsterdam: Elsevier; 1996. p. 87-9.
115. Rossi A, Daniele L, Bonaccorsi P, Calvieri S. Microanalysis: study of hair affected by trichothiodystrophy. In: Van Neste D, Randall VA, editors. *Hair research for the next millenium*. Amsterdam: Elsevier; 1996. p. 95-7.
116. Rice RH, Wong VJ, Price VH, Hohl D, Pinkerton KE. Cuticle cell defects in lamellar ichthyosis hair and anomalous hair shaft syndromes visualized after detergent extraction. *Anat Rec* 1996;246:433-40.
117. Gummer CL, Dawber RPR, Price VH. Trichothiodystrophy: an electron-histochemical study of the hair shaft. *Br J Dermatol* 1984;110:439-49.
118. Meyvisch K, Song M, Dourov N. Review and new case reports on scanning electron microscopy of pili annulati, monilethrix and trichothiodystrophy. *Scanning Microsc* 1992;6:537-41.
119. Forslind B, Andersson MK, Alsterborg E. Hereditary hair changes revealed by analysis of single hair fibres by scanning electron microscopy. *Scanning Microsc* 1991;5:867-75.
120. Micali G, Rizzo R, Parano E, Rossi A, Ambrosi B, Giustini S, et al. Trichothiodystrophy: ultrastructural studies [abstract]. *Clin Exp Dermatol* 1991;16:144.
121. De Boer J, De Wit J, Van Steeg H, Berg RJ, Morreau H, Visser P, et al. A mouse model for the basal transcription/DNA repair syndrome trichothiodystrophy. *Mol Cell* 1998;1:981-90.
122. Song HJ, Poy G, Darwiche N, Licht U, Kuroki T, Steinert PM, et al. Mouse Sprr2 genes: a clustered family of genes showing differential expression in epithelial tissues. *Genomics* 1999;55:28-42.
123. Fischer DF, Van Druenen CM, Winkler GS, Van de Putte P, Backendorf C. Involvement of a nuclear matrix association region in the regulation of the SPRR2A keratinocyte terminal differentiation marker. *Nucleic Acids Res* 1999;26:5288-94.
124. De Boer J, Hoeijmakers JH. Cancer from the outside, aging from the inside: mouse models to study the consequences of defective nucleotide excision repair. *Biochimie* 1999;81:127-37.
125. Itin PH. *Embryologie der Haut*. In: Traupe H, Hamm H, editors. *Pädiatrische Dermatologie*. Berlin: Springer Verlag; 1999. p. 1-9.
126. Powell BC, Rogers GE. The role of keratin proteins and their genes in the growth, structure and properties of hair. In: Jollès P, Zahn H, Höcker H, editors. *Formation and structure of human hair*. Basel: Birkhäuser Verlag; 1997. p. 59-148.
127. Jollès P, Zahn H, Höcker H. *Formation and structure of human hair*. Basel: Birkhäuser Verlag; 1997.
128. Emonet N, Michaille JJ, Dhouailly D. Isolation and characterization of genomic clones of human sequences presumably coding for hair cysteine-rich proteins. *J Dermatol Sci* 1997;14:1-11.
129. Van Neste DJJ, Gillespie JM, Marshall RC, Taieb A, De Brouwer B. Morphological and biochemical characteristics of trichothio-

- dystrophy-variant hair are maintained after grafting of scalp specimens on to nude mice. *Br J Dermatol* 1993;128:384-7.
130. Van Neste D, Degreef H, Van Haute N, Van Hee J, Vandermaesen J, Taieb A, et al. High-sulfur protein deficient human hair: clinical aspects and biochemical study of two unreported cases of a variant type of trichothiodystrophy. In: Van Neste D, Lachapelle JM, Antoine JL, editors. *Trends in human hair growth and alopecia research*. Dordrecht: Kluwer Academic; 1989. p. 195-206.
 131. Gillespie JM, Marshall RC. A comparison of the proteins of normal and trichothiodystrophic human hair. *J Invest Dermatol* 1983;80:195-202.
 132. Gatto H, Taieb A, Thivolet J, Dhouailly D. The high sulfur proteins of human hair: a comparative study between normal hair and some pilary dystrophies [abstract]. *J Invest Dermatol* 1991;96:644.
 133. Gillespie JM, Marshall RC, Rogers M. Trichothiodystrophy: biochemical and clinical studies. *Australas J Dermatol* 1988;29:85-93.
 134. De Brouwer B, Phan KH, Föhles J, Van Neste DJJ. Trichothiodystrophy (TTD) hair production by TTD-scalp grafts maintained onto nude mice: biochemical study [abstract]. *J Invest Dermatol* 1993;101:493.
 135. Lehmann AR, Arlett CF. Trichothiodystrophy: a UV-sensitive disorder. In: Friedberg EC, Hanawalt PC, editors. *Mechanisms and consequences of DNA damage processing*. New York: Alan R Liss; 1988. p. 355-460.
 136. Blanchet-Bardon C, Sarasin A, Renault G, Dumez Y, Civatte J. Prenatal diagnosis of BIDS and IBIDS syndromes: trichothiodystrophies with DNA repair defect [abstract]. *Br J Dermatol* 1989; 123(Suppl 34):18.
 137. Savary JB, Vasseur F, Vinatier D, Manouvrier S, Thomas P, Deminatti MM. Prenatal diagnosis of PIBIDS. *Prenat Diagn* 1991;11:859-66.
 138. Alapetite C, Benoit A, Moustacchi E, Sarasin A. The comet assay as a repair test for prenatal diagnosis of xeroderma pigmentosum and trichothiodystrophy. *J Invest Dermatol* 1997; 108:154-9.
 139. Stary A, Sarasin A. The genetic basis of xeroderma pigmentosum and trichothiodystrophy syndromes. *Cancer Surv* 1996; 26:155-71.
 140. Stefanini M, Lagomarsini P, Giliani S, Nardo T, Botta E, Peserico S, et al. Genetic heterogeneity of the excision repair defect associated with trichothiodystrophy. *Carcinogenesis* 1993;14: 1101-5.
 141. Mezzina M, Eveno E, Chevallier-Lagente O, Benoit A, Carreau M, Vermeulen W, et al. Correction by the ERCC2 gene of UV sensitivity and repair deficiency phenotype in a subset of trichothiodystrophy cells. *Carcinogenesis* 1994;15:1493-8.
 142. Carreau M, Quilliet X, Salvetti A, Danos O, Heard JM, Mezzina M. Functional retroviral vector for gene therapy of xeroderma pigmentosum group D patients. *Hum Gene Ther* 1995;6:1307-16.
 143. Cleaver JE, Thompson LH, Richardson AS, States JC. A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. *Hum Mutat* 1999;14:9-22.
 144. Nuzzo F, Stefanini M. The association of xeroderma pigmentosum with trichothiodystrophy: a clue to a better understanding of XP-D? In: Castellani A, editor. *DNA damage and repair*. New York: Plenum Press; 1989. p. 61-72.
 145. Hanawalt PC, Sarasin A. Cancer-prone hereditary diseases with DNA processing abnormalities. *Trends in Genetics* 1986;2:124-9.
 146. Venema J, Mullenders LHF, Natarajan AT, Van Zeeland AA, Mayne LV. The genetic defect in Cockayne syndrome is associated with a defect in repair of UV-induced DNA damage in transcriptionally active DNA. *Proc Natl Acad Sci U S A* 1990; 87:4707-11.
 147. Hoeijmakers JHJ. Human nucleotide excision repair syndromes: molecular clues to unexpected intricacies [abstract]. *Eur J Cancer* 1994;30A:1912-21.
 148. De Boer J, Hoeijmakers JH. Nucleotide excision repair and human syndromes. *Carcinogenesis* 2000;21:453-60.
 149. Le Page F, Gentil A, Sarasin A. Repair and mutagenesis survey of 8-hydroxyguanine in bacteria and human cells. *Biochimie* 1999;81:147-53.
 150. Le Page F, Kwok EE, Avrutskaya A, Gentil A, Leadon S, Sarasin A, et al. Transcription-coupled base excision repair and mutation avoidance at 8-oxoguanine: requirement for XPG, TFIIH, and CSB and implication for Cockayne syndrome. *Cell* 2000;101: 159-71.
 151. Leadon SA. Transcription-coupled repair of DNA damage: unanticipated players, unexpected complexities. *Am J Hum Genet* 1999;64:1259-63.
 152. Hanawalt PC. Transcription-coupled repair and human disease. *Science* 1994;266:1957-8.
 153. Eveno E, Bourre F, Quilliet X, Chevallier-Lagente O, Roza L, Eker APM, et al. Different removal of ultraviolet photoproducts in genetically related xeroderma pigmentosum and trichothiodystrophy diseases. *Cancer Res* 1995;55:4325-32.
 154. Schaeffer L, Roy R, Humbert S, Moncollin V, Vermeulen W, Hoeijmakers JHJ, et al. DNA repair helicase: a component of BTF2 (TFIIH) basic transcription factor. *Science* 1993;260:58-63.
 155. Schaeffer L, Moncollin V, Roy R, Staub A, Mezzina M, Sarasin A, et al. The ERCC2/DNA repair protein is associated with the class II BTF2/TFIIH transcription factor. *EMBO J* 1994;13:2388-92.
 156. Tirode F, Busso D, Coin F, Egly JM. Reconstitution of the transcription factor TFIIH: assignment of functions for the three enzymatic subunits, XPB, XPD, and cdk7. *Mol Cell* 1999;3:87-95.
 157. Winkler GS, Araujo SJ, Fiedler U, Vermeulen W, Coin F, Egly JM, et al. TFIIH with inactive XPD helicase functions in transcription initiation but is defective in DNA repair. *J Biol Chem* 2000;275:4258-66.
 158. Wang XW, Yeh H, Schaeffer L, Roy R. P53 modulation of TFIIH-associated nucleotide excision repair activity. *Nature Genet* 1995;10:188-95.
 159. Vermeulen W, Van Vuuren AJ, Chipoulet M, Schaeffer L. Three unusual repair deficiencies associated with transcription factor BTF2 (TFIIH): evidence for the existence of a transcription syndrome. *Cold Spring Harbor Symposium LIX* 1994. p. 317-29.
 160. Weeda G, Eveno E, Donker I, Vermeulen W, Chevallier-Lagente O, Taieb A, et al. A mutation in the XPB/ERCC3 DNA repair transcription gene, associated with trichothiodystrophy. *Am J Hum Genet* 1997;60:320-9.
 161. Stefanini M, Vermeulen W, Weeda G, Giliani S, Nardo T, Sarasin A, et al. A new nucleotide-excision-repair gene associated with the disorder trichothiodystrophy. *Am J Hum Genet* 1993;53: 817-21.
 162. Lamerdin JE, Stilwagen SA, Ramirez MH, Stubbs L, Carrano AV. Sequence analysis of the ERCC2 gene regions in human, mouse, and hamster reveals three linked genes. *Genomics* 1996;34:399-409.
 163. Sung P, Bailly V, Weber C, Thompson LH, Prakash L, Prakash S. Human xeroderma pigmentosum group D gene encodes a DNA helicase. *Nature* 1993;365:852-5.
 164. Marionnet C, Quilliet X, Benoit A, Armier J, Sarasin A, Stary A. Recovery of normal DNA repair and mutagenesis in trichothiodystrophy cells after transduction of the XPD human gene. *Cancer Res* 1996;56:5450-6.

165. Weeda G, Van Ham RCA, Vermeulen W, Bootsma D, Van der Erb AJ, Hoeijmakers JHJ. A presumed DNA helicase encoded by ERCC-3 is involved in the human repair disorders xeroderma pigmentosum and Cockayne's syndrome. *Cell* 1990;62:777-91.
166. Scott RJ, Itin P, Kleijer WJ, Kolb C, Arlett C, Muller H. Xeroderma pigmentosum-Cockayne syndrome complex in two patients: absence of skin tumors despite severe deficiency of DNA excision repair. *J Am Acad Dermatol* 1993;29:883-9.
167. Lehmann AR. Cockayne's syndrome and trichothiodystrophy: defective repair without cancer. *Cancer Res* 1987;7:82-103.
168. Berneburg M, Clingen PH, Harcourt SA, Lowe JE, Taylor EM, Green MHL, et al. The cancer-free phenotype in trichothiodystrophy is unrelated to its repair defect. *Cancer Res* 2000;60:431-8.
169. Mondello C, Nardo T, Giliani S, Arrand JE, Weber CA, Lehmann AR, et al. Molecular analysis of the XP-D gene in Italian families with patients affected by trichothiodystrophy and xeroderma pigmentosum group D. *Mutat Res* 1994;314:159-65.
170. Stamm C, Goujon C, Sarasin A, Frappaz A, Chouvet B, Faure M, et al. Trichothiodystrophy (TTD) and mutation in the XPD-ERCC2 repair/transcription gene. *Ann Dermatol Venerol* 1998;125(Suppl 1):95.
171. Bootsma D, Kraemer KH, Cleaver JE, Hoeijmakers JHJ. Nucleotide excision repair syndromes: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *Metabolic and molecular bases of inherited disease*. 8th ed. New York: McGraw-Hill; 2001. p. 677-703.
172. Taylor EM, Broughton BC, Botta E, Stefanini M, Sarasin A, Jaspers NGJ, et al. Xeroderma pigmentosum and trichothiodystrophy are associated with different mutations in the XPD (ERCC2) repair/transcription gene. *Proc Natl Acad Sci U S A* 1997;94:8658-63.
173. Coin F, Mariononi JC, Rodolfo C, Fribourg S, Pedrini AM, Egly JM. Mutations in the XPD helicase gene result in XP and TTD phenotypes, preventing interaction between XPD and the p44 subunit of TFIIH. *Nat Genet* 1998;20:184-8.
174. Coin F, Bergmann E, Tremeau-Bravard A, Egly JM. Mutations in XPB and XPD helicases found in xeroderma pigmentosum patients impair the transcription function of TFIIH. *EMBO J* 1999;18:1357-66.
175. Vermeulen W, Scott RJ, Rodgers S, Müller HJ, Cole J, Arlett J, et al. Clinical heterogeneity within xeroderma pigmentosum associated with mutations in the DNA repair and transcription gene ERCC3. *Am J Hum Genet* 1994;54:191-200.
176. Weeda G, Ma L, Van Ham RCA, Bootsma D, Van der Eb AJ, Hoeijmakers JHJ. Characterization of the mouse homolog of the XPBC/ERCC-3 gene implicated in xeroderma pigmentosum and Cockayne's syndrome. *Carcinogenesis* 1991;12:2361-8.
177. Riou L, Zeng L, Chevallier-Lagente O, Stary A, Nikaldo O, Taieb A, et al. The relative expression of mutated XPB genes results in xeroderma pigmentosum/Cockayne's syndrome or trichothiodystrophy cellular phenotypes. *Hum Mol Genet* 1999;8:1125-33.
178. Vermeulen W, Bergmann E, Auriol J, Rademakers S, Frit P, Appeldoorn E, et al. Sublimiting concentration of TFIIH transcription/DANN repair factor causes TTD-A trichothiodystrophy disorder. *Nat Genet* 2000;26:307-13.
179. Lehmann AR, Norris PG. DNA repair and cancer: speculations based on studies with xeroderma pigmentosum, Cockayne's syndrome and trichothiodystrophy. *Carcinogenesis* 1989;10:1353-6.
180. Broughton BC, Lehmann AR, Harcourt SA, Arlett CF, Sarasin A, Kleijer WJ, et al. Relationship between pyrimidine dimers, 6-4 photoproducts, repair synthesis and cell survival: studies using cells from patients with trichothiodystrophy. *Mutat Res* 1990;235:33-40.
181. Takayama K, Salazar EP, Broughton BC, Lehmann AR, Sarasin A, Thompson LH, et al. Defects in the DNA repair and transcription gene ERCC2 (XPD) in trichothiodystrophy. *Am J Hum Genet* 1996;58:263-70.
182. Broughton BC, Steingrimsdottir H, Weber CA, Lehmann AR. Mutations in the xeroderma pigmentosum group D DNA repair/transcription gene in patients with trichothiodystrophy. *Nat Genet* 1994;7:189-94.
183. Madzak C, Armier J, Stary A, Daya-Grosjean L, Sarasin A. UV-induced mutations in a shuttle vector replicated in repair deficient trichothiodystrophy cells differ with those in genetically-related cancer prone xeroderma pigmentosum. *Carcinogenesis* 1993;14:1255-60.
184. Marionnet C, Benoit A, Benhamou S, Sarasin A, Stary A. Characteristics of UV-induced mutation spectra in human XP-D/ERCC2 gene-mutated xeroderma pigmentosum and trichothiodystrophy cells. *J Mol Biol* 1995;252:550-62.
185. Lehmann AR, Arlett CF, Broughton BC, Harcourt SA, Steingrimsdottir H, Stefanini M, et al. Trichothiodystrophy, a human DNA repair disorder with heterogeneity in the cellular response to ultraviolet light. *Cancer Res* 1988;48:6090-6.
186. Otto AI, Riou L, Marionnet C, Mori T, Sarasin A, Magnaldo T. Differential behaviors toward ultraviolet A and B radiation of fibroblasts and keratinocytes from normal and DNA-repair-deficient patients. *Cancer Res* 1999;59:1212-8.
187. Dumaz N, Duthu A, Ehrhart JC, Drougard C, Appella E, Anderson CW, et al. Prolonged p53 protein accumulation in trichothiodystrophy fibroblasts dependent on unrepaired pyrimidine dimers on the transcribed strands of cellular genes. *Mol Carcinog* 1997;20:340-7.
188. Dumaz N, Drougard C, Quillet X, Mezzina M, Sarasin A, Daya-Grosjean L. Recovery of the normal p53 response after UV treatment in DNA repair-deficient fibroblasts by retroviral-mediated correction with the XPD gene. *Carcinogenesis* 1998;19:1701-4.
189. Abrahams PJ, Schouten R, Van Laar T, Houweling A, Terleth C, Van der Erb AJ. Different regulation of p53 stability in UV-irradiated normal and DNA repair deficient human cells. *Mutat Res* 1995;336:169-80.
190. Cleaver JE. Hair today, gone tomorrow: transgenic mice with human repair deficient hair disease. *Cell* 1998;93:1099-102.
191. De Boer J, Van Steeg H, Berg RJW, Garssen J, De Wit J, Van Oostrum CTM, et al. Mouse model for the DNA repair/basal transcription disorder trichothiodystrophy reveals cancer predisposition. *Cancer Res* 1999;59:3489-94.
192. Vuillaume M, Daya-Grosjean L, Vincens P, Pennetier JL, Tarroux P, Baret A, et al. Striking differences in cellular catalase activity between two DNA repair-deficient diseases: xeroderma pigmentosum and trichothiodystrophy. *Carcinogenesis* 1992;13:321-8.
193. Hoffschir F, Daya-Grosjean L, Petit PX, Nocentini S, Dutrillaux B, Sarasin A, et al. Low catalase activity in xeroderma pigmentosum fibroblasts and SV40-transformed human cell lines is directly related to decreased intracellular levels of the cofactor, NADPH. *Free Rad Biol Med* 1998;24:809-16.
194. Terleth C, Van Laar T, Schouten R, Van Steeg H, Hodemaekers H, Wormhoudt T, et al. A lack of radiation-induced ornithine decarboxylase activity prevents enhanced reactivation of herpes simplex virus and is linked to non-cancer proneness in xeroderma pigmentosum patients. *Cancer Res* 1997;57:4384-92.
195. Mariani E, Facchini A, Honorati MC, Lalli E, Berardesca E, Ghetti P, et al. Immune defects in families and patients with xeroderma pigmentosum and trichothiodystrophy. *Clin Exp Immunol* 1992;88:376-82.

196. Norris PG, Limb GA, Hamblin AS, Lehmann AR, Arlett CF, Cole J, et al. Immune function, mutant frequency, and cancer risk in the DNA repair defective genodermatoses xeroderma pigmentosum, Cockayne's syndrome, and trichothiodystrophy. *J Invest Dermatol* 1990;94:94-100.
197. Gaspari AA, Fleisher TA, Kraemer KH. Impaired interferon production and natural killer cell activation in patients with the skin cancer-prone disorder, xeroderma pigmentosum. *J Clin Invest* 1993;92:1135-42.
198. Ahrens C, Grewe M, Berneburg M, Grether-Beck S, Quilliet X, Mezzina M, et al. Photocarcinogenesis and inhibition of intercellular adhesion molecule 1 expression in cells of DNA-repair-defective individuals. *Proc Natl Acad Sci U S A* 1997;94:6837-41.
199. OMIM. Available at: <http://www.ncbi.nlm.nih.gov/omim>. Accessed September 2000.
200. Vermeulen W, Rademakers S, Jaspers NGJ, Appeldoorn E, Klein B, Kleijer WJ, et al. A temperature-sensitive disorder in basal transcription and DNA repair in humans. *Nat Genet* 2001;27:299-303.
201. Mounkes LC, Jones RS, Liang BC, Gelbart W, Fuller MT. A *Drosophila* model for xeroderma pigmentosum and Cockayne's syndrome: haywire encodes the fly homolog of ERCC3, a human excision repair gene. *Cell* 1992;71:925-37.
202. Raff EC, Fuller MT, Kaufman TC, Kempfues KJ, Rudolph JE, Raff RA. The testis-specific beta-tubulin subunit in *Drosophila melanogaster* has multiple functions in spermatogenesis. *Cell* 1982;28:33-40.
203. Readhead C, Popko B, Takahashi N, Shine HD, Saavedra RA, Sidman RL, et al. Expression of a myelin basic protein gene in transgenic shiverer mice: correction of the dysmyelinating phenotype. *Cell* 1987;48:703-12.
204. Howell RR, Arbisser AI, Parsons DS, Scott CI, Fraustadt U, Collie WR, et al. The Sabinas syndrome. *Am J Hum Genet* 1981;33:957-67.
205. Baden HP, Katz A. Trichothiodystrophy without retardation: one patient exhibiting transient combined immunodeficiency syndrome. *Pediatr Dermatol* 1988;5:257-9.
206. Van Neste D, Boré P. Trichothiodystrophie: une étude morphologique et biochimique. *Ann Dermatol Venerol* 1983;110:409-17.
207. Lucky PA, Kirsch N, Lucky AW, Carter DM. Low-sulfur hair syndrome associated with UVB photosensitivity and testicular failure. *J Am Acad Dermatol* 1984;11:340-6.
208. Sigmundsson J, Woolf L, Magenis E, Steiner RD, Roberts J, Piller, et al. A severe case of trichothiodystrophy due to a DNA repair defect [abstract]. *Am J Hum Genet* 1999;65:A344.
209. Kousseff BG, Esterly NB. Trichothiodystrophy, IBIDS syndrome or Tay syndrome? *Birth Defects* 1988;24:169-81.
210. Motley RJ, Finlay AY. A patient with Tay's syndrome. *Pediatr Dermatol* 1989;6:202-5.
211. Stefanini M, Lagomarsini P, Arlett CF, Marinoni S, Borrone C, Crovato F, et al. Xeroderma pigmentosum (complementation group D) mutation is present in patients affected by trichothiodystrophy with photosensitivity. *Hum Genet* 1986;74:107-12.
212. Poissonnier M, Blanc A, Bat P. Conseil génétique dans une neuro-ectodermose: la trichothiodystrophie (TTD) de Vera Price. Cheveux cassants dont la teneur en soufre est réduite. *J Genet Hum* 1988;36:361-5.
213. King MD, Gummer CL, Stephenson JBP. Trichothiodystrophy-neurotrichocutaneous syndrome of Pollitt: a report of two unrelated cases. *J Med Genet* 1984;21:286-9.
214. Venencie PY, Dupré A, Gouttières F, Saurat JH. Trichothiodystrophie. *Soc Fr Dermatol J Paris, cas* 78, 1982.
215. Foulc P, David A, Stalder JF. Manifestations évolutives dans les trichothiodystrophies. *Ann Dermatol Venerol* 1997;124 (Suppl):S103-4.
216. Calvieri S, Giustini S, Nini G, Ribuffo D. Trichothiodystrophy: two cases. In: Wilkinson DS, Mascaró JM, Orfanos CE, Albers J, editors. *Clinical Dermatology The CMD case collection*. Stuttgart: Schattauer; 1987. p. 65-6.
217. White MC, Hayes TJ. Trichothiodystrophy. *J Assoc Mil Dermatol* 1987;13:4-6.
218. Meynadier J, Guillot B, Barnéon G, Djian B, Lévy A. Trichothiodystrophie. *Ann Dermatol Venerol* 1987;114:1529-36.
219. Gummer CL, Dawber RPR. Trichothiodystrophy: an ultrastructural study of the hair follicle. *Br J Dermatol* 1985;113:273-80.
220. De Prost Y, Lemaistre R, Dupré A. Trichothiodystrophie associée à une ichthyose et à un retard statural et psychomoteur (Syndrome de Tay). *Ann Dermatol Venerol* 1986;113:1016-7.
221. Van Neste D, Caulier B, Thomas P, Vasseur F. PIBIDS: Tay's syndrome and xeroderma pigmentosum. *J Am Acad Dermatol* 1985;12:372-3.
222. Diaz-Perez JL, Vasquez JA. Flattened hair syndrome: a new disease. *Arch Dermatol* 1983;119:854-5.
223. Larrègue M, Ottavy N, Bressieux JM, Lorette J. Bébé collodion: trente-deux nouvelles observations. *Ann Dermatol Venerol* 1986;113:773-85.
224. Van Neste D, Degreef H, Van Haute N, Van Hee J, Vandermaesen J, Taieb A, et al. TTD variante: une variante clinique de trichothiodystrophie: aspects cliniques à propos de deux cas non publiés. *Nouv Dermatol* 1988;7(Suppl 1):49.
225. Fois A, Balestri P, Calvieri S, Zampetti M, Giustini S, Stefanini M, et al. Trichothiodystrophy without photosensitivity: biochemical, ultrastructural and DNA repair studies. *Eur J Pediatr* 1988;147:439-41.
226. Rebora A, Crovato F. PIBI(D)S syndrome: trichothiodystrophy with xeroderma pigmentosum (group D) mutation. *J Am Acad Dermatol* 1987;16:940-7.
227. Van Neste DJ, Antoine JL, Vasseur F, Thomas P. Tay's syndrome and xeroderma pigmentosum [abstract]. 17th World Congress of Dermatology, Part 1 1987. WS-18.
228. Crovato F, Rebora A. PIBI(D)S syndrome: a new entity with defect of the deoxyribonucleic acid excision repair system. *J Am Acad Dermatol* 1985;13:683-5.
229. Crovato F, Borrone C, Rebora A. The Tay syndrome (congenital ichthyosis with trichothiodystrophy). *Eur J Pediatr* 1984;142:233-4.
230. Yong SL, Cleaver JE, Tullis GD, Johnston MM. Is trichothiodystrophy part of the xeroderma pigmentosum spectrum? [abstract] *Am J Hum Genet* 1984;36(Suppl):825.
231. Stefanini M, Lagomarsini P, Giorgi R, Nuzzo F. Complementation studies in cells from patients affected by trichothiodystrophy with normal or enhanced UV photosensitivity. *Mutat Res* 1987;191:117-9.
232. Stefanini M, Lagomarsini P, Fois A, Balestri P, Nuzzo F. Sensitivity to sunlight in patients affected by trichothiodystrophy is related to the capacity to repair the UV-induced DNA damage [abstract]. *Br J Cancer* 1986;54:355.
233. Marinoni S, Trevisan G, Not T, Stefanini M, Lagomarsini P. Trichothiodystrophy with photosensitivity: overlook of six Italian cases [abstract]. *Clinical Dermatology 2000 London* 1990. P9.
234. Pruksachatkunakorn C, Duarte AM, Schachner L. A girl with IBIDS syndrome [abstract]. *Pediatr Dermatol* 1992;9:215.
235. Amoric JC, Dutartre H, David A, Sarasin A, Litoux P, Stadler JF. Trichothiodystrophy (TTD) and impaired DNA repair in two siblings [abstract]. *Pediatr Dermatol* 1995;12:96.
236. Sasi R, Rosenfeld B, Eyedoux P, Teebi AS. Heterogeneity of trichothiodystrophy-neurocutaneous syndrome [abstract]. *Am J Hum Genet* 1995;57:1783.

237. Pruksachatkunakorn C, Duarte AM, Schachner LA. A girl with IBIDS. Presented as an abstract at the 52nd Annual Meeting of the American Academy of Dermatology, Washington, DC, Dec 4-9, 1993. p. 275.
238. Judge M, Harper J. The ichthyoses: a re-appraisal based on a study of 100 patients. *Br J Dermatol* 1990;123(Suppl 37):50.
239. Przedborski S, Ferster A, Song M, Tonnesen T, Ketelbant P, Vamos E. Brittle hair, intellectual impairment, decreased fertility and short stature (BIDS) syndrome in three sibs [abstract]. *J Neurol* 1985;232(Suppl):127.
240. Rebora A, Guarrera M, Crovato F. Amino acid analysis in hair from PIBI(D)S syndrome. *J Am Acad Dermatol* 1986;15:109-11.
241. Coulter DL, Beals TF, Allen RJ. Neurotrichosis: hair-shaft abnormalities associated with neurological diseases. *Dev Med Child Neurol* 1982;24:634-44.
242. Cahuzac P, Vanlerberghe O, Morel P. Trichothiodystrophie. *Soc Fr Dermatol J Paris cas* 80, 1984.
243. Dellac M, Loesche C, Van Neste D, Thomas P. PIBI(D)S and cataract [abstract]. 18th World Congress of Dermatology 1992. 231A.
244. Bertolino AP, O'Guin WM. Differentiation of the hair shaft. In: Olsen EA, editor. *Disorders of hair growth: diagnosis and treatment*. New York: McGraw-Hill; 1994. p. 21-37.
245. Moustacchi E, coordinator. DNA repair. *Biochimie* 1999;81:1-181.

Answer sheets are bound into the Journal for US and Canadian members. Request additional answer sheets from American Academy of Dermatology, Member Services Department, PO Box 4014, Schaumburg, IL 60168-4014. Phone 847-330-0230; E-mail: tsmith@aad.org

CME examination

Identification No. 801-106

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-28, Itin PH, Sarasin A, Pittelkow MR. *J Am Acad Dermatol* 2001;44:891-920.

Directions for questions 1-28: Give single best response.

- The term *trichothiodystrophy* refers to
 - sulfur-deficient nail disease
 - hair with methionine deficiency
 - excessive sulfur-containing hair disorder
 - sulfur-deficient hair with malabsorption
 - sulfur-deficient, brittle hair syndrome
- Trichothiodystrophy is inherited in the following pattern:
 - autosomal dominant
 - autosomal recessive
 - X-linked dominant
 - X-linked recessive
 - paradominant
- Which light-microscopic finding is not characteristic of trichothiodystrophy?
 - Trichoschisis
 - Trichorrhexis nodosa
 - Trichorrhexis invaginata
 - Irregular surface
 - Irregular diameter
- Which condition has never been associated with "dark and light banding" by polarizing microscopy?
 - Argininosuccinic aciduria
 - Acrodermatitis enteropathica
 - Kwashiorkor
 - Methionine-deficient hair
 - Alkaptonuria
- Which feature is not part of the Tay syndrome?
 - Ichthyosiform erythroderma
 - Hair shaft abnormalities
 - Mental and somatic retardation
 - Neutropenia
 - Collodion baby
- The name "Sabinas" syndrome derives from
 - the author of the first description
 - the name of the first patient
 - the name of a town where patients lived
 - the acronym sulfur deficiency alternating dark and light banding, brittle hair, ichthyosis, aminoaciduria, sclerosteosis
 - the Greek god of hair
- Which condition does not feature low sulfur hair content?
 - Marinesco-Sjögren syndrome
 - Onychotrichodysplasia
 - Kwashiorkor
 - Pili bifurcati
 - Itin syndrome
- Which disease has never been observed to harbor a DNA repair defect?
 - BIDS syndrome
 - Trichothiodystrophy
 - PIBIDS syndrome
 - Xeroderma pigmentosum
 - Cockayne syndrome
- Embryologically, trichothiodystrophy can best be explained as an
 - endodermal dysplasia
 - mesodermal dysplasia
 - endodermal-mesodermal dysplasia
 - ectodermal dysplasia with mesodermal and rare endodermal dysplasia
 - pure "one-layer disease" of ectodermal origin
- Which feature is necessary for the diagnosis of trichothiodystrophy?
 - Somatic retardation
 - Brittle hair
 - Neutropenia
 - Ichthyosis
 - Mental retardation
- The most common similarity between trichothiodystrophy and Cockayne syndrome is
 - agenesis of corpus callosum
 - central nervous system dysmyelination
 - brittle hair and nails

- d. heterotopia of gray matter
e. ataxia
12. "Dark and light banding" under polarizing microscopy may be explained by
a. alternating arrangement of microfibrils
b. alternating calcium and sulfur content
c. alternating absence of cuticle
d. pili annulati
e. preparation artifact
13. Which statement concerning hair composition is *incorrect*?
a. Hair is composed mainly of keratins and keratin-associated proteins.
b. Keratin-associated proteins can be further classified into at least 8 subfamilies.
c. Keratin-associated proteins are divided into cyst(e)ine-rich and glycine-tryosine-rich polypeptides.
d. As a rule, hair of patients with trichothiodystrophy has at least a 50% decrease in cyst(e)ine and sulfur content.
14. Hair brittleness in trichothiodystrophy results from
a. reduction in the content of the hair-specific cyst(e)ine-rich proteins within the matrix
b. excessive keratin-associated protein oxidation
c. markedly reduced diameter
d. absent microfibrils within the hair shaft
e. "weathering" or other exogenous factors
15. Prenatal diagnosis for photosensitive trichothiodystrophy is best performed by
a. polarizing microscopy of hair collected by fetoscopy
b. comet assay as a DNA repair test
c. histologic examination of ichthyosis after biopsy performed after fetoscopy
d. fibroblast cultivation and assay of unscheduled DNA synthesis
e. scanning electron microscopy of hair collected by fetoscopy
16. Patients with trichothiodystrophy have an associated DNA repair defect in approximately what percentage of cases?
a. 5
b. 10
c. 30
d. 50
e. 80
17. Which of the following mechanisms is not part of the nuclear excision repair program?
a. Recognition of DNA lesion
b. Removal of damaged oligonucleotides
c. Homologous recombination of UV-induced DNA defects
d. Gap filling by DNA synthesis
e. Ligation of DNA strands
18. Most of the DNA repair defects in patients with trichothiodystrophy can be assigned to which complementation group?
a. XPA
b. XPB
c. XPC
d. XPD
e. XPE
19. Which statement concerning the classification of trichothiodystrophy based on photosensitivity and excision repair is *incorrect*?
a. Patients may show photosensitivity and no defect in excision repair of UV damage.
b. Patients may show no photosensitivity but a nuclear excision repair defect.
c. Patients may show photosensitivity and a nuclear excision repair defect in the same gene as in xeroderma pigmentosum D.
d. Patients may show photosensitivity and a nuclear excision repair defect in the same gene as in xeroderma pigmentosum B.
e. Patients may show photosensitivity and a nuclear excision repair defect in the same gene as in xeroderma pigmentosum F.
20. The gene responsible for human xeroderma pigmentosum group D has been identified as a
a. DNA ligase
b. DNA helicase
c. catalase
d. hydroxylase
e. the gene has not yet been assigned
21. Catalase activity is
a. increased in trichothiodystrophy compared with xeroderma pigmentosum
b. increased in xeroderma pigmentosum compared with trichothiodystrophy
c. decreased in trichothiodystrophy
d. equivalent in xeroderma pigmentosum and trichothiodystrophy
e. similar in xeroderma pigmentosum compared with normal controls
22. The human *ERCC2/XPD* gene maps to the long arm of
a. chromosome 2
b. chromosome 6
c. chromosome 7
d. chromosome 12
e. chromosome 19
23. The *XPD/ERCC2* gene is involved in
a. recognition of DNA lesions
b. unwinding DNA in the vicinity of a lesion
c. ligation of DNA strands
d. DNA base substitution
e. gap filling by DNA synthesis
24. The most common mutation identified in photosensitive patients with trichothiodystrophy is
a. Arg112His substitution
b. Leu461Val substitution
c. Arg683Trp substitution

- d. Arg722Trp substitution
 - e. Arg658His substitution
25. Predisposition to cancer is favored in xeroderma pigmentosum but not in trichothiodystrophy because
- a. catalase activity is not decreased in trichothiodystrophy.
 - b. no alteration of intercellular adhesion molecule 1 expression is present in trichothiodystrophy but is present in xeroderma pigmentosum.
 - c. p53 tumor suppressor gene product is enhanced after UV radiation in xeroderma pigmentosum but not in trichothiodystrophy.
 - d. CD3 and CD4 lymphocytes are reduced in trichothiodystrophy.
 - e. None of the above-mentioned mechanisms are correct.
26. What sign or symptom is not observed in mice with trichothiodystrophy?
- a. Brittle hair
 - b. Developmental abnormalities
 - c. Neutropenia
 - d. UV sensitivity
 - e. Skin abnormalities
27. The mice with trichothiodystrophy were obtained by
- a. spontaneous mutation
 - b. radiation mutagenesis
 - c. chemical mutagenesis
 - d. transgenic procedure
 - e. mating of an ichthyotic mouse with the hairless mice
28. What is the most important difference between the mouse model of trichothiodystrophy and the human disease?
- a. Normal hair in the mouse
 - b. Increased cancer risk from chemical carcinogens in the mouse
 - c. No other developmental abnormalities
 - d. Normal life span in mice
 - e. Normal size compared with control mice

AVAILABILITY OF JOURNAL BACK ISSUES

As a service to our subscribers, copies of back issues of the Journal of the American Academy of Dermatology for the preceding 5 years are maintained and are available for purchase from Mosby until inventory is depleted. The following quantity discounts are available: 25% off on quantities of 12 to 23, and one third off on quantities of 24 or more. Please write to Mosby, Subscription Customer Service, 6277 Sea Harbor Dr, Orlando, FL 32887, or call 800-654-2452 or 407-345-4000 for information on availability of particular issues and prices. If unavailable from the publisher, photocopies of complete issues may be purchased from Bell & Howell Information and Learning, 300 N Zeeb Rd, Ann Arbor, MI 48106, (313)761-4700.

Answers to CME examination

Identification No. 801-106

June 2001 issue of the Journal of the American Academy of Dermatology

Questions 1-28, Itin PH, Sarasin A, Pittelkow MR. J Am Acad Dermatol 2001;44:891-920.

- | | |
|-------|-------|
| 1. e | 15. b |
| 2. b | 16. d |
| 3. c | 17. c |
| 4. e | 18. d |
| 5. d | 19. e |
| 6. c | 20. b |
| 7. d | 21. a |
| 8. a | 22. e |
| 9. d | 23. b |
| 10. b | 24. a |
| 11. b | 25. a |
| 12. b | 26. c |
| 13. e | 27. d |
| 14. a | 28. b |

AMERICAN BOARD OF DERMATOLOGY EXAMINATION DATES

In 2001, the Certifying Examination of the American Board of Dermatology (ABD) will be held at the Holiday Inn O'Hare International in Rosemont, Illinois on Oct 14 and 15, 2001. **The deadline for receipt of applications is May 1, 2001.**

The next examination for subspecialty certification in Dermatopathology will be held in Tampa, Florida on Friday, Nov 16, 2001. **The deadline for receipt of applications is July 1, 2001.**

The next examination for subspecialty certification in Clinical and Laboratory Dermatological Immunology will be held in Rosemont, Illinois, on Oct 12, 2001.

The next Recertification Examination of the ABD will be mailed to approved candidates on June 1, 2001.

A certification process is being developed for the subspecialty of Pediatric Dermatology. It is anticipated that the first examination will be administered in 2002 or 2003. Further details about the examination will be available from the Board office.

For further information about these examinations, please contact:

Antoinette F. Hood, MD
Executive Director, American Board of Dermatology
Henry Ford Hospital
1 Ford Place
Detroit, MI 48202-3450
Telephone: (313)874-1088
Fax: (313)872-3221