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Debilitating hip degeneration in trichothiodystrophy: Association with *ERCC2/XPD* mutations, osteosclerosis, osteopenia, coxa valga, contractures, and osteonecrosis

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Abstract

Trichothiodystrophy (TTD) is a rare, autosomal recessive, multisystem disorder of DNA repair and transcription with developmental delay and abnormalities in brain, eye, skin, nervous, and musculoskeletal systems. We followed a cohort of 37 patients with TTD at the National Institutes of Health (NIH) from 2001 to 2019 with a median age at last observation of 12 years (range 2–36). Some children with TTD developed rapidly debilitating hip degeneration (DHD): a distinctive pattern of hip pain, inability to walk, and avascular necrosis on imaging. Ten (27%) of the 37 patients had DHD at median age 8 years (range 5–12), followed by onset of imaging findings at median age 9 years (range 5–13). All 10 had mutations in the *ERCC2*/*XPD* gene. In 7 of the 10 affected patients, DHD rapidly became bilateral. DHD was associated with coxa valga, central osteosclerosis with peripheral osteopenia of the skeleton, and contractures/tightness of the lower limbs. Except for one patient, surgical interventions were generally not effective at preventing DHD. Four patients with DHD died at a median age of 11 years (range 9–15). TTD patients

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CONFLICT OF INTEREST

The authors have no financial conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

with *ERCC2*/*XPD* gene mutations have a high risk of musculoskeletal abnormalities and DHD leading to poor outcomes. Monitoring by history, physical examination, imaging, and by physical medicine and rehabilitation specialists may be warranted.

Keywords

trichothiodystrophy; avascular necrosis of the hip; skeletal abnormalities; osteonecrosis; DNA repair diseases; developmental abnormalities

INTRODUCTION

Trichothiodystrophy (TTD) is a rare, autosomal recessive, and multisystem disorder with defects in genes involved in nucleotide excision repair and transcription (DiGiovanna & Kraemer, 2012; Zhou et al., 2010). These important genes preserve genome stability by repairing DNA damage and also function in the regulation of transcription and possibly translation as well. TTD patients have short, brittle, sulfur-deficient hair with the diagnostic alternating light and dark “tiger-tail” bands under polarized light microscopy (Liang et al., 2005, 2006). They also have a wide spectrum of developmental and multisystem abnormalities including photosensitivity, developmental abnormalities and delay, recurrent infections, and increased mortality (Faghri et al., 2008).

TTD usually manifests in the neonatal period as low birth weight, mild collodion/erythrodermic skin, and failure to thrive (Faghri et al., 2008). The presence of fetal and maternal abnormalities during pregnancy indicates that the spectrum of TTD abnormalities includes developmental defects (Moslehi et al., 2010; Tamura et al., 2011, 2012). Some TTD patients have germline mutations in nucleotide excision repair/transcription genes (*ERCC2*/*XPD*, *ERCC3*/*XPB*, *GTF2E2*, or *GTF2H5*/*TTDA*); others have mutations in *MPLKIP*/*TTDN1*, a gene whose function is not known (DiGiovanna & Kraemer, 2012; Heller et al., 2015) or *RN113A* an X-linked type of TTD (Corbett et al., 2015). Recent findings of mutations in the genes encoding several aminoacyl-tRNA synthetases including *TARS* (threonyl-tRNA synthetase; Theil et al., 2019) *CARS* (cysteinyl-t-RNA synthetase; Kuo et al., 2019) *AARS1* (alanyl-tRNA synthetase 1) and *MARS1* (methionyl-tRNA synthetase 1; Botta et al., 2021) have implicated aberrant transcription and protein translation as a cause of TTD. These enzymes function by loading amino acids onto their associated tRNA’s through aminoacylation reactions.

Common skeletal abnormalities of TTD include short stature, *microcephaly*, *micrognathia,* and a distinctive combination of osteosclerosis of the axial skeleton (central osteosclerosis [CO]) and osteopenia of the distal, appendicular skeleton (peripheral osteopenia [PO]) (Civitelli et al., 1989; Faghri et al., 2008; Harreld et al., 2010; Wakeling et al., 2004). Rarely, osteonecrosis (avascular necrosis [AVN]) of the hip has been reported (Jambhekar & Dhongade, 2008; Wakeling et al., 2004).

We followed a cohort of 37 patients with TTD at the NIH and found a very high frequency of rapidly progressive, debilitating hip degeneration (DHD) among patients with mutations in the *ERCC2*/*XPD* gene. We assessed bone imaging, bone density, and clinical

physiatry findings, and identified a group of patients with severe, progressive, bilateral hip abnormalities associated with rapidly progressive osteonecrosis of the hips.

SUBJECTS AND METHODS

From 2001 to 2019, we studied 37 TTD patients referred to the Clinical Center at the National Institutes of Health (NIH). All patients were enrolled in a natural history protocol [99-C-0099] approved by the National Cancer Institute Institutional Review Board, and patients and/or parents provided informed consent. Clinical features and laboratory abnormalities of some of these patients have been previously reported (Atkinson et al., 2014; Boyle et al., 2008; Brooks et al., 2011; Heller et al., 2015; Kraemer et al., 2007; Kuschal et al., 2016; Liang et al., 2005, 2006; Moslehi et al., 2010; Tamura et al., 2011, 2012; Zhou et al., 2010, 2013) The diagnosis of TTD was confirmed in all 37 patients by identification of tiger-tail banding and structural abnormalities of hair shafts with polarizing microscopy and by reduced hair sulfur content analysis (on 33 patients) (Liang et al., 2005). All patients had an initial family evaluation at the NIH Clinical Center including history, physical examination, blood tests, and imaging guided by medical concerns and prior history. Studies and consultations were selected with family and referring physician input in an attempt to establish relevant clinical baselines for organ systems at risk for TTD features, and to further evaluate medical concerns. The patients were primarily cared for by their local physicians and periodically returned to NIH for evaluation. History and outside records were sought. For age at last observation, either the date of last NIH visit or the date of last documented data was used.

Imaging studies

Relevant imaging studies were obtained during NIH visits. We also sought to obtain outside reports and images for review by NIH radiologists. Our standard NIH imaging evaluation included a skeletal survey (AP and lateral views of the skull and of both feet; AP view of the long bones of the upper and lower limbs, both hands, and pelvis) when feasible. While the skeletal survey included radiographic views of the hips, specific hip images were obtained in patients when there was concern of hip discomfort. Targeted imaging was done based on clinical concerns which often included CT and MRI images of clinically relevant areas (such as brain or symptomatic areas). Bone density evaluation by dual-energy X-ray absorptiomentry (DXA, Hologic, Inc, Marlborough, MA) examination was performed when feasible (Spine, Forearm, Hip, Whole Body). In one patient unable to cooperate with the DXA scan, bone density was evaluated using CT Bone Densitometry. Z-scores were used to classify bone mineral density values according to the guidelines of the International Society of Clinical Densitometry; Densitometry TISFC, 2019). For low bone mass, Z-score less than or equal to −2.0, we have used the term osteopenia. For situations of increased density (osteosclerosis), we have used a Z-score of >+2.5 to indicate abnormally increased bone density according the convention described by Whyte (2005).

A subset (combination of CO/PO subgroup) of 32 patients had skeletal radiographs reviewed by one radiologist (SCH) with expertise in bone imaging (a Certificate of Added

Qualification in Pediatric Radiology) to assess the evolution of osteosclerosis and osteopenia over time.

Physiatry assessment

For all patients, relevant outside records were sought, and when available were reviewed, including imaging. Physiatry consultation was performed at the NIH when possible. We conducted a retrospective review of the clinical assessments performed on each of the 18 patients seen by physicians and therapists in the Rehabilitation Medicine Department at the NIH Clinical Center in conjunction with relevant reports from outside medical records (physiatry, orthopedic surgery, physical therapy, and other musculoskeletal records). Data describing impairments including range of motion, strength, sensation, deep tendon reflexes, muscle tone, sensation, and disabilities, including relating to supine to sit ability, sitting balance, crawl, scoot, ambulation mobility, and balance were sought from the clinical reports. Clinical notes were examined for documentation of W-sitting (when a child sits with hips in internal rotation and knees flexed). Clinical reports and imaging studies were reviewed for presence of scoliosis.

Walking ability assessment

Walking ability and hip pain was assessed through parent history, clinical examination of the patients, and review of physiatry, physical, and occupational therapy reports obtained at NIH and from external records. We developed a “Walking Ability Scale” (W2 to W0) to measure limitation of walking which appeared to be associated with hip pain, as distinguished from inability to walk because of neurologic impairments such as ataxia or developmental delay. As these patients may be poorly communicative, we could not rule out a contribution of change in bone/joint morphology in limiting walking ability. In this scale, W2 corresponds to able to walk without pain, which includes both independent and dependent ambulation using a walker; W1 is associated with a limitation of walking ability, which appeared to be associated with hip pain; W0 is characterized by being unable to walk. We compared this measure to the imaging studies of the hips. This scale was scored when sufficiently detailed clinical data was available. For children unable to clearly communicate pain, clinical judgment was used to distinguish inability to walk on the basis of neurologic disease (e.g., ataxia) from inability to walk due to pain and/or change in bone/joint morphology (e.g., limping).

Laboratory evaluation

Blood testing for calcium, phosphorous, vitamin D, and parathormone levels were reviewed.

RESULTS

Clinical case

TTD354BE-D (Figure 1a) was a girl first evaluated at NIH at the age of 3 years (Zhou et al., 2013) She had multiple features of TTD including *microcephaly* (head circumference <3%-tile), short stature (height <3%-ile), poor weight gain (weight <3%-ile), global developmental delay, skin photosensitivity, recurrent infections (otitis, pneumonias), bilateral cataracts requiring surgery (at age 7 years), mild ichthyosis, dental caries, and

characteristic tiger tail banding of her hair shafts under polarized microscopy (Figure 1b). She walked with the aid of a walker until age 6 (W2). She developed difficulty walking associated with hip pain (W1) at the age of 7 years (Figure 2, Panel a). Pelvis radiographs at age 6 years showed only delayed bone age and faint osteosclerosis but films obtained to evaluate the walking problem at age 7 years 5 months demonstrated slight widening of the right hip joint suggesting joint effusion and bilateral coxa valga (Figure 3a). MRI 3 months later showed osteonecrosis of the right femoral epiphysis, joint effusion, and mild subluxation (Figure 3b). The left hip was normal. By age 7 years 11 months the patient was unable to walk (Figure 1, Panel a, W0) and hip radiographs demonstrated minimal deformity with osteonecrosis of the right femoral epiphysis (Figure 3c). At that time, surgery was performed including bilateral adductor tenotomies and hip reduction (Table S1). Two and a half months later (8 years 1.5 months old) there was additional deterioration of the right hip with further flattening of the femoral epiphysis and increase in subluxation (Not shown). She was not able to walk for the year following surgery (W0, Figure 1, Panel a) and radiographs performed at 9 years old (13 months after surgery) demonstrated similar deformities of the left hip with subluxation and osteonecrosis (Figure 3d). NIH physiatry evaluation at that time found kyphosis, W-sitting, bilateral lower limb weakness with hamstrings tightness, and severely limited hip range of motion. Her primary method of mobility was scooting on her buttocks. She was unable to do weight bearing in standing position. She died at 9 years 3 months of age secondary to methicillin-resistant *Staphylococcus aureus* pneumonia with evidence of low serum IgG (Table S1).

Nine additional TTD patients with DHD

Clinical course including physical examinations and radiologic assessments on nine additional cases of DHD are summarized in Supporting Information (Supporting Cases 1–9 and Figures S1–S4). The 10 patients with DHD had a median age of 15 years (range 9–29; Table 1). There were five males and five females. Onset of hip pain associated walking difficulty occurred at median age 8 years (range 5–12).

Walking ability assessment—Impaired ability to walk in the patients who developed DHD appeared to be in large part associated with hip pain, but there may have been a contribution by the mechanical failure of the hip. Figure 2 (and Table S1) shows the progressive changes in walking ability in the deceased (Panel a) and living (Panel b) patients graphed as inflection points with relevant surgeries and times of death. The graphs show rapid progression from difficulty walking to inability to walk. Of the 10 patients with DHD, time from median age of development of pain on walking (9 years old: range 5.5–12.5 years) to inability to walk (10.3 years old: range 6–17 years) was about 1 year (Table S1). Seven of the 10 patients with DHD had one or more surgeries to address hip problems. Four of the six living patients had hip surgery. In two of these, the surgeries did not restore walking. The two others regained ability to walk without pain (TTD328BE-D and TTD421BE-D) but one of these (TTD421BE-D) subsequently lost walking ability. Of the four deceased patients, time from onset of inability to walk to death ranged from 0.1 to 3.7 years. Three of these patients had hip surgeries, which did not restore walking and were followed by death within ~2-years period (time from surgery to death ranged from 0.6 to 2.2 years; Table S1). One patient (TTD506BE-D; Figure 4), who did not develop DHD, did well after surgery.

After leg bracing and physical therapy, the patient had persistent gait abnormalities, bilateral equinus contractures, and difficulty walking. Internal rotation of her bilateral femurs and tibiae were treated with bilateral femoral derotational osteotomies (right at age 8 years, left at age 9 years) and she was able to walk postsurgery.

Cohort analysis

Thirty-seven patients (20 males and 17 females) with TTD were enrolled in the study. Their ages at last observation ranged from 2 to 36 years with a median age of 12 years. Twenty-three patients were found to have mutations in the *ERCC2*/*XPD* gene, five in *MPLKIP*/*TTDN1*, three in *GTF2H5*/*TTDA*, one in *GTF2E2*, and in five the underlying gene was not determined. Ten of the 37 patients died at a median age of 9 years (2–36 years). Table 1 displays the demographics of the cohort subgroups arrayed by mutated gene, age at last observation, age at death, and characteristics of hip degeneration. Ten (27%) of the 37 patients had DHD, which began as onset of hip pain related to walking difficulty at median age 8 years (range 5–12 years), followed by onset of imaging findings at median age 9 years (range 5–13 years). In seven (70%) of the affected patients, DHD rapidly became bilateral at a median age 9 years (range 6–17 years).

We found that all the patients with DHD were in the subgroup with mutations in the *ERCC2*/*XPD* gene, comprising 43% of the 23 patients in the *ERCC2*/*XPD* mutation subgroup (Table 1 and Figure 4). This finding was present in none of the 14 TTD patients with mutations in other TTD related or unknown genes. Eight (35%) of the 23 *ERCC2*/*XPD* mutation patients died at a median age of 8 years (range 2–15). There was one death (36 years) in the subgroup with *GTF2H5*/*TTDA* mutations, none in the patients with *MPLKIP*/*TTDN1* mutations and one (9 years) in the unknown mutation subgroup.

Several of the musculoskeletal features identified by history, physical examination, imaging, consultations, and outside record review were found to be associated with DHD. Figure 4 displays each patient in a column, organized by underlying mutation with associated findings arrayed in rows. All patients with DHD also had coxa valga, CO, and PO. Nine of the 10 patients with DHD had documented lower limb joint contractures/tightness. The one in which we were unable to document this finding (TTD355BE-D) had problems with lower limb spasticity and limited outside records. Table 2 shows the frequency of musculoskeletal findings in each genotype within our cohort. While diffuse osteopenia was present in some patients within each gene subset, the combination of CO/PO was only seen in the *XPD* subgroup. The overlap of subgroups of findings are shown as a Venn diagram in Figure S4.

Imaging studies—Plain radiology hip images were obtained on all patients. Thirty five of the 37 patients had at least one skeletal survey, which included AP views of the hips. Twenty-one of the 37 had at least one specific hip radiograph, including the two patients (TTD568BE-D and TTD343BE-N) who did not have skeletal surveys. Some patients also had CT or MRI evaluations of the hip. Ten of the 37 patients had DHD (Figures 3 and 4). In 7 of these 10 patients, the character of the DHD was consistent with AVN of the femoral head (Figure 4).

Bone mineral density—Twelve patients (32% of the 37 patients) had bone mineral density evaluations by DXA scan. Because of lack of patient cooperation, in one patient (TTD355BE-D) DXA study was inadequate, and the patient had an evaluation by 3-D CT Bone Densitometry of the lumbar spine; in another (TTD480BE-D) results were obtained only from hips. Six (Figure 4) of the 12 had Z scores of the spine +2.5, which are very consistent with the radiographic findings of osteosclerosis (Whyte, 2005). Four of the 11 had Z scores of the forearm or hip ≤−2.0, which were consistent with the patient's radiographic images showing osteopenia (Figure 4).

Osteopenia—A radiographic bone series was obtained on 35 of the 37 patients (not obtained on TTD568BE-D and TTD343BE-N). Osteopenia was found in 77% (27 of 35 evaluable) patients (Figure 4, Table 2, and Figure S4) and they were distributed across all gene subgroups. In 11 of these the osteopenia was diffuse and in 16 involved the peripheral skeleton only. In 4 of the 11 with diffuse osteopenia, DXA examination supported the finding of osteopenia with a Z score ≤ −2.0 (Figure 4). Two of the 23 *ERCC2*/*XPD* patients had generalized osteopenia, 15 had peripheral osteopenia. Radiographs on one of these 15 initially showed generalized osteopenia and subsequent images showed CO/PO, suggesting that the development of CO may have obscured or replaced the initial osteopenia of the central skeleton. Of the 13 evaluable non-*ERCC2*/*XPD* patients, nine had generalized osteopenia and one had peripheral osteopenia, but none had CO.

Central Osteosclerosis/peripheral osteopenia—Eighteen patients had osteosclerosis (CO) of the central (axial) skeleton, and in six of these the osteosclerosis was supported by DXA examination finding of a Z score >2.5, and in one was supported by CT densitometry with a Z score >2.5 (Table 2 and Figure 4). Three of the 18 with osteosclerosis did not have osteopenia.

Fifteen patients had the pattern of CO/PO (Table 2 and Figure 4). While osteopenia was seen in patients across the gene mutation spectrum, all 18 patients with CO, and all 14 of the patients with lower limb contracture/tightness had mutations in the ERCC2/*XPD* gene. None of the 11 patients who had diffuse osteopenia had osteosclerosis of the central skeleton diagnosed at the same time. Two young patients had osteopenia without CO. In one of these (TTD484BE-U; 46 months old), the osteopenia was peripheral and in one (TTD471BE-D; 9 months old) it was generalized.

Evolution of the CO/PO subgroup—Imaging findings of the 32 patients in the CO/PO subgroup (see Methods), showing progression over time, are shown in Figure 5, arrayed by underlying mutation. Sixteen of the 32 patients had radiographs available for only one date and 16 had repeat imaging.

Within the group of 20 patients with *ERCC2*/*XPD* mutations, 10 had one observation (age 13–149 months; Figure 5). Two of these 10 had no CO or osteopenia, one had only CO and seven had CO/PO.

Of the 10 patients with mutations in *ERCC2*/*XPD* who had repeat imaging (age 1–147 months), only one (TTD471BE-D at 2 months and 9 months of age) did not have CO and

that patient did have generalized osteopenia. The youngest age at diagnosis of CO was 21 months (TTD496BE-D, TTD412BE-D).

Of the 20 *ERCC2/XPD* patients in this CO/PO subgroup, the three who did not have CO were young (9, 13, and 45 months; Figure 5).

Onset of CO in the CO/PO subgroup—Four of the 10 *ERCC2/XPD* patients with repeated imaging displayed the onset of CO (i.e., negative imaging becoming positive for CO over time), with a mean delay of 58 months (range 9–83; Figure 5). Two of these four did not have osteopenia, one had CO/PO, and one (TTD472BE-D) showed evolution of skeletal distribution of osteopenia. Interestingly, imaging in the evolving patient (TTD472BE-D) at 10 months of age showed generalized osteopenia. Repeat imaging at 29 months showed the development of CO at which point the patient evolved into CO/PO.

Progression of CO in the CO/PO subgroup—There were five patients who had repeat imaging and who showed CO on initial images (Figure 5). All five had progression of CO over time and all had the pattern of CO/PO. These data indicate that CO may not be present in early childhood but develop later. The oldest age of negative CO (65 months) that later became positive (at 122 months) [TTD353BE-D).

There were seven patients with serial radiographs who had absence of CO (latest image median age 176; range 9–354 months).

Throughout the time course of obtaining images, 17 of the 20 *ERCC2/XPD* patients had CO and none of the 12 patients who did not have mutations in *ERCC2/XPD* had CO.

Evaluation of musculoskeletal impairments and disabilities—There were 18 patients evaluated by the staff in the Rehabilitation Medicine Department at the NIH Clinical Center who also reviewed relevant reports from outside medical records. One patient was only seen by outside physiatrist and 17 patients were not seen by physiatry. Multiple clinical assessments (see Methods section) were evaluated by two coauthors (SMP and GR) in the subgroup of patients evaluated by NIH physiatrists and were not found to be associated with DHD. Inspection for scoliosis was part of the evaluation but not found in the TTD patients evaluated by physiatry.

Contractures/tightness at hips—Several patients developed contractures or tightness around the hip joints, sometimes treated with physical therapy, casting/splinting, botulinum toxin injection, or surgical intervention. All of the 14 patients with contractures/tightness were in the *ERCC2/XPD* mutation group. In 9 of the 10 patients with DHD, we were able to find documentation of this finding (Table 2 and Figure 4). Patient TTD355BE-D had spasticity and while he was considered for botox injections we were unable to document the presence of lower limb tightness.

Musculoskeletal abnormalities by genotype—Patients are organized in Figure 4 by mutated gene of interest. Within the group of 23 *ERCC2/XPD* patients, 18 (78%) had CO, 17 (74%) had osteopenia (15 peripheral; 2 diffuse), 14 of the 21 evaluable (67%) had coxa

valga, 14 of 21 evaluable (67%) had lower extremity contractures/tightness and 12 of the 21 evaluable (57%) had W-sitting. All 10 patients with DHD were in the *ERCC2/XPD* group (43%).

All 10 of the patients with DHD had CO, PO, and coxa valga, and all nine of the evaluable had lower extremity tightness. In seven patients, the hip degeneration was bilateral (Table 1). The DHD was usually diagnosed by imaging as AVN of the femoral head and the clinical course was usually rapid and progressive.

All five patients with unknown gene mutations had osteopenia (diffuse in four, peripheral in one), two had coxa valga, but none had osteosclerosis, W-sitting, contractures/tightness nor DHD. Three of the four evaluable patients in the *MPLKIP/TTDN1* group and one in the *GTF2H5/TTDA* group had diffuse osteopenia. The single patient with mutation in *GTF2E2* had diffuse osteopenia as the only musculoskeletal abnormality.

Mortality—Ten patients (27%; 7 males and 3 females) in our cohort died at a median age of 9 years (2–36 years) (Table 1, Figure 4, and Figure S4). The cause of death was usually respiratory failure or infection (Table 1). Among this group, eight patients had *ERCC2/XPD* mutations. Of these eight, seven had osteosclerosis, seven had peripheral, one had diffuse osteopenia, and seven had the combination of CO with PO. Six patients had coxa valga and four patients had W-sitting. Four patients had DHD and two of these were consistent with AVN. Two (Table 1) patients died from prolonged post-operative complications of hip surgery.

Two patients died who did not have *ERCC2/XPD* mutations. Of these, one (TTD332BE-A), died at age 36 years of age of cardiogenic shock while hospitalized for pneumonia, had a mutation in *GTF2H5/TTDA* and had no identifiable skeletal abnormalities. The other (TTD347BE-U) with an unknown mutation, died at age 9 years while hospitalized for infection. He developed respiratory difficulty and had a cardiac arrest during intubation. He had diffuse osteopenia but no other identified skeletal abnormalities.

Photosensitivity—Some patients with TTD have photosensitivity manifested as exaggerated sun burning, sometimes on minimal sun exposure. While severity of sun sensitivity can be subjective, we graded reported sun sensitivity as absent or mild, and when documented as present (Table 1). Thirteen (57%) of the 23 patients within the *ERCC2/XPD* gene subgroup had a history of abnormal burning on sun exposure including 8 (80%) of the 10 patients with DHD and 5 (38%) of the 13 who did not have DHD.

Laboratory results—Bloodtesting was performed for patients at each NIH visit. For the 10 patients with hip degeneration, none had low calcium levels. One patient had a slightly elevated calcium level at one visit and this was felt not to be clinically significant. No abnormalities in phosphorus were noted. All 10 patients had parathyroid hormone (PTH) levels measured. Four of the nine patients had at least one elevated PTH level; of these, three were mildly elevated and resolved at follow up. One patient had significantly elevated PTH that, upon further work-up was felt to be episodic and not consistent with

primary hyperparathyroidism. Three patients additionally had low PTH levels which again normalized at follow-up.

Serum 25-OH vitamin D, a measure of the body vitamin D stores, was also measured in all 10 patients with hip degeneration. Six of the 10 patients had at least one low vitamin D level, three mild, and three moderate in severity. It is important to note that many of these patients were on nutritional supplementation, including vitamins, which may have influenced some of these values. Overall, blood work results from this cohort were felt not to be associated with their musculoskeletal abnormality.

DISCUSSION

TTD includes a spectrum of abnormalities, which begin early in development. First manifestations may be during the pregnancies of mothers carrying an affected fetus where pregnancy abnormalities can include preeclampsia or more severely HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Babies may be born small for gestational age, with collodion membrane, short stature, *microcephaly*, *micrognathia*, and congenital cataracts. Interestingly, despite a broad spectrum of clinical features, all patients have the characteristic feature of tiger tail banding of hair shafts when viewed under polarizing microscopy. Over time, children with TTD may exhibit a spectrum of developmental delays, including reduced function related to the musculoskeletal system, and a high risk of infection with increased mortality. These children often have walking difficulties thought to be associated with motor delay, ataxia, and/or contractures. However, hip osteonecrosis has only rarely been identified in association with TTD (Jambhekar & Dhongade, 2008; Wakeling et al., 2004).

In our cohort of patients with TTD followed at the NIH, we observed children develop hip pain followed by rapid, usually bilateral DHD, and inability to walk. We reviewed all available data for musculoskeletal abnormalities. We found a high frequency (43%) of DHD, usually characterized as AVN, only in our patients with mutations in the *ERCC2*/*XPD* gene, a helicase, which is part of the TFIIH a transcription initiation factor and also functions in DNA repair (Boyle et al., 2008; DiGiovanna & Kraemer, 2012; Kraemer et al., 2007; Zhou et al., 2013) We found no cases of DHD in patients with mutations in *MPLKIP*/*TTDN1*, *GTF2H5*/*TTDA*, and *GTF2E2*, nor those with unknown mutation. Seven of the 10 affected had imaging indicating AVN, three had hip degeneration that did not reach imaging criteria for AVN. DHD was associated with osteosclerosis of the central skeleton, osteopenia of the peripheral skeleton, coxa valga, lower limb joint contractures/tightness, and W-sitting. However, we do not know if these musculoskeletal abnormalities are causative of DHD. Of the seven patients who had hip surgeries, only one resulted in long term walking ability.

Surgeries were often not well tolerated, and three children died within ~2 years postsurgery. TTD patients have failure to thrive, difficulty with weight gain, are frail appearing and at increased risk of infection. Reasons for post-surgical and anesthesia complications are not clear. After observing patients tolerate anesthesia and surgeries poorly, one patient (TTD421BE-D) had a presurgical conference conducted with her care providers in an effort to find measures to minimize stress and prepare for possible complications. The procedure

was performed with epidural rather than general anesthesia, followed by planned admission to the pediatric intensive care unit for close monitoring of fluids to avoid pulmonary edema. As the patient avoided serious surgical complications, we suggest a presurgical assessment of patient status and attention to post-surgical monitoring for frail patients.

We observed an interesting relationship between osteosclerosis and osteopenia in TTD patients. We found osteopenia in 77% (27 of 35 evaluable) of patients and in all gene subgroups. However, the distribution (generalized vs. peripheral) differed across subgroups. Only diffuse involvement was seen in the non-*ERCC2/XPD* subgroups. In contrast, only 2 of the 17 patients with osteopenia in the *ERCC2/XPD* subgroup had diffuse involvement and the remainder had peripheral involvement with osteosclerosis of the central skeleton. One patient (TTD472BE-D) initially had generalized osteopenia and over time developed osteosclerosis of the central skeleton. Thus, in our observation, generalized osteopenia was found in some patients in each of the genetic subgroups. CO developed and progressed over time, but only in the *ERCC2/XPD* subgroup, suggesting that diffuse osteopenia may occur first across the genetic spectrum. However, in the *ERCC2/XPD* patients, the preceding osteopenia of the central skeleton may be obscured by the progressive development of osteosclerosis of the central skeleton. Despite the high prevalence of this peripheral osteopenia, only one patient had evidence of fracture, and this was in association with bone surgery and hardware removal.

DHD is rare in the general population. A common cause of hip abnormalities in children is Legg Calve Perthes (LCP) disease, which occurs most commonly between ages 2 and 14 years with peak age of onset of 5 years (Perry & Hall, 2011). In LCP, both hips are involved in ~10%–15% of patients (Perry & Hall, 2011) but usually not at the same time, and the radiographic findings ultimately result in stable radiographic hip deformities (Joseph, 2011). In contrast, in 7 of our 10 TTD patients the DHD rapidly progressed to bilateral involvement and quickly progressed to hip destruction, lack of femoral head re-ossification and poor outcome. Patients with dominant inherited multiple epiphyseal dysplasia (MED; Fairbank's disease) have multiple joint involvement and generalized abnormality of epiphyseal ossification (Hesse & Kohler, 2003; Lachman et al., 2005). In our TTD patients, we found degeneration of the hips, but no similar involvement of other joints.

The cause of DHD in TTD patients is unknown. We did not find congenital dislocation of the hips. In the general population, osteonecrosis is believed to be caused by lack of blood supply to the femoral head and can occur in adults (usually 35–50 years old, in males more than females) in association with risk factors that include: medications (steroids, chemotherapy), medical procedures (radiation treatment, organ transplants), alcohol use, injury (trauma to hip), increased pressure inside of the bone, Caisson disease (diver's disease or "the bends"), sickle cell disease, myeloproliferative disorders, Gaucher's disease, systemic lupus erythematosus, Crohn's disease, arterial embolism, thrombosis, vasculitis, hypercoagulable states, viral (CMV, hepatitis, HIV, rubella, rubeola, varicella), protease inhibitors, pancreatitis, vascular insult, subacute bacterial endocarditis, polyarteritis nodosa, rheumatoid arthritis, giant cell arteritis, and sarcoidosis (Foran & Miller, 2018; Hsu &

Nallamothu, 2022; Lafforgue, 2006). Our TTD patients were not receiving glucocorticoid treatment and did not have other known risk factors.

One biomechanical hypothesis for TTD-DHD may be that these patients remain in coxa valga as they mature (Birkenmaier et al., 2010). This may be due to decreased mobility and, thus, weight bearing through the hips, which may be a function of developmental delay, contractures, and/or motor impairments such as ataxia. These challenges are also associated with impaired stability of the trunk in sitting.

An intriguing molecular basis may be related to collagen alterations, which have been observed in studies of TTD cells as well as in other hip degenerative disorders including Legg-Calve-Perthe disease (COL2, mutation in *COL2A1*), familial AVN of the femoral head-1 (COL2, mutation in *COL2A1*), and MED (COL9, mutation in *COL9A1*, *COL9A2*, OR *COL9A3*; Arseni et al., 2018). *ERCC2*/*XPD* mutations in TTD cells have been associated with abnormal collagen 6 expression by dysregulation of *COL6A1* through a mechanism of failure of transcription derepression (Orioli et al., 2013). In addition, overexpression of matrix metalloproteinase 1 (*MMP*-1), the gene encoding the metalloproteinase, has been found in TTD cells with mutations in *ERCC2*/*XPD* (Arseni et al., 2015). MMP-1 degrades the interstitial collagens of the extracellular matrix, which is functionally important in multiple connective tissue disorders with abnormalities in the bone, cartilage, skin, muscle, brain, eye, and cardiovascular systems.

We have identified a high frequency of DHD in children with TTD who have mutations in the *ERCC2*/*XPD* gene. This DHD is characterized by pain, rapid bilateral progression, and inability to walk. While we now know that DHD exists, little is known about the cause, best management, nor measures for prevention. Patients with LCP and MED usually respond well to surgical interventions directed at alignment of the femur and acetabulum. In our cohort, a total of eight patients had hip surgeries. One patient without DHD (TTD506BE-D, Figure 4) had bilateral femoral derotational osteotomies and has not developed DHD by age 9 years. However, of the 10 children with DHD, seven had hip surgery, and the only one who had durable restoration of pain free walking had hip resurfacing/replacement. In addition, children with TTD seem to have greater infection and anesthesia risk and may require longer recovery periods.

Children with *ERCC2*/*XPD* associated TTD should have close monitoring of hip geometry and motor function. Early identification of signs of DHD, such as hip pain and associated impairments may assist in developing a better understanding of their associations in order to develop treatment plans. Interventions to promote developmentally appropriate weight bearing and mobility, while preventing secondary morbidities such as soft tissue contractures, may help maintain hip health. To optimize these interventions while minimizing risk and avoiding overwhelming the child with caregivers, a coordinated team of professionals, which could include rehabilitation medicine (pediatric physiatrist, occupational, and physical therapists), orthopedic surgery, genetics, neurology, child life specialist, psychologist, and social worker, would be valuable. The team would function to develop and implement a program specific to the child to identify and address the child and family's medical, physical and emotional needs. We hope these findings will encourage

astute clinical observation of TTD children to better understand and manage this serious hip disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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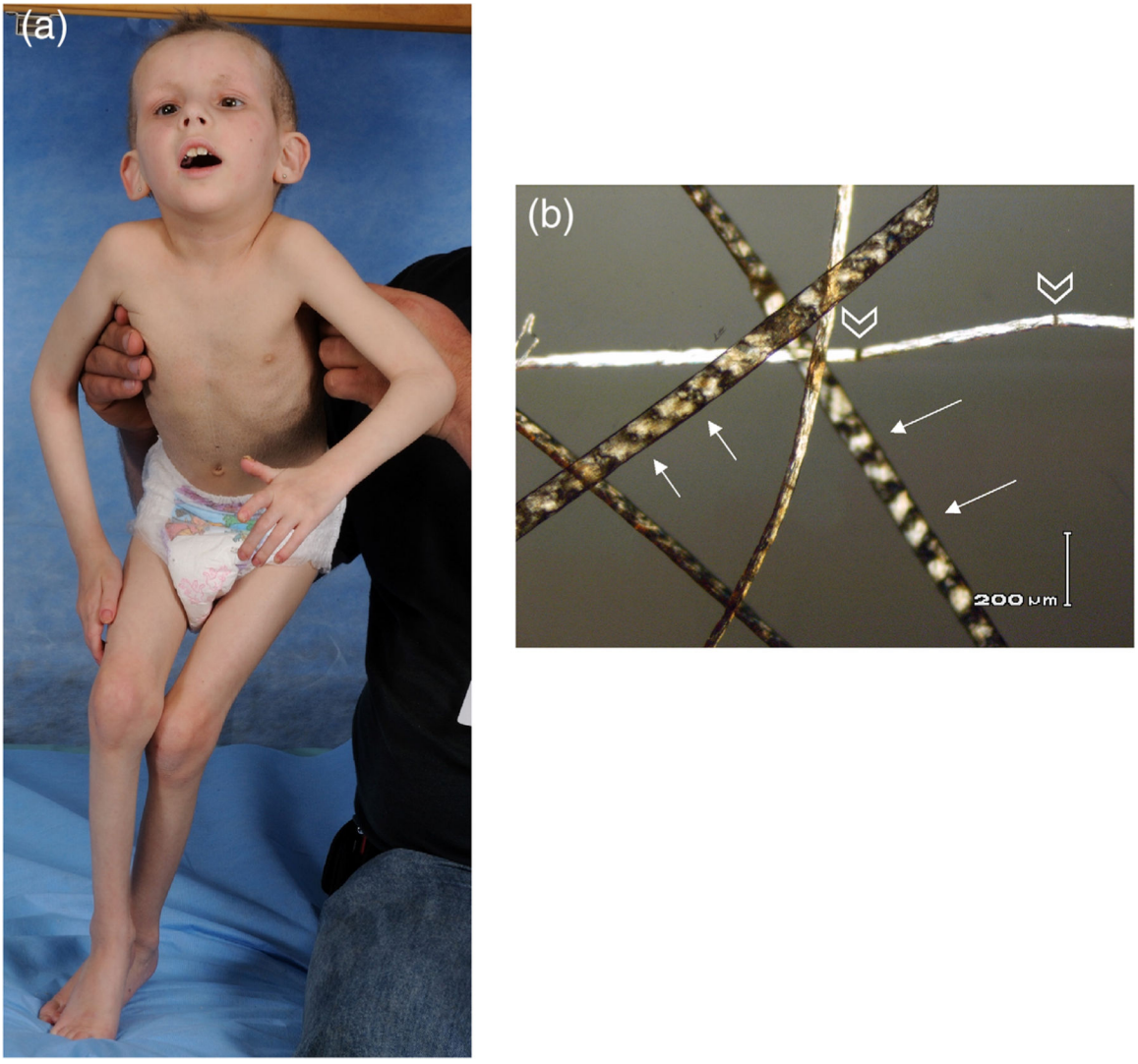


FIGURE 1.

Eight year 11 months old girl (TTD354BE-D) with TTD. (a) She is thin with short stature, short brittle hair, and contractures. (b) Polarized microscopy of her hair shafts show tiger tail banding (arrows) and sharp breaks of trichoschisis (arrowheads)

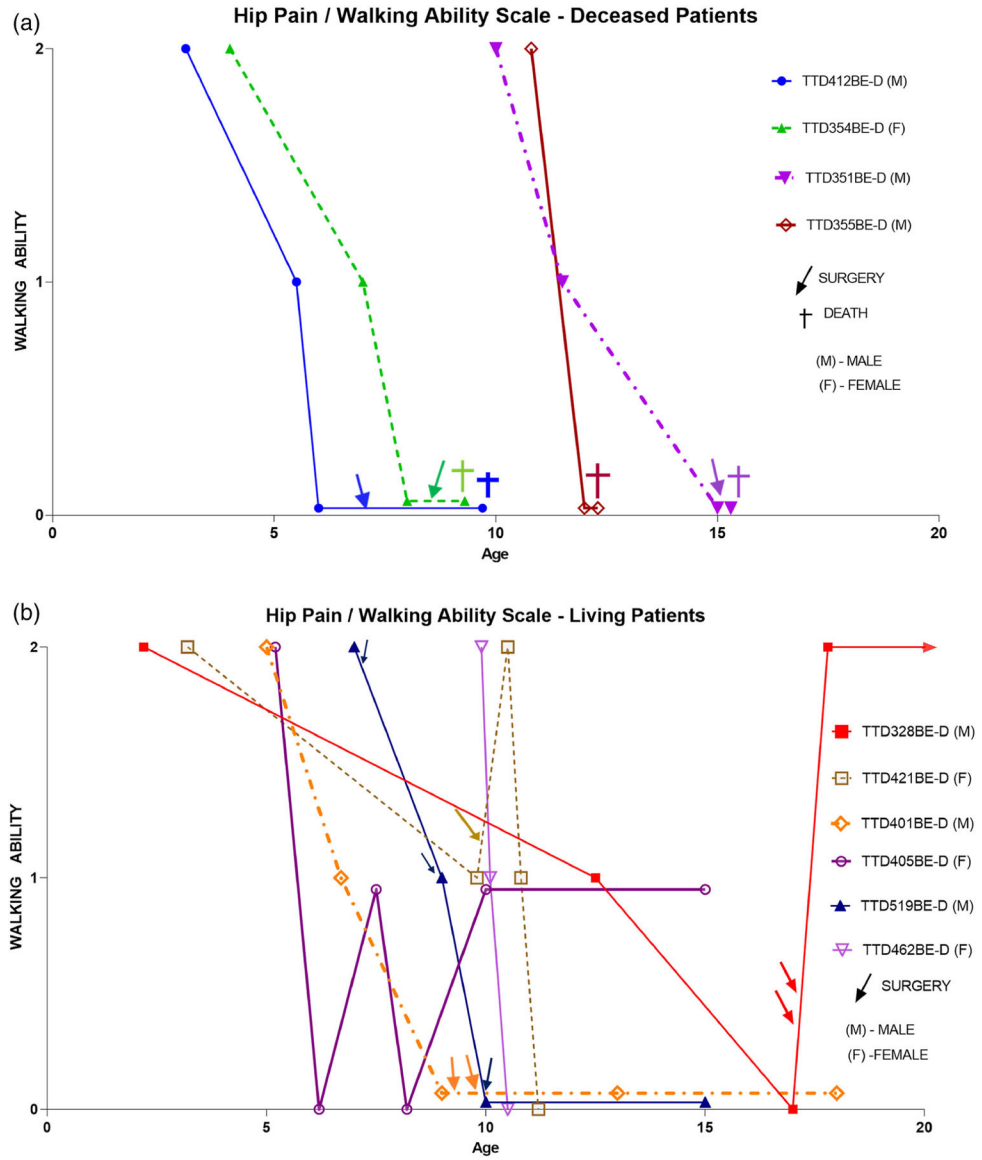


FIGURE 2.

Loss of walking ability due to hip pain in 10 children with TTD. Progressive changes in walking ability are shown for the four deceased patients (panel a) and the six living patients (panel b). The inflection points in progressive changes in walking ability score are shown in association with hip surgical interventions, (arrows). Seven children had hip surgery, and only one had durable restoration of pain free walking (hip resurfacing/replacement). Three of the four deaths (panel a) occurred within ~2 years after hip surgery. Hip pain walking ability scale: W2, able to walk without pain; W1, limitation of walking associated with hip pain; W0, unable to walk (see methods for more details)

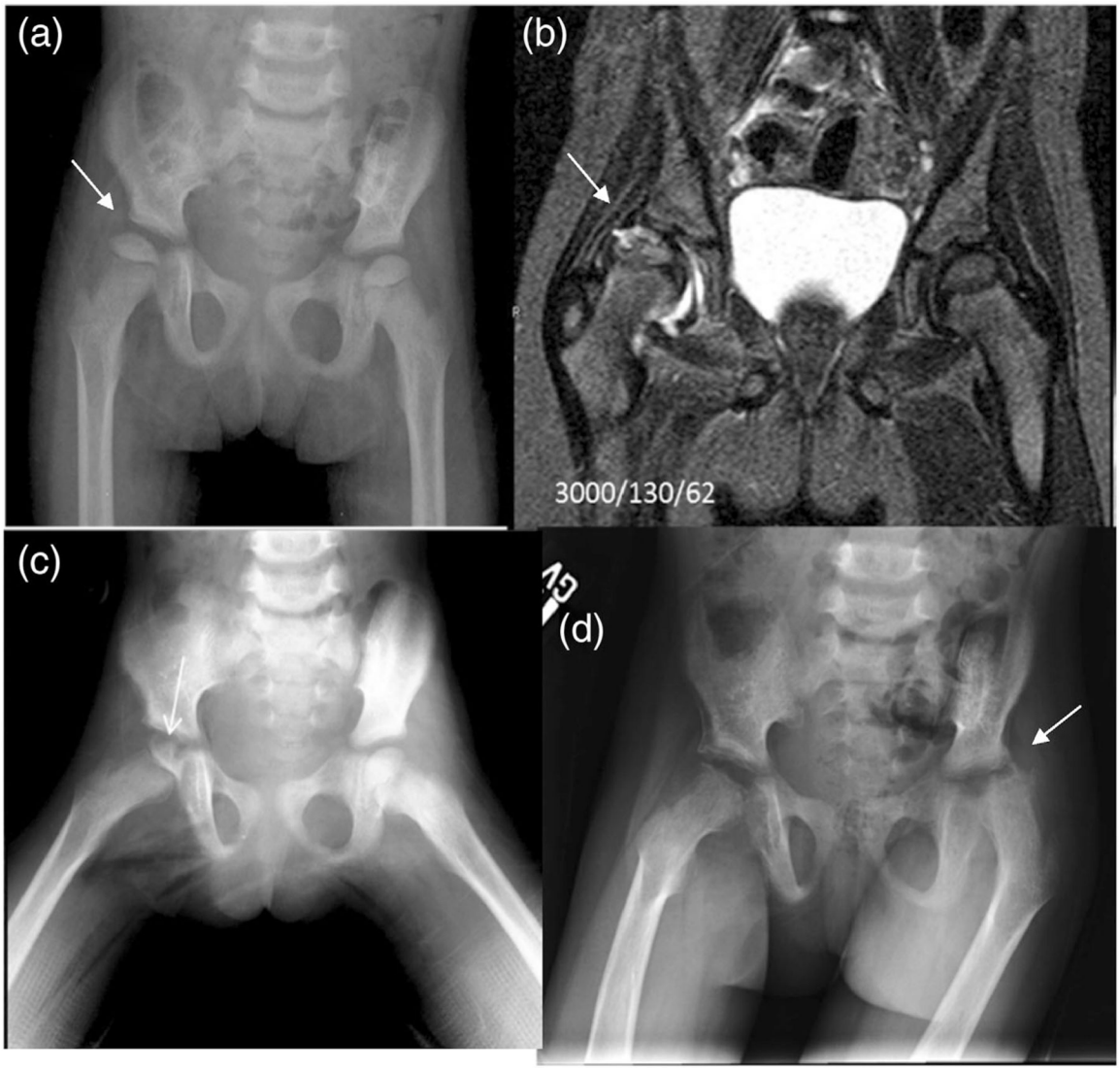
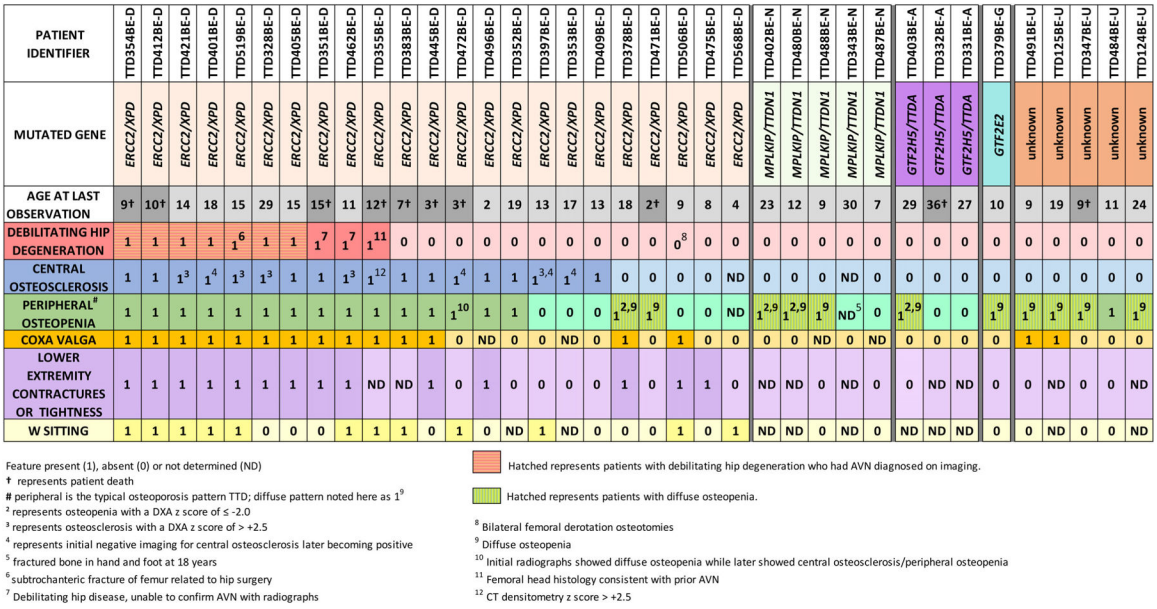


FIGURE 3.

Progression of osteonecrosis over 2 years in a girl with TTD. Hip radiographs and MRI of patient TTD354BE-D who began to develop hip pain at age 7 years. (a) Anterior–posterior view of both hips at age 7 years and 5 months showed bilateral coxa valga, slight widening of the right hip joint; (b) coronal STIR (TR/TI/TE 3000/130/62) image of the hips 3 months later showed abnormal signal in the right femoral epiphysis with small right hip joint effusion and mild subluxation; (c) frog leg view of the hips 3 months later showed minimal deformity with lucencies (arrow) in the right femoral epiphysis. Surgery (bilateral adductor tenotomies) was performed at this time; (d) 13 months after surgery (9 years old) a similar deformity had developed in the left hip with subluxation and osteonecrosis



Feature present (1), absent (0) or not determined (ND)
† represents patient death
# peripheral is the typical osteoporosis pattern TTD; diffuse pattern noted here as 1[9]
[2] represents osteopenia with a DXA z score of ≤ -2.0
[3] represents osteosclerosis with a DXA z score of > +2.5
[4] represents initial negative imaging for central osteosclerosis later becoming positive
[5] fractured bone in hand and foot at 18 years
[6] subtrochanteric fracture of femur related to hip surgery
[7] Debilitating hip disease, unable to confirm AVN with radiographs

Hatched represents patients with debilitating hip degeneration who had AVN diagnosed on imaging.
Hatched represents patients with diffuse osteopenia.

[8] Bilateral femoral derotation osteotomies
[9] Diffuse osteopenia
[10] Initial radiographs showed diffuse osteopenia while later showed central osteosclerosis/peripheral osteopenia
[11] Femoral head histology consistent with prior AVN
[12] CT densitometry z score > +2.5

FIGURE 4.

TTD patients sorted by underlying mutation and associated musculoskeletal findings. Patient features arrayed by presence or absence of gene mutated and clinical findings. Patients are sorted by gene mutated, then presence of each musculoskeletal feature in each row, including DHD/AVN, CO, PO, coxa Valga, lower extremity contractures/tightness, and W-sitting

PATIENT #		AGE AT FIRST RADIOGRAPH (MONTHS)	CENTRAL OSTEOSCLEROSIS* (CO)	AGE AT SECOND RADIOGRAPH (MONTHS)	CO*	AGE AT THIRD RADIOGRAPH (MONTHS)	CO*	AGE AT FOURTH RADIOGRAPH (MONTHS)	CO*	ONSET OR PROGRESION OF CO	CO/PO*	GENERALIZED OSTEOPENIA*	GENERALIZED OSTEOPENIA FOLLOWED BY CO/PO*
TTD475BE-D	SINGLE OBSERVATION	13	0										
TTD506BE-D		45	0										
TTD496BE-D		21	1								1		
TTD405BE-D		27	1								1		
TTD462BE-D		31	1								1		
TTD445BE-D		34	1								1		
TTD409BE-D		37	1										
TTD383BE-D		73	1								1		
TTD351BE-D		105	1								1		
TTD328BE-D		149	1								1		
TTD471BE-D	MULTIPLE OBSERVATIONS	2	0	9	0							1	
TTD401BE-D		1	0	84	1					ONSET	1		
TTD472BE-D		10	0	29	1					ONSET	1	Initially	1
TTD397BE-D		16	0	75	1					ONSET			
TTD353BE-D		65	0	122	1					ONSET			
TTD412BE-D		21	1	46	2	68	3	74	2	PROGRESSION	1		
TTD355BE-D		39	1	129	2					PROGRESSION	1		
TTD421BE-D		57	1	70	2					PROGRESSION	1		
TTD354BE-D		78	1	94	2	97	2			PROGRESSION	1		
TTD352BE-D		91	1	147	2					PROGRESSION	1		
TTD403BE-A		208	0	266	0							1	
TTD331BE-A		282	0	323	0								
TTD332BE-A		313	0	354	0								
TTD487BE-N1		13	0										
TTD488BE-N1		32	0									1	
TTD402BE-N1		127	0									1	
TTD480BE-N1		42	0	58	0							1	
TTD379BE-G		22	0									1	
TTD347BE-U		28	0									1	
TTD484BE-U		46	0									PERIPHERAL	
TTD125BE-U		64	0	118	0							1	
TTD124BE-U		120	0	176	0							1	

LEGEND

- NO APPEARANCE OF CENTRAL OSTEOSCLEROSIS
- PRESENCE OF CENTRAL OSTEOSCLEROSIS
- PROGRESSION OF PRE-EXISTING CENTRAL OSTEOSCLEROSIS
- CENTRAL OSTEOSCLEROSIS WITH PERIPHERAL OSTEOPENIA
- GENERALIZED/DIFFUSE OSTEOPENIA

* PRESENCE/PROGRESSION

0 - NO APPEARANCE OF CENTRAL OSTEOSCLEROSIS
i - PRESENCE OF CENTRAL OSTEOSCLEROSIS OR PERIPHERAL/GENERALIZED OSTEOPENIA
ii - PROGRESSION OF CENTRAL OSTEOSCLEOSIS COMPARED TO PRIOR RADIOGRAPH
iii - FURTHER PROGRESSION OF CENTRAL OSTEOSCLEROSIS COMPARED TO PRIOR RADIOGRAPH

FIGURE 5.

Progression of osteosclerosis and osteopenia in 32 TTD patients. For a subset of TTD patients (CO/PO group) sequential radiographs taken over time were evaluated by one radiologist (SCH) and graded for osteosclerosis and osteopenia. Presence or absence, age at first observation, and progression are noted. initial radiographs from patient TTD472BE-D showed generalized osteopenia followed by the development over time of CO to eventually show the pattern of CO/PO

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TABLE 1

Cohort demographics

Patient	Mutated gene	Sex	Age at last observation (years)	Age at death (years)	Age onset of hip pain-related walking difficulty (years)	Age onset of imaging findings of AVN/hip degeneration (years)	Age bilateral diagnosis of AVN/hip degeneration (years)
Patients with hip degeneration							
TTD412BE-D^{NP}	*ERCC2/XPD*	M	9	10[a]	5	5	8
TTD405BE-D^{P}	*ERCC2/XPD*	F	15		6	6	6
TTD401BE-D^{NP}	*ERCC2/XPD*	F	18		6	9	9
TTD354BE-D^{P}	*ERCC2/XPD*	F	9	9[b]	7	7	9
TTD519BE-D^{P}	*ERCC2/XPD*	M	15		7	9	9
TTD421BE-D^{P}	*ERCC2/XPD*	F	14		9	11	Right only
TTD462BE-D^{P}	*ERCC2/XPD*	F	11		10	10.5	Left only
TTD355BE-D^{P}	*ERCC2/XPD*	M	12	12[c]	10	ND	Left only
TTD351BE-D^{P}	*ERCC2/XPD*	M	15	15[d]	11	12	14
TTD328BE-D^{MP}	*ERCC2/XPD*	M	29		12	13	17
			Median age 15	Median age 11	Median age 8	Median age 9	Median age 9
			Range 9–29	Range 9–15	Range 5–12	Range 5–13	Range 6–17
Patients without hip degeneration							
TTD471BE-D^{NP}	*ERCC2/XPD*	M	2	2[e]			
TTD496BE-D^{MP}	*ERCC2/XPD*	M	2				
TTD445BE-D^{NP}	*ERCC2/XPD*	M	3	3[f]			
TTD472BE-D^{P}	*ERCC2/XPD*	M	3	3[g]			
TTD568BE-D^{NP}	*ERCC2/XPD*	F	4				
TTD383BE-D^{MP}	*ERCC2/XPD*	F	7	7[h]			
TTD475BE-D^{NP}	*ERCC2/XPD*	M	8				
TTD397BE-D^{NP}	*ERCC2/XPD*	M	13				
TTD409BE-D^{NP}	*ERCC2/XPD*	M	13				
TTD506BE-D^{MP}	*ERCC2/XPD*	M	15				

Patient	Mutated gene	Sex	Age at last observation (years)	Age at death (years)	Age onset of hip pain-related walking difficulty (years)	Age onset of imaging findings of AVN/hip degeneration (years)	Age bilateral diagnosis of AVN/hip degeneration (years)
TTD353BE-D^{NP}	*ERCC2/XPD*	F	17				
TTD378BE-D^{P}	*ERCC2/XPD*	F	18				
TTD352BE-D^{NP}	*ERCC2/XPD*	F	19				
			Median age 8	Median age 3			
			Range 2–19	Range 2–19			
TTD402BE-N^{NP}	*MPLKIP/TTDN1*	M	23				
TTD480BE-N^{NP}	*MPLKIP/TTDN1*	F	12				
TTD488BE-N^{NP}	*MPLKIP/TTDN1*	F	9				
TTD343BE-N^{P}	*MPLKIP/TTDN1*	M	30				
TTD487BE-N^{NP}	*MPLKIP/TTDN1*	M	7				
			Median age 12				
			Range 7–30				
TTD403BE-A^{P}	*GTF2H5/TTDA*	F	29				
TTD332BE-A^{MP}	*GTF2H5/TTDA*	M	36	36[i]			
TTD331BE-A^{P}	*GTF2H5/TTDA*	M	27				
			Median age 29				
			Range 27–36				
TTD379BE-G^{NP}	*GTF2E2*	M	10				
			Median age N/A				
			Range N/A				
TTD491BE-U^{MP}	Unknown	F	9				
TTD125BE-U^{NP}	Unknown	F	19				
TTD347BE-U^{p}	Unknown	F	9	9[i]			
TTD484BE-U^{p}	Unknown	F	11				
TTD124BE-U^{NP}	Unknown	M	24				
			Median age 11				
			Range 9–24				

Abbreviations: AVN, avascular necrosis; MP, mild photosensitive; NP, nonphotosensitive; P, photosensitive.

[a] Died of sepsis and respiratory arrest after prolonged hospitalization following hip tendon release surgery.

[b] Died 2 years after onset of hip pain due to methicillin-resistant *S. aureus* pneumonia.

[c] Died after being found unresponsive after dose of methadone.

[d] Died of respiratory failure and sepsis during recovery from hip surgery.

[e] After laparoscopic G-tube placement and fundoplication, he rapidly developed respiratory insufficiency and was unable to be recusicated.

[f] Died at age 3 years of multiple organ failure after long (4–5 months) illness and NICU treatment following dental surgery.

[g] Died at age 3 years after G-tube placement. While inpatient, he became unresponsive, developed respiratory failure, and was unable to be recusicated.

[h] Died 2006.

[i] Died while hospitalized with pneumonia possibly from cardiogenic shock.

[j] While hospitalized to rule out sepsis, she developed respiratory difficulty. Died of cardiac arrest while attempting intubation.

TABLE 2

Musculoskeletal findings by mutated gene in COHORT of 37 patients with TTD[a]

Mutated gene	Number of patients	DHD	CO	Peripheral osteopenia	CO/PO	Osteopenia diffuse	Coxa valga	Lower extremity contractures/ tightness	W sitting	Death
ERCC2/XPD	23	10/23	18/22	15/22	15/22	2/22	14/21	14/21	12/21	8/23
MPLKIP/TTDN1	5	0/5	0/4	0/4	0/4	3/4	0/3	0/2	0/2	0/5
GTF2H5/TTDA	3	0/3	0/3	0/3	0/3	1/3	0/3	0/1	ND	1/3
GTF2E2	1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1
Unknown	5	0/5	0/5	1/5	0/5	4/5	2/5	0/3	0/3	1/5
Total	37	10/37	18/35	16/35	15/35	11/35	16/33	14/28	12/27	10/37

[a]Shown as # with feature/# tested.