Trichothiodystrophy, a Human DNA Repair Disorder with Heterogeneity in the Cellular Response to Ultraviolet Light


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ABSTRACT

Trichothiodystrophy (TTD) is an autosomal recessive disorder characterized by brittle hair with reduced sulfur content, ichthyosis, peculiar face, and mental and physical retardation. Some patients are photosensitive. A previous study by Stefanini et al. (Hum. Genet., 74: 107-112, 1986) showed that cells from four photosensitive patients with TTD had a molecular defect in DNA repair, which was not complemented by cells from xeroderma pigmentosum, complementation group D. In a detailed molecular and cellular study of the effects of UV light on cells cultured from three further TTD patients who did not exhibit photosensitivity we have found an array of different responses. In cells from the first patient, survival, excision repair, and DNA and RNA synthesis following UV irradiation were all normal, whereas in cells from the second patient all these responses were similar to those of excision-defective xeroderma pigmentosum (group D) cells. With the third patient, cell survival measured by colony-forming ability was normal following UV irradiation, even though repair synthesis was only 50% of normal and RNA synthesis was severely reduced. The excision-repair defect in these cells was not complemented by other TTD cell strains. These cellular characteristics of patient 3 have not been described previously for any other cell line. The normal survival may be attributed to the finding that the deficiency in excision-repair is confined to early times after irradiation. Our results pose a number of questions about the relationship between the molecular defect in DNA repair and the clinical symptoms of xeroderma pigmentosum and TTD.

INTRODUCTION

Trichothiodystrophy is an autosomal recessive disorder characterized by sulfur-deficient brittle hair. Hair shafts split longitudinally into small fibers and this brittleness is associated with levels of cysteine/cystine in hair proteins which are 15-50% of those in normal individuals (1-3). The condition is also accompanied by physical and mental retardation of varying severity (1, 3-6). The patients often have an unusual facial appearance, with protruding ears and a receding chin. Mental abilities range from low normal to severe retardation. Ichthyosis (scaling of the skin) has been reported in many of the affected patients (3, 6-8). The disorder was first recognized by Pollitt et al. (1) and about 20 reports of similar cases have appeared in the literature. The accompanying symptoms are very heterogeneous. Severe photosensitivity has been reported for about one-half of the patients (e.g., Refs. 3, 7, and 9). Skin cancer has not been reported in any patient with TTD. The condition has been reviewed recently by Nuzzo and Stefanini (10).

The association of TTD with a DNA repair defect was first reported briefly by Yong et al. (9) and van Neste et al. (11). These reports both stated that in cells from photosensitive patients with TTD there was a defect in excision repair following UV damage, similar to that observed in patients with xeroderma pigmentosum. A more extensive study by Stefanini et al. (7) showed that four Italian patients with TTD and associated photosensitivity all showed a deficiency in excision-repair of UV damage in both lymphocytes and fibroblasts. Furthermore, cell fusion studies with cells from different XP complementation groups showed that there was no complementation between TTD cells and those from XP group D. In contrast an Italian TTD patient without photosensitivity had no defect in excision-repair (12).

We have carried out a detailed study of the response to UV light of fibroblasts from three further patients with TTD, and our results, which show remarkable heterogeneity between patients, are presented in this paper. We find that the cells from one patient have a completely normal response to UV, whereas those from a second patient show characteristics of XP-D cells, like those described by Stefanini et al. (7). The cells from the third patient show some normal responses, whereas other aspects are markedly deficient depending on the nature of the assay.

MATERIALS AND METHODS

Patients. Two of the TTD patients whose cells are used in our experiments are those described by King et al. (6). Reevaluation of the clinical data on these patients has revealed that, contrary to previous suggestions (6), neither of them exhibited any photosensitivity. Cultures from these patients are correctly designated TTD1GL and TTD2GL, respectively, but we shall refer to them in this paper, for simplicity, as P1 and P2.

The third strain, TTD1B1 (referred to as P3), was from a 6-year-old boy with brittle hair and trichorrhexis nodosa. His height is 86.5 cm and weight is 10.7 kg (both below the 3rd percentile), his head circumference is 47 cm (also below 3rd percentile). He has a thin face, full cheeks, stubbly hair and nystagmus with remnants of cataracts which were removed at 3 months of age. His nails are dysplastic and his skin is ichthyotic. There are no indications of photosensitivity. Although he is able to smile, socialize, laugh, and chuckle, he has no real language. He sits, stands, and manipulates simple toys but does not walk unaided.

At birth he had the characteristic "collodion baby" appearance of the skin, and he had a slightly abnormal facial appearance with brittle stubby hair. In infancy he had many respiratory infections and did not thrive well, and at age 4 years he was followed by general debility and according to his mother a regression of development. Progress thereafter has been slow, but he appears to be stable with no further degeneration.

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To whom requests for reprints should be addressed.

The abbreviations used are: TTD, trichothiodystrophy; CS, Cockayne's syndrome; SCE, sister chromatid exchange; UDS, unscheduled DNA synthesis; XP, xeroderma pigmentosum.

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DNA REPAIR DEFECT IN TRICHTHIODYSTROPHY

Cell Culture. The fibroblast cell strains used in our experiments were all established from skin biopsies in our own or other laboratories. They are listed in Table 1. Cells were maintained in Eagle’s minimum essential medium supplemented with 15% fetal calf serum. To bring them into a state approaching quiescence, they were plated in complete medium, which was replaced the following day with medium containing 0.5% serum. The cells were then incubated for at least 2 days prior to experiments. Although not all of the population will have completely ceased dividing after 2 days, for brevity we refer to such populations as nondividing.

Cellular Responses to UV. Procedures for cell culture (13), cell survival (14), mutation (15), UDS (16), recovery of RNA synthesis (17, 18), stationary phase survival (17), and complementation (12) following UV irradiation are routinely used in our laboratories and have all been described previously. For determination of SCEs exponentially growing cells were UV irradiated and cultured for two cycles (44–50 h) in the presence of 5 μM bromodeoxyuridine. The cells were processed as described previously (19). Measurement of repair replication using alkaline CsCl gradients followed the procedure of Smith and Hanawalt (20). UV endonuclease-sensitive sites were assayed in permeabilized cells by the high-salt procedure of van Zeeland et al. (21). For measurement of incision breaks 2 × 10⁶ normal cells and TTD cells were labeled with 0.05 μCi/ml [³²P]thymidine (50 mCi/mmol) and 5 μCi/ml [³H]-thymidine (2.5 Ci/mmol), respectively. The following day the medium was replaced with fresh medium containing 0.5% fetal calf serum. After a further 2 or 3 days of incubation, the cells were incubated for 30 min in 0.5% serum medium containing 10⁻³ M hydroxymeurea, 10⁻⁴ M 1-β-D-arabinofuranosycytosine, UV irradiated, and incubated for a further 30 min in the presence of the inhibitors. Cells were then scraped off the dishes into 0.2 ml 0.02% EDTA in buffered saline, the ³²P-labeled normal cell suspension was mixed with the ³H-labeled TTD cell suspension which had been exposed to the same treatment, and 150 μl were lysed on top of alkaline sucrose gradients which were subsequently centrifuged at 30,000 rpm for 60 min. Fractions were collected and the radioactivity measured as described previously (22).

RESULTS

We have examined the responses of TTD cells to UV irradiation using several different assay systems.

Patient 1. The responses to UV light of cell strain P1 were normal in all assays in which they were tested, as shown by the filled inverted triangles in the figures. Thus cell survival (Fig. 1), mutability (Fig. 2A), and SCE induction (Fig. 2B) were all similar to those in normal cells. The spontaneous and induced mutation frequencies of P1 appear from Fig. 2A to be lower than those of normal cells. The scale of these experiments is such that we did not consider confirmation and more detailed investigation of this observation to be warranted at this time. The only conclusion we wish to draw from the data is that P1 cells are clearly not more mutable than normals.

Biochemical measurements showed that unscheduled DNA synthesis was very similar to that in normal cells from data accumulated over a period of many years. B, induction of SCEs by UV light. For each experimental point, 25 cells were scored.

Patient 2. The responses of strain P2 were, in contrast, those of cells with a severe deficiency in excision-repair (see filled circles in the figures). The survival of P2 was much lower than that of P1.

Table 1 Cell strains used

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Cell strains</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Normal</td>
<td>IBR</td>
<td>GM730</td>
</tr>
<tr>
<td></td>
<td>VH</td>
<td>4BR</td>
</tr>
<tr>
<td></td>
<td>KB</td>
<td>SB</td>
</tr>
<tr>
<td>TTD</td>
<td>TTD1GL (P1)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>TTD2GL (P2)</td>
<td>6</td>
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<tr>
<td></td>
<td>TTD3BI (P3)</td>
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</tr>
<tr>
<td></td>
<td>TTD4PV</td>
<td>7</td>
</tr>
<tr>
<td>CS</td>
<td>CS1BR</td>
<td>42</td>
</tr>
<tr>
<td>CS1BO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS2BE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XP</td>
<td>XP1BR (D)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>XP5BR</td>
<td>43</td>
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<tr>
<td></td>
<td>XP2BI (E)</td>
<td>44</td>
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<tr>
<td></td>
<td>XP2RO (C)</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>XP25RO (A)</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>XP4LO (A)</td>
<td>14</td>
</tr>
</tbody>
</table>

* Letters in parentheses, complementation groups.
that of normal cells, its response being similar to that of cells from patients with XP or Cockayne's syndrome and of a strain TTD4PV from an Italian patient previously described by Ste-  

fanini et al. (7) (Fig. 1). Likewise the mutability of P2 cells to 6-thioguanine resistance was greatly enhanced like that of XP cells (Fig. 2B), as has previously been shown for excision-defective XP cells (23). These cellular abnormalities could be attributed to a deficiency in excision-repair, as shown by a reduced rate of removal of UV-induced damage, measured as endonuclease-sensitive sites (Fig. 5), and a low rate of UDS as shown in Fig. 3A. The reduced survival and UDS in P2 are properties similar to those of cell strains from four photosensitive Italian TTD patients (7).

The deficiency in UDS forms the basis of a genetic complementation test for XP, and it has been used to reveal nine different complementation groups. In these studies cells from different XPs were fused and UDS was measured in the resulting heterokaryons. Restoration of UDS to levels found in normal cells indicates that the two donor cells are in different complementation groups. Conversely, if UDS remains at the reduced levels of the donor cells the two donors are assigned to the same complementation group. Previous work (7) showed that four TTD strains failed to complement XPs from complementation group D. Results shown in Table 2 show that P2 did not complement two of these previously studied TTD strains, TTD3PV and TTD4PV. UDS in the heterokaryons remained at the same level as in the parental cells. In contrast, when these strains were fused with an XP strain from complementation group C (XP9PV), UDS in the heterokaryons was restored to normal levels. In contrast, in heterokaryons from P1 and TTD3PV or TTD4PV, UDS was restored to normal levels. Thus P1 cells, unlike P2 cells, are able to correct the defect in TTD3PV and TTD4PV.

The genetic disorder Cockayne's syndrome is, like XP, UV sensitive at the cellular level but, in contrast to XP, shows no obvious deficiency in excision-repair (24). Nevertheless in CS cells RNA synthesis fails to recover following its depression by UV irradiation, whereas in normal cells rapid recovery occurs to normal levels (17). Observation of this deficiency in CS cells can be optimized by using nondividing cells and measuring RNA synthesis 16–24 h after irradiation with a high UV fluence (25). Fig. 4A shows that under these conditions, as reported previously, RNA synthesis in XP and CS cells was reduced to very low levels whereas in normal cells it had recovered almost to unirradiated levels. In contrast to the normal response of P1, RNA synthesis was reduced to 10% of unirradiated levels in P2.

Patient 3. The cellular responses of P3 (filled squares in figures) to the lethal (Fig. 1), mutagenic (Fig. 2A), and SCE-inducing (Fig. 2B) effects of UV irradiation were, as with P1, indistinguishable from those of normal cells. Likewise the rate of removal of UV endonuclease-sensitive sites in normal and P3 cells were the same (Fig. 5). In marked contrast, however, measurements of UDS revealed a clear deficiency in P3, partic-
DNA repair defect in trichothiodystrophy

Fig. 5. Removal of UV endonuclease-sensitive sites. Cells were incubated for various times after UV irradiation with 4 J/m². Normal cells labeled with [³⁵S]thymidine (0.05 μCi/ml) mixed with TTD cells labeled with [³²P]thymidine (5 μCi/ml) were permeabilized and incubated with a crude fraction of Micrococcus luteus extract containing UV endonuclease activity. The mixture was lysed on top of alkaline sucrose gradients. The number of breaks (UV endonuclease-sensitive sites) was calculated from weight-average molecular weights of the molecular weight distribution of the DNA molecules. Bars, SEM.

Fig. 6. Incision breaks. Nondividing cells were incubated for 30 min in the presence of hydroxyurea and 1-α-D-arabinofuranosylcytosine following UV irradiation with different doses. The weight-average molecular weights of the DNA molecules were calculated after centrifugation in alkaline sucrose gradients, and the number of breaks was determined.

Fig. 7. Time course of repair replication. [³²P]labeled exponentially growing cells were UV irradiated with a fluence of 10 J/m² and incubated for various times in the presence of hydroxyurea, [³²P]thymidine, and bromodeoxyuridine. The specific activity of the repaired DNA was measured by centrifugation in alkaline CsCl gradients.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>1BR</th>
<th>GM730</th>
<th>P3</th>
</tr>
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<tbody>
<tr>
<td>0-3 h</td>
<td>0.84</td>
<td>0.93</td>
<td>0.39</td>
</tr>
<tr>
<td>6-24 h</td>
<td>0.60</td>
<td>0.77</td>
<td>0.70</td>
</tr>
</tbody>
</table>

The discrepancy between the normal responses of P3 cells shown in Figs. 1, 2, and 5 and the defective repair synthesis shown in Fig. 3 prompted us to carry out a more detailed examination of excision-repair in P3 cells.

Kinetics of Excision-Repair. The rate of the incision step of excision-repair can be measured by inhibiting the repair synthesis step with a combined treatment of hydroxyurea and 1-α-D-arabinofuranosylcytosine and then measuring the accumulation of incision breaks in the DNA (26). The dose responses for the number of breaks accumulated in 30 min following UV irradiation (Fig. 6) were very similar to those obtained in the repair synthesis experiments (Fig. 3). Breaks were rarely detectable in strain P2, and in P3 they were reduced to about 50% of that in normal cell strains.

The UDS and incision break experiments in which a deficiency in P3 cells was revealed differed from the cellular experiments and the UV endonuclease assay in two respects. The former assays were carried out over a short period of time immediately after UV irradiation, and they used nondividing cells, whereas the latter were long-term measurements using dividing cells. In order to ascertain whether these differences in conditions could account for the apparent discrepancies in our observations we have measured repair replication in dividing cells and extended our measurements over a period of 24 h. Fig. 3D shows the dose response for repair replication in dividing cells over a 3-h period. The results are similar to those in nondividing cells, with a deficiency in P3 cells which is more marked at high doses. A time course experiment revealed, however, that this reduced rate of repair synthesis is confined to the first few hours after irradiation (Fig. 7). The rate of repair from 6-24 h appears to be similar in normal and P3 cells. In three experiments like those in Fig. 7 the amount of repair synthesis in P3 cells was 50 ± 14% (SEM) of that in GM730 cells when measured over 3 h, but 73 ± 17% when measured over 24 h. This is confirmed by the results in Table 3. When measured over the 0-3-h period the repair synthesis in P3 cells was about 40-50% of that in normal cells. If, however, the measurements were made in the period from 6 to 24 h after irradiation the amount of repair synthesis was similar in P3 and in normal cells. We conclude that the deficiency in P3 cells is confined to repair processes which occur at early times after irradiation and as shown in Figs. 3 and 6 is more marked at higher doses.

RNA Synthesis and Cell Survival in Nondividing Cells. We have measured the recovery of RNA synthesis under standard conditions used routinely in our laboratory (i.e., 24 h after a UV fluence of 15 J/m²). As seen in Fig. 4A under these conditions RNA synthesis is severely depressed in P3 cells remaining at 25% of that in unirradiated cells. The dose-
response curve in Fig. 4B again shows, however, that this failure to recover to normal rates is observed only at fluences above 5 J/m². In contrast in P2 cells a drastic depression of RNA synthesis is observed after 5 J/m².

We have also measured cell survival in P3 cells by a procedure in which nondividing cells are irradiated (27). Dead cells detach from the dishes after a few days, and the living cells which continue to adhere are scored. Using this procedure we found that under these conditions nondividing P3 cells were indeed more sensitive to the killing action of UV than were normal cells (Fig. 8). Note that the lowest UV fluence used in this procedure is 10 J/m².

DISCUSSION

The UV responses of our three TTD cell strains are compared with those of XP and CS strains in Table 4. P1 was normal in all respects whereas the responses of P2 were identical to those of XP cells from complementation group D. P3 also had a deficiency in excision-repair which was not complemented by other excision-deficient TTD cell strains. This deficiency was less severe than in P2 cells, and dividing P3 cells were not in fact hypersensitive to either the lethal, mutagenic, or SCE-producing effects of UV light (Figs. 1 and 2). Our results pose a number of important questions about the relationship of defects in DNA repair to cell survival, the heterogeneity of the response of TTD cells, and the relationship between TTD and XP.

DNA Repair and Cell Survival: The Anomalous Response of P3. The cellular responses to UV of P3 are, as far as we are aware, unique. The molecular defect is not complemented by other TTD strains, which in turn were not complemented by XP-D cell strains (7). The simplest interpretation of these complementation data is that the TTD and XP-D strains have defects in the same gene, although this remains unproved, and other interpretations are possible. The level of UDS in XP-D cell lines is generally between 10 and 50% of that in normal cells (14, 16, 28–30), so that P3 is at the higher end of this spectrum. However, all XP-D strains examined show extreme hypersensitivity to the lethal effects of UV with D₀ values being between 3- and 10-fold less than that of normal strains (Refs. 30–32 and our own unpublished results). In contrast dividing P3 cells were not hypersensitive to UV light. We have shown that the molecular defect in P3 is most marked after high UV fluences and during the period immediately following irradiation. It is possible that sufficient repair occurs at later times to bring about normal survival, mutability, and SCEs after relatively low UV fluences in dividing cells. After high UV fluences in nondividing cells, however, RNA synthesis fails to recover and cells are killed.

What is the nature of the deficiency in excision-repair at early times after UV irradiation of P3 cells? The amount of repair synthesis measured in experiments such as those shown in Fig. 3 is the product of the number of repaired sites and the size of the repaired patch of DNA at each site. Decreased repair synthesis could result either from fewer repaired sites or from shorter repair patches. We consider that in P3 cells the former explanation is much more likely since the dose response for repair synthesis (Fig. 3) is very similar to that for incision breaks (Fig. 6). The latter parameter is not affected by the size of the repaired patch. Two excision-repair processes are known to occur early after UV irradiation. Repair of pyrimidine dimers in actively transcribing regions of DNA occurs rapidly (33), and recent work has shown that CS cells are specifically deficient in this repair process (34). As shown in Table 4, however, CS cells differ from P3 cells in having no detectable defect in overall excision-repair (24) (the defect can be observed only by studying specific genes) and CS cells are hypersensitive to the lethal, mutagenic, and SCE-producing effects of UV light.

Excision of 6-4 photoproducts has also been shown to occur rapidly after irradiation (35), and it is not inconceivable that P3 cells, like XP cells from various complementation groups including group D (36), are deficient in removal of these lesions from cellular DNA. Experiments are under way to test this hypothesis. In the meantime a definitive explanation for the normal cellular properties of P3 being associated with deficient excision-repair must await further experimentation.

Heterogeneity of TTD. Although the clinical symptoms of TTD are diverse, they form a defined syndrome. Our results at the cellular level emphasize this heterogeneity. At the two extremes we have P1, which like a TTD cell strain described by Stefanini et al. (12) has no cellular defect in its responses to UV light, and P2 and several TTD strains of Stefanini et al. (7) with extreme hypersensitivity and very defective excision repair attributable to the “XP-D mutation.” In between is P3 with some defective responses and others normal. It is of interest that none of our patients exhibited any photosensitivity. In the Italian patients defective excision-repair correlated with photosensitivity.

XP and TTD. An intriguing implication of the findings of Stefanini et al. (7, 12) and of those described in this report concerns the relationship between the defect in DNA repair and the clinical symptoms of XP and TTD (also discussed in Ref. 10). The extensive literature on XP has established, almost as a dogma, that a defect in excision-repair is the underlying cause of most of the skin lesions, especially of the enhanced

Fig. 8. Survival of nondividing cultures. Nondividing cells, maintained for 7 days in medium containing 0.5% serum, were UV irradiated with various fluences. After a further 7 days the cells adhering to the dishes were trypsinized and counted.

Table 4 Summary of UV responses in TTD cells

<table>
<thead>
<tr>
<th></th>
<th>P1</th>
<th>P2</th>
<th>P3-D</th>
<th>CS</th>
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<tr>
<td>Survival (CFA)</td>
<td>N</td>
<td>SS</td>
<td>N</td>
<td>SS</td>
</tr>
<tr>
<td>Survival (ND)</td>
<td>S</td>
<td>SS</td>
<td>S</td>
<td>SS</td>
</tr>
<tr>
<td>Mutability</td>
<td>SS</td>
<td>N</td>
<td>SS</td>
<td>SS</td>
</tr>
<tr>
<td>SCEs</td>
<td>N</td>
<td>S</td>
<td>SS</td>
<td>SS</td>
</tr>
<tr>
<td>UDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scint</td>
<td>100</td>
<td>50</td>
<td>10–50</td>
<td>100</td>
</tr>
<tr>
<td>Autoradiography</td>
<td>100</td>
<td>50</td>
<td>10–50</td>
<td>100</td>
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<tr>
<td>Eq. Cent.</td>
<td>100</td>
<td>50</td>
<td>10–50</td>
<td>100</td>
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<tr>
<td>Incision breaks</td>
<td>SS</td>
<td>SS</td>
<td>SS</td>
<td>N</td>
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<td>UV endonuclease</td>
<td>S</td>
<td>N</td>
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<td>N</td>
</tr>
<tr>
<td>RNA synthesis</td>
<td>SS</td>
<td>SS</td>
<td>SS</td>
<td>SS</td>
</tr>
</tbody>
</table>

* Data from XP-D and CS strains are from the literature. N, normal; S, sensitive or defective; SS, very sensitive or defective. UDS values are expressed as approximate percentages of values in normal strains. CFA, Colony-forming ability; ND, Nondividing cells; Scint., scintillation counting; Eq. Cent., equilibrium centrifugation.
frequency of carcinoma and melanoma associated with the disease. The clinical symptoms of XP may result from a combination of an enhanced frequency of somatic mutations (e.g., Ref. 37) and a possible depression of the immune response following solar exposure of XP patients (38, 39), although the immunodeficiency is controversial. The implication of this is that any individual with an XP-like defect in excision-repair would be expected to exhibit the clinical symptoms of XP. In the excision-defective TTD patients such as P2 this is manifestly not the case. The skin symptoms of TTD are quite different from those of patients with XP group D, and there are no reports of skin cancer associated with TTD (although skin cancers are not particularly frequent in young patients from XP group D; e.g., see Refs. 29 and 30). Conversely XP patients do not show the sulfur-deficient brittle hair, the ichthyosis, the short stature or the peculiar facies associated with TTD. An explanation that the mutation causing one of the diseases is a deletion extending into the gene responsible for the other disorder is not consistent with these differences in the clinical symptoms. If one of the disorders (e.g., TTD) resulted from a deletion which extended into the XP-D gene, the symptoms of TTD would be expected to include all the symptoms of XP. Furthermore cytogenetic analysis has failed to detect any abnormalities in cells from three TTD patients (40).

TTD and XP-D may therefore be phenotypes of patients with different defects in the same gene. Very diverse clinical symptoms resulting from different mutations in the globin genes have been widely reported for the thalassemias (e.g., see Ref. 41). The eventual cloning of the genes defective in XP-D and TTD and analysis of the mutations resulting in the two disorders should help to unravel the relationships between them.

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REFERENCES


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