



## Trichothiodystrophy: A systematic review of 112 published cases characterizes a wide spectrum of clinical manifestations

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**TRICHOThIODYSTROPHY: A SYSTEMATIC REVIEW OF 112 PUBLISHED CASES  
CHARACTERIZES A WIDE SPECTRUM OF CLINICAL MANIFESTATIONS**

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**KEY WORDS:** DNA repair, dysmyelination, developmental disabilities, cataracts,  
pregnancy complications

**ABBREVIATIONS USED:**

TTD Trichothiodystrophy, XP Xeroderma pigmentosum, CS Cockayne syndrome

## **ABSTRACT**

Trichothiodystrophy (TTD) is a rare, autosomal recessive disease, characterized by brittle, sulfur-deficient hair and multisystem abnormalities. A systematic literature review identified 112 patients ranging from 12 weeks to 47 years (median 6 years). In addition to hair abnormalities, common features reported were developmental delay/ intellectual impairment (86%), short stature (73%), ichthyosis (65%), abnormal characteristics at birth (55%), ocular abnormalities (51%), infections (46%), photosensitivity (42%), maternal pregnancy complications (28%) and defective DNA repair (37%). There was high mortality, with 19 deaths under age 10 years (13 infection-related), which is 20-fold higher compared to the US population. The spectrum of clinical features varied from mild disease with only hair involvement to severe disease with profound developmental defects, recurrent infections and a high mortality at a young age. Abnormal characteristics at birth and pregnancy complications, unrecognized but common features of TTD, suggest a role for DNA repair genes in normal fetal development.

## **INTRODUCTION**

Trichothiodystrophy (TTD) is a rare, autosomal recessive disease, in which patients have brittle, sulfur-deficient hair [1, 2]. When the hair from TTD patients is observed under polarizing microscopy, it displays a diagnostic alternating light and dark banding pattern, called “tiger tail banding” [3, 4] (Figure 1). TTD results from mutations in one of several different DNA repair genes (XPB, XPD or TTDA)[5, 6] and TTDN1, a gene of unknown function[7]. Although XPB and XPD mutations are also seen in xeroderma pigmentosum (XP), a disease with a 1000-fold increase in skin cancer, [6, 8-11] TTD patients have not been reported to have an increase in cancer.

TTD patients display a wide variety of clinical features, including cutaneous, neurological, and growth abnormalities. As a result, a variety of names have been used to describe the disease. In 1979, Price coined the term “trichothiodystrophy,” which encompasses a wide spectrum of neurocutaneous findings, to describe the unifying feature[12]. The name reflects the brittle, sulfur deficient hair seen in all TTD patients (from Greek, *tricho-* meaning hair; *-thio-*, sulfur; *-dys-*, faulty; *-trophy*, nourishment). Several acronyms have been used to describe the clinical features of these patients. PIBIDS [13], IBIDS [14, 15] and BIDS[16] describe six features of TTD: *Photosensitivity*, *Ichthyosis*, *Brittle hair*, *Intellectual impairment*, *Decreased fertility*, and *Short stature*. In order to assess the prevalence of the reported clinical features of TTD, we performed an extensive literature review to find all published case reports of patients with TTD. We analyzed the frequency of the clinical findings described in an effort to better characterize the spectrum of the disease. We modeled this review after a similar study on XP [9].

## **METHODS**

We developed a standard Excel spreadsheet listing more than 200 clinical and laboratory characteristics. The search was restricted to published information in reports, and no effort was made to obtain unpublished data on the reported patients. This approach results in underreporting of characteristics not noted at the time of publication. However, when reported patients were identifiable as being the same individual in a subsequently reported paper, the data was consolidated. We searched PubMed/ MEDLINE, Web of Science, and the references cited in retrieved articles.

Search terms were trichothiodystrophy, TTD, Tay Syndrome, Pollitt Syndrome, PIBIDS, IBIDS, and BIDS.

The most definitive clinical criteria include microscopic examination of hair shafts for tiger tail banding and structural abnormalities and the analysis of hair shaft sulfur content. However, diagnostic criteria for TTD have evolved over the decades since these reports have been published. As a result, some reports included patients with convincing clinical features of TTD and a confirmed DNA repair abnormality, but the clinical workup did not include hair analysis. In order to standardize selection of patients, we chose criteria, which determined whether or not a case report was included. Inclusion criteria were based on having at least two of the four following clinical or laboratory abnormalities: (I) presence of brittle hair and/or hair shaft abnormalities, (II) tiger tail banding with polarized microscopy, (III) decreased sulfur or cystine content of hair, and (IV) DNA repair abnormality. While any one of these features is highly suggestive of TTD [3, 11, 17], we required a minimum of two features to confirm the diagnosis. We chose criteria which we reasoned would allow us to capture reports of most patients with TTD and which were important in forming the basis for the various subtypes which have led to our current understanding of the disease. These criteria were developed in order to provide a uniform approach to inclusion of case reports with varied amounts of information and published over more than 40 years and not to be used as criteria for clinical diagnosis of new patients [3, 4].

In the case of reported siblings with similar clinical features, if one sibling qualified according to the above criteria, then both siblings were included. Patients described collectively as a group were not included when the clinical features could not be traced to individual patients. We did not include cases reported only in meeting proceedings, where the report was not indexed.

We considered intrauterine growth restriction (IUGR) as fetuses specified to have intrauterine growth retardation or intrauterine growth restriction in the report. If this was not stated we used the standard of less than the tenth percentile for gestational age at the time of birth based on the criteria specified in Lubchenco [18]. Low birth weight was stated in the report or was defined as infants or who were less than 2500 grams at birth.

## RESULTS

### HISTORY OF TTD

Vera Price first proposed the name “trichothiodystrophy” in 1979 in the book *Haar und Haarkrankheiten* [12]. In 1980, Price [17] reported 2 patients with a wide range of clinical features, and associated the low sulfur (cystine) content of the hair with the alternating bright and dark banding with polarized microscopy, now known as tiger-tailed banding. This work established specific hair findings as the unifying marker for this neuroectodermal symptom complex, which we now know as trichothiodystrophy (TTD).

Before the name TTD was coined in 1979, several papers were published describing cases that are today considered to be the earliest reports of TTD. Some of these papers, however, did not have sufficient hair analysis to meet the inclusion criteria that

we chose for this paper [19-21]. The earliest paper that we included in this study is from R.J. Pollitt [22] in 1968, which described two severely affected siblings with brittle, sulfur-deficient hair, as well as intellectual and growth retardation. This report led to the name Pollitt Syndrome. In 1970, Brown [23] described alternating birefringence in the hair viewed under polarized microscopy in a 4-year-old girl with brittle hair and normal intelligence. Tay [24], in 1971, reported three siblings in Singapore with brittle hair, mental deficiency and growth retardation, who also had nonbullous congenital ichthyosiform erythroderma. Tay suggested an autosomal recessive pattern of inheritance. Tay's 1971 report did not, however, include sufficient hair analysis to meet the inclusion criteria for this analysis. In 1974, Jackson [25] described decreased fertility and autosomal recessive inheritance in an Amish kindred with brittle hair, intellectual impairment and short stature. Two index cases were sufficiently described to be included in this analysis. Jackson's report led to the name "Amish Brittle Hair Brain Syndrome". As a result of these similar clinical descriptions, the acronym BIDS (*Brittle hair, Intellectual impairment, Decreased fertility and Short stature*) was suggested in 1976 [16]. Subsequently, the additional presence of ichthyosis led to the acronym IBIDS [14, 15]. Unlike some later cases of TTD with ichthyosis, it has been suggested that Tay Syndrome specifically refers to the presence of congenital ichthyosis in addition to BIDS [26].

Two siblings from Sabinas, Mexico were reported in 1976 [27] as having brittle hair, developmental delay, and normal stature. This report in conjunction with a report [28] of a group of 11 additional TTD cases from Sabinas, led to the name Sabinas Syndrome in 1981, which refers to the presence of hair and nail abnormalities in association with mental retardation. The 1981 report [28] was not included in this review because the patients were described as a general group and not individually.

The addition of photosensitivity to the acronym IBIDS (resulting in PIBIDS) was recommended in 1983 by Crovato [13]. There was also some debate as to whether TTD was in fact a single entity, due to the various presentations of this neuroectodermal disorder [29]. In 1988, Chapmann reported a patient and recommended the addition of skeletal abnormalities instead of photosensitivity to the acronym, resulting in SIBIDS [30]. The patient described in this report did not meet our inclusion criteria for this analysis.

In 1985, Van Neste [31] reported defective DNA excision repair in UV exposed lymphocytes from a TTD patient. The first such gene mutation was identified the next year [32], when cells from four patients with TTD were found to have cellular UV hypersensitivity, very low levels of unscheduled DNA synthesis, and characteristics of the XP-D complementation group. Despite some patients having the same gene defects seen in XP (*XPB* and *XPD*), patients with TTD do not have an increased incidence of skin cancers [2, 11]. In 1993, patient TTD1BR was reported to have a new DNA repair complementation group, called TTD-A [33]. A second patient with TTD-A has since been reported [34]. The TTD-A gene (called *GTF2H5*) was identified in 2004 [35]. The recently discovered TTDN1 gene with unknown function was described in association with non-photosensitive patients [7]. To date, four genes have been identified as causing TTD: *XPD*, *XPB*, *TTDA*, and *TTDN1* [7, 32, 33, 36].

## CASES REPORTS INCLUDED IN THIS STUDY

A total of 94 articles were found that met our inclusion criteria for TTD case reports. The articles were published from 1968 to 2005 [7, 17, 13-16, 22-23, 25-27, 31-34, 36-114]. They contained data on 112 patients. The reported cases met at least two of the four entry criteria as follows. Ninety-six percent (108 cases) had brittle hair or hair shaft abnormalities. There were 73% (82 cases) with tiger tail banding of the hair with polarized microscopy. Seventy percent (78 cases) had decreased sulfur or cystine content of their hair. Thirty seven percent (41 cases) had a DNA repair abnormality reported. Four patients were included based on having brittle hair and a diagnosed sibling with TTD [85, 90, 98].

Table 1 shows patient location and origin. As this data was only reported for 50 patients, the author's location was used for the remaining 62 patients, assuming that the patients were from the same location as the author. Patients/authors were reported from 20 countries from all over the world, including Europe, North and South America, Africa, Asia and Australia. The greatest numbers of reports were from Italy (23%), the United States (16%), and the United Kingdom (16%).

**Table 1- Distribution of patient location or origin for reported TTD patients (N=112)**

<b>AUTHOR LOCATION<sup>a</sup></b>	<b>PATIENTS, NO. (%)</b>
Italy	27 (23%)
United States	19 (16%)
United Kingdom	18 (16%)
France	12 (11%)
Germany	3 (3%)
Canada	4 (4%)
Morocco	4 (4%)
Turkey	4 (4%)
Switzerland	4 (4%)
Other <sup>b</sup>	17 (15%)
<b>TOTAL</b>	<b>112 (100%)</b>

<sup>a</sup>Author location used as surrogate for 62 patients whose location/origin was not reported;

<sup>b</sup>“Other” refers to one or two patients from each of the following countries: Australia, Belgium, Denmark, Mexico, Austria, India, Spain, Poland, Finland, Czechoslovakia and the Netherlands

## MODE OF INHERITANCE, DEMOGRAPHICS, AGE, AND SURVIVAL

Gender was reported for 105 patients in this review, and consisted of 54 males (51%) and 51 females (49%). Trichothiodystrophy is an autosomal recessive disease, and is therefore expected to have an equal distribution between males and females. There was one report [65] suggesting the possibility of x-linked inheritance in a TTD patient with urea cycle dysfunction.

Age was reported for 110 of the 112 patients included in this study (Figure 2). The age at last report ranged from 12 weeks to 47 years, with a median of 6 years. There was a median age of 6.5 years for males and 6 years for females. The ages ranged from 12 weeks to 44 years for males and 5 months to 47 years for females.

Twenty patients were reported as deceased, ranging in age from 12 weeks to 47 years (Figure 2). All but one of these patients were under 10 years old and the median age at death was 3 years. The cause of death was pneumonia or other infection (especially sepsis) for 13 of these patients (Figure 3) [40, 41, 63, 74, 85, 90, 91, 94, 98, 99, 107]. One additional patient [85] died at 12 months after developing a fever, despite antibiotic use. The remaining patients died of drowning [62], cachexia and dehydration [98], respiratory failure [46], or a sudden or unexpected death [32, 68]. One patient [32] who died suddenly had a history of frequent hospitalizations for respiratory and gastrointestinal illnesses, and thus may have also died from infectious complications. The oldest patient [56] died at 47 years after presenting with generalized edema and urinary retention, which progressed to coma. Cause of death was not reported for one patient [111].

Kaplan-Meier analysis of the reported deaths indicated that at age 3 years there was 10.7% probability of reported death, and by age 9 years the probability had increased to 21.3%. This represents an approximately 20-fold higher mortality compared to the US general population. While we would expect that unusual and severe outcomes might be preferentially reported, this large number of deaths at a young age highlights the potential severity of TTD in the neonatal and early childhood period.

Recessively inherited disorders occur more commonly in populations where consanguinity is frequent. This literature review revealed 17% consanguinity, 49% non-consanguinity and 36% unreported. None of the parents were reported to have TTD. Data was given on the presence or absence of siblings in 80 patients. Thirty-seven patients have a sibling who is also described as a patient in this review (represents 18 families for these 37 patients). The total number of siblings ranged from 0 to 9, with a median of 1.

### **SPECTRUM OF CLINICAL ABNORMALITIES REPORTED IN TTD PATIENTS**

Figure 4 displays the common clinical features reported for each patient in the format of a clinical array. Each column represents one patient, with each clinical feature indicated as present, absent, or not mentioned in the report. The columns are grouped to facilitate identification of patients by gender with features of PIBI(D)S (28%), IBI(D)S (20%), BI(D)S (16%) and those that did not fit these categories (36%). Because decreased fertility (D) is age dependent and difficult to quantify from these reports, this feature was not included in this figure. Instead, we have indicated patients with gonadal dysgenesis. Arraying patients in this format highlights those who fit the clinical criteria defined by these acronyms and those where the acronym inadequately describes the clinical presentation. Other commonly reported clinical features are also shown in this figure, including abnormal characteristics at birth, pregnancy complications, ocular abnormalities, and infections. DNA repair abnormalities that were identified are also shown.

**Table 2- Frequency of skin abnormalities reported (N = 89) in TTD patients.**

	<b>PATIENTS, NO. (%)</b>
<b>SKIN ABNORMALITY</b>	89 (79%)
Ichthyosis (all forms)	73 (65%)
Lamellar ichthyosis	10 (9%)
Photosensitivity	47 (42%)
Eczema	9 (8%)
Freckles	8 (7%)
Dry skin, NOS	7 (6%)
Erythroderma	5 (4%)
Other <sup>a</sup>	20 (18%)
<b>NORMAL SKIN; NOT REPORTED</b>	7 (6%); 16 (14%)
<b>TOTAL</b>	112 (100%)

<sup>a</sup>“Other” refers to telangiectasia (5 patients), pruritis (4), folliculitis (3), cheilitis (3), follicular keratosis (3), hypohidrosis (3), hemangioma of skin (2), poikiloderma (2).

### SKIN FINDINGS

Seventy-nine percent of the 112 reported TTD patients had skin abnormalities (Table 2). Seven patients were reported to have normal skin and 16 reports did not include any skin descriptions. The most frequently reported skin finding was ichthyosis (65%)(Table 2 and Figure 4). Of the 73 patients with ichthyosis, 27 had collodion membrane at birth. Ten patients were reported to have lamellar ichthyosis and 6 of these had collodion membrane at birth. Ichthyosis was seen in almost all age groups.

**Table 3- Cellular studies reported (N = 58) in TTD patients.**

<b>Gene Defect</b>	<b>PATIENTS, NO. (%)</b>
<b>REDUCED DNA REPAIR</b>	41 (37%)
XP-D	32 (29%)
XP-B	2 (2%)
TTD-A	2 (2%)
<b>TTDN1</b>	6 (5%)
<b>NORMAL DNA REPAIR; NOT REPORTED</b>	11 (10%); 54 (48%)
<b>TOTAL</b>	112 (100%)

The second most frequent skin finding reported was photosensitivity (42%). Seventy percent of the 112 patients in this study had photosensitivity and/or ichthyosis (28% of all patients had both photosensitivity and ichthyosis) (Figure 4). Twenty-seven of the 47 patients with photosensitivity were reported as having mutations in XPD, one in XPB, and one in TTDA (Table 3 and Figure 4). Four patients were not assigned to a complementation group, but were found to have cellular UV hypersensitivity[31, 59, 100]. Although the XPD gene mutation has been reported to be associated with the clinical finding of photosensitivity, there was one case of a TTD patient [112] with an XPD gene mutation reported as non-photosensitive. Other cutaneous findings include dry skin (21%), eczema (8%), and freckles (7%). Freckling is generally associated with



XP and not TTD. Two of the TTD patients [45] with freckles were reported to also have XP (the XP/TTD complex), and one of them had a skin cancer. Six other patients with freckles were not reported to have skin cancer [32, 41, 58, 81]. One additional TTD patient [54] had a well-differentiated, invasive squamous carcinoma on his nose, but was not reported to have freckles. Other more rare skin findings include two reports of hemangioma [84, 105] and three reports of cheilitis [13, 22, 65].

**Table 4 - Frequency of hair and nail features (N = 112) in reported TTD patients.**

	<b>PATIENTS, NO. (%)</b>
<b>HAIR FEATURE</b>	112 (100%)
Brittle hair or hair shaft abnormality	108 (96%)
Brittle hair	98 (88%)
Hair shaft abnormality	76 (68%)
Tiger tail	82 (73%)
Decreased sulfur or cystine	79 (71%)
Sparse hair	54 (48%)
Alopecia	44 (39%)
Hair loss with fever or infection	8 (7%)
Dry hair	24 (21%)
Fine hair	16 (14%)
Slow growing hair	8 (7%)
Long hair	5 (4%)
<b>NAIL FEATURE</b>	70 (63%)
Onychodystrophy <sup>a</sup>	41 (37%)
Brittle nails	16 (14%)
Hypoplasia	15 (13%)
Koilonychia	13 (12%)
Splitting (Onychoschizia); Peeling	8 (7%)
Ridging	7 (6%)
Other <sup>b</sup>	3 (3%)
<b>NORMAL NAILS; NOT REPORTED</b>	14 (13%); 28 (25%)
<b>TOTAL</b>	112 (100%)

<sup>a</sup>We collated reports of dysplasia, dystrophic nails, thickening and yellow discoloration as onychodystrophy;

<sup>b</sup>Slow growing nails (2 patients) and soft nails (1)

### HAIR AND NAIL FINDINGS

Hair abnormalities were reported in all 112 patients (Table 4 and Figure 4). They are a defining feature of TTD, and were part of the inclusion criteria. The most frequent hair findings were brittle hair or hair shaft abnormalities (96%), tiger tail banding (73%), and decreased sulfur or cystine (71%). Two patients with the XP/TTD complex were reported not to have brittle hair, but did have decreased sulfur, tiger tail banding with

polarized microscopy, and *XPD* mutations [45]. Sparse hair (48%) and alopecia (39%) were also commonly reported. Eight patients had hair loss with fever or infection[50, 58, 59, 62, 68, 87, 107]. Although TTD is usually associated with short hair (due to its brittle and easily breakable nature), there were also 5 reports of patients with long or normal length hair [36, 38, 45, 78, 115], including 1 XP/TTD patient[45].

Nail abnormalities (Table 4) were reported in 70 patients (63%). The most frequent nail abnormality reported was onychodystrophy in 41 patients (37%), which included dysplasia, dystrophic nails, thickening or yellow discoloration. Other common nail findings were brittle nails (14%), hypoplasia (13%), and koilonychia (12%).

**Table 5- Frequency of neurologic features reported (N = 100) in TTD patients.**

	<b>PATIENTS, NO. (%)</b>
<b>DEVELOPMENTAL DELAY OR INTELLECTUAL IMPAIRMENT</b>	96 (86%)
Intellectual impairment	84 (75%)
Developmental Delay	76 (68%)
Impaired motor control / Psychomotor retardation	41 (37%)
Sociable / Outgoing behavior	17 (15%)
<b>CLINICAL NEUROLOGIC FINDINGS</b>	84 (75%)
Microcephaly	46 (50%)
Abnormal gait / Ataxia	29 (26%)
Audiologic exam performed [normal hearing; sensorineural hearing loss]	[20 (18%); 5 (4%)]
Abnormal deep tendon reflex [increased; decreased]	[15 (13%); 1 (1%)]
EEG [normal; abnormal]	[14 (13%); 13 (12%)]
Abnormal muscle tone [increased; diminished]	[8 (7%); 11 (10%)]
Nerve conduction velocity performed [normal; slow]	[9 (8%); 3 (3%)]
Spasticity	11 (10%)
Intention tremor	8 (7%)
Seizure	7 (6%)
Paresis / Plegia	6 (5%)
Dysarthria	5 (4%)
Pyramidal signs	5 (4%)
Peripheral neuropathy	2 (2%)
<b>NEUROIMAGING ABNORMALITY</b>	26 (23%)
Dysmyelination	16 (14%)
Atrophy [cerebellar; cortical]	[5 (4%); 3 (3%)]
Dilated ventricles	4 (4%)
Calcifications	2 (2%)
Other <sup>a</sup>	5 (4%)
<b>NO ABNORMALITY REPORTED</b>	12 (11%)
<b>TOTAL</b>	112 (100%)

<sup>a</sup>“Other” refers to partial agenesis of corpus callosum (1 patient), slight widening of subarachnoid spaces (1), thin corpus callosum (1), cerebral infarction (1), focal gray matter heterotopia and acute necrotizing encephalopathy (1)

## NEUROLOGIC FINDINGS

Neurologic abnormalities were reported in 100 patients (Table 5 and Figure 4). Developmental delay or intellectual impairment was reported in 86% of patients, and spanned all age groups. These usually presented as failing to achieve developmental milestones, such as sitting, walking, or talking, on time [112]. Eleven of the 16 patients who were not reported to have developmental delay or intellectual impairment were less than 5 years old [23, 38, 46, 61, 78, 84, 90, 107]. Of the patients with developmental delay or intellectual impairment, 41 also had impaired motor control or psychomotor retardation. Seventeen of the patients with neurologic abnormalities were also described as having notably sociable or outgoing behavior. This outgoing, sociable interaction is also a feature of patients with Cockayne syndrome (CS) [11].

Intelligence quotient (IQ) was given for 21 patients. These tests included Terman-Merrill (3 patients, IQ range 25 to 40) [89], Wechsler Intelligence Scale for Children (2 patients, IQ range 45 to 89)[25, 39], Stanford-Binet (3 patients, IQ range 32 to 79)[14, 15, 93] and not specified or other exam (such as Leiter scale and Ruth Griffiths test) (13 patients, IQ range 34 to 88)[17, 27, 37, 60, 64, 69, 71, 76, 77, 79, 83]. As a result, an average value could not be determined. Ichthyosis was closely linked to developmental delay since 67 (92%) of 73 patients reported with ichthyosis were also reported to have developmental delay.

Other abnormal neurologic findings described include microcephaly (50%), abnormal gait (26%), and increased deep tendon reflexes (13%). Audiologic examination was performed in 25 patients, and found normal hearing in 20 and sensorineural hearing loss in the other 5. Nine patients were reported to have high-pitched/raspy voice [14, 17, 57, 73, 76, 77, 82] and one patient had dysphonia [40]. Six patients were reported to have attention deficit or hyperactivity [22, 27, 50, 69, 81, 89] and 3 patients as autistic-like [75, 81, 101].

Neuroimaging abnormalities were given in 23% of patients. The most common findings were dysmyelination (14%), cerebellar atrophy (4%), and dilated ventricles (4%), which are similar to features found in CS [11]. One patient had a progressive encephalopathy with ataxia and a gradual deterioration of previously acquired skills [63]. In one patient [70], an attack of measles at age 4 years was reported to be followed by general disability, and according to his mother a regression of development, but subsequent to that had slow progress with no further degeneration. Another patient [56], however, did not change during a 30-year period. EEG was reported in 27 patients, of which 14 were normal and 13 were abnormal (4 of these patients had seizures) [25, 60, 113].

Five cases reported “mild TTD,” in which the patients had involvement of only hair, skin or nails [23, 37, 38, 84]. Two of these patients [38] had abnormal nails and one [84] had dry skin, but none had the neurologic abnormalities seen in many TTD patients. No gene defect was reported for these patients.

Facial dysmorphism was reported in 66% of patients (Table 6). These included microcephaly (50%), large or protruding ears (30%), and micrognathia (29%). As in CS, there have been descriptions of TTD patients with aged (9%) or “bird-like” appearances (8%).

**Table 6- Facial dysmorphism reported (N = 74) in TTD patients.**

	<b>PATIENTS, NO. (%)</b>
<b>FACIAL DYSMORPHISM</b>	<b>74 (66%)</b>
Microcephaly	56 (50%)
Large or protruding ears	34 (30%)
Micrognathia	33 (29%)
Aged appearance	10 (9%)
“Bird like”	9 (8%)
High arched palate	8 (7%)
Epicanthal fold	8 (7%)
Frontal bossing	5 (4%)
Hypotelorism; Hypertelorism	6 (5%); 3 (3%)
Craniosynostosis	1 (1%)
<b>NOT REPORTED</b>	<b>38 (34%)</b>
<b>TOTAL</b>	<b>112 (100%)</b>

### **GROWTH ABNORMALITIES**

Eighty-one percent of patients were reported to have either low height and/or weight (which includes six patients described as having “growth retardation”) (Figure 4). Sixty-one percent of patients had both short stature and low weight or poor weight gain. An additional 13 patients [27, 45, 56, 60] had short stature with either normal or unreported weight. Six patients had normal height and weight [27, 38, 62, 84, 97, 113].

### **GONADAL DYSGENESIS**

Sixteen patients (14%) had sexual/reproductive abnormalities reported (Figure 4). Thirteen of these patients had hypogonadism [15, 26, 40, 45, 56, 71, 76, 77, 86, 89, 101] of which 2 were females [40, 56] and 9 had cryptorchidism [15, 25, 26, 40, 58, 73, 76, 77, 86]. Two cases reported delayed pubertal development [70, 111]. Additional genito-urinary abnormalities in females included poor sexual maturation [14, 22] and partial panhypopituitarism [114].

### **PREGNANCY AND BIRTH CHARACTERISTICS**

Thirty-four patients overall were reported to have parents in good health. When the TTD patients were born, the median reported maternal age was 25 years (based on 16 patients) and the median reported paternal age was 27 years (14 patients).

Two previously unrecognized findings not commonly associated with TTD are abnormal characteristics at birth (Figure 5) and pregnancy complications (Figure 6). Abnormal characteristics at birth were reported in 62 patients (55%) (Figure 5). The most common finding was low birth weight (defined as birth weight less than 2500 g or specified as being low) which was reported in 41 patients (37%). In the United States for the year 2005 8.2% of infants were born with low birth weight (less than 2500 gms) [116]. The actual birth weight was specified for 53 patients and ranged from 0.94 kg to 4 kg, with a median of 2.2 kg. This is much smaller than the median birth weight of 3.0 to 3.5 kg of infants born between 37 and 40 weeks of gestation in the US general population [116]. Five additional cases specified low birth weight without giving a value [14, 85, 98, 107]. The length of gestation was reported in 53 patients and ranged from

25 to 42 weeks. The median gestational age for all reported cases was 37 weeks. Thirty-two of these patients (29%) were born prematurely (less than 37 weeks). Apgar scores were given for 8 patients, two of which [76, 100] were less than 7 at 5 minutes, indicating perinatal asphyxia. Twenty-nine of the infants (26%) had a collodion membrane at birth. Twenty-seven of these also were reported to develop ichthyosis (6 of which were lamellar ichthyosis). For the two patients with collodion presentation not reported to have ichthyosis, one paper had very limited information about the patient [46], and the other paper only reports that the patient later had dry scaly skin [76]. Thirteen patients had brittle or abnormal hair. There were 14 patients (13%) reported to have short birth length [22, 34, 40, 45, 68, 70, 81, 85, 98, 99, 106] and 8 patients (7%) to have small birth head circumference [40, 85, 98, 99, 106]. Values for birth length were given for 18 patients, ranging from 36 cm to 51 cm, with a median of 46 cm. Values for birth head circumference were given for 10 patients, ranging from 28 cm to 35 cm, with a median of 31 cm. Five additional patients were specified to have low birth length and head circumference, but no value was given [85, 98]. Cryptorchidism was reported for 9 (17%) of the boys. Congenital cataracts were identified in 8 (7%) of the reported cases. This is also a feature of CS and is greatly elevated compared to the frequency of 1-2.5 per 10,000 live born infants [117] in the general population. In addition, 5 patients were described as having infections (including respiratory infections) in the neonatal period (Figure 3).

The course of pregnancy refers to the pregnancy of the patient's mother, when she was pregnant with the reported TTD case (Figure 6). There was no information reported for 52 (48%) of the pregnancies. This is not surprising since many of the reports were in the dermatologic literature. In 29 of the 112 cases (26%) the pregnancy was described as uncomplicated, however 8 of these neonates had abnormal characteristics at birth. Pregnancy complications were reported in 31 cases (28%) and the TTD neonates from these pregnancies all had abnormal characteristics at birth (Figure 5). The reports contained information on gestational age at birth and birth weight of the newborns. Twenty-three patients (21%) had intrauterine growth retardation (IUGR) stated in the report or alternatively, which we determined as low weight for the gestational age at birth [18]. Pre-eclampsia was reported in 8 pregnancies (7%) [22, 32, 39, 68, 94, 100, 105, 115] and eclampsia or seizures in 3 [17, 63, 108]. There did not seem to be a correlation between IUGR and pre-eclampsia, as only 3 cases had both [32, 68, 100]. In addition, one pregnancy [85] was reported as having an abnormal prenatal screening test (elevated maternal serum alpha-fetoprotein). There were 13 cases of caesarian section and 4 cases of breech presentation [57, 73, 99, 108]. The caesarian sections were performed secondary to both maternal indications (5 cases) and fetal indications (8 cases). The maternal indications were pre-eclampsia (3)[32, 39, 105], toxemia and seizures (1) [63] and abruptio placenta (1) [26]. Fetal indications included intrauterine growth retardation (4)[40, 75, 85], breech presentation (2)[57, 99], fetal distress (1)[69] and fetal asphyxia (1)[74]. Other pregnancy complications reported were bleeding (2), oligohydramnios (1) and placental abnormality (1). Pregnancy loss was reported in 5 pregnancies of mothers who also had a child with TTD. One loss was an intrauterine fetal demise at 19 weeks 4 days of gestation; the other 4 losses were described as spontaneous abortions or miscarriage with no gestational age provided [32, 90, 97-99].

In addition to the patients described in this review, 5 additional patients were diagnosed with TTD in utero by prenatal diagnostic methods. Prenatal diagnosis was reported in families with a previous child diagnosed with TTD. None of the pregnancies with the affected fetuses went to term. Methods of prenatal diagnosis reported included fetal hair biopsy and DNA repair measurements [90, 98, 100, 118, 119]. One study measured UV-induced unscheduled DNA synthesis (UDS) in cultivated amniotic fluid cells at 17 weeks gestation. After a therapeutic abortion, the diagnosis was confirmed by severe DNA excision repair defect in fetal skin fibroblasts. While UV-induced UDS cannot differentiate among different DNA repair abnormalities [11], this family had a previous child with diagnosed TTD [100]. During a later pregnancy in the same reported family, prenatal diagnosis was made by chorionic villus sampling at 9 weeks gestation and finding quantitatively normal DNA excision-repair [119]. Another study that same year looked at two pregnancies using DNA repair defects in trophoblasts (at 9 weeks gestation) or amniotic cells (at 21 weeks gestation) and then further supported by fetal hair analysis [98]. Alkaline comet assay (single cell gel electrophoresis assay) was performed on amniotic or chorionic villus cells to diagnose a fetus as having TTD [118]. A later study used endoscopically-guided fetal eyebrow biopsy during the second trimester, and found tiger tail banding under polarized light [90].

### **OCULAR ABNORMALITIES AND INFECTION**

Ocular abnormalities were reported in 51% of patients (Figure 7). Thirty-two of these patients had cataracts, of which 20 were specified as bilateral and 8 as congenital (Figure 5). The median age of reported patients with cataracts was 7.5 years, and all but one patient were less than 25 years old. Three patients [15, 70, 99] were reported to have surgery to correct their cataracts. Other ocular findings include nystagmus (14%) and strabismus (10%).

Infections were described in 51 patients (Figure 3). Fourteen patients were described as having infections (especially respiratory infections) within the first year of life, including 5 in the neonatal period. Forty patients (36%) had recurrent infections. Reported infections were most commonly respiratory (29%), gastro-intestinal (13%), and ear (11%). Recurrent urinary infections were reported in 5 patients, all starting less than age 5 [32, 66, 69, 73, 83]. Etiologies of infections included bacterial, fungal and viral. Two patients [38, 91] were reported to have hypogammaglobulinemia, for which they both received intravenous immunoglobulin. One patient [91] was reported to receive prophylactic trimethoprim-sulfamethoxazole, but was also the only patient reported to have combined immunodeficiency. Three patients [41] with recurrent infections in childhood were reported in adolescence to no longer be prone to infections. In addition, patients were reported as having asthma or allergies (5 patients) [15, 17, 34, 51, 69] and hypergammaglobulinemia (2 patients) [56, 66]. Thirteen patients [40, 41, 46, 63, 85, 90, 91, 94, 98, 99, 107] died of infection, which mostly consisted of respiratory infection or sepsis. The immune system of one patient with combined immunodeficiency was studied in two papers. One found the patient to have defective dendritic cell maturation and the second found decreased TCR repertoire complexity suggesting a possible T cell regulation abnormality [49, 91].

**Table 7- Skeletal and dental abnormalities (N = 46) in reported TTD patients.**

	<b>PATIENTS, NO. (%)</b>
<b>RADIOGRAPHIC BONE ABNORMALITY</b>	<b>43 (38%)</b>
Osteosclerosis <sup>a</sup>	16 (14%)
Delayed Bone Age	14 (13%)
Osteopenia	10 (9%)
Kyphosis	7 (6%)
Coxa valga	4 (4%)
Other <sup>b</sup>	8 (7%)
<b>JOINT ABNORMALITY</b>	<b>15 (13%)</b>
Contractures <sup>c</sup>	8 (7%)
Joint dislocation	4 (4%)
Other <sup>d</sup>	7 (6%)
<b>TOOTH ABNORMALITY</b>	<b>23 (21%)</b>
Caries	21 (19%)
Enamel hypoplasia	4 (4%)
Other <sup>e</sup>	4 (4%)
Normal teeth	18 (16%)
<b>NORMAL OR NO SKELETAL OR TOOTH ABNORMALITY REPORTED</b>	<b>66 (59%)</b>
<b>TOTAL</b>	<b>112 (100%)</b>

<sup>a</sup>4 patients had both osteosclerosis and osteopenia;

<sup>b</sup>Pectus excavatum (3 patients), scoliosis (2), hallux valgus (2), bilateral hammer toe deformities (2);

<sup>c</sup>Contractures of hips and knees (3), and hands (3);

<sup>d</sup>Clinodactyly of 5th finger, short limbs, tapering fingers, syndactyly, joint hypermobility;

<sup>e</sup>Dystrophic teeth (2) and hypoplastic teeth (enamel not specified) (2)

### **SKELETAL AND DENTAL ABNORMALITIES**

Skeletal and dental findings are listed in Table 7. All except one [47] of these 46 patients also had neurologic abnormalities. Radiographic bone abnormalities were reported in 38% patients. The most common findings were osteosclerosis (14%), delayed bone age (13%), and osteopenia (9%). When specified, the osteosclerosis was usually axial, and the osteopenia distal. Four patients had both osteosclerosis and osteopenia[17, 51, 63, 106]. Seven additional patients were reported as having normal bone age, and no radiographic bone abnormalities.

The most common joint abnormalities were contractures (7%) and joint dislocation (4%). Contractures were of hip and knees (3 patients) [51, 69, 82] and hands (3 patients)[56, 71, 103]. Subluxation was of the hip (3 patients) [51, 56, 114] and toes (1 patient)[76]. The most common tooth abnormality was caries (19%). Eleven of these 21 patients had severe caries [13, 17, 22, 47, 57, 58, 69, 72, 76, 77, 99].

### **CARDIAC AND HEPATIC ABNORMALITIES**

In addition, cardiac defects were noted in 8 patients and included cardiomyopathy, pulmonic stenosis and ventricular septal defect [22, 74, 75, 85, 107]. Three additional

patients were reported to have a murmur, but no cardiac defect identified [36, 63, 72]. Two patients [85] were reported to have multiple liver hemangioendotheliomas.

### HEMATOLOGIC ABNORMALITIES

Hematologic abnormalities were reported in 24 patients (Table 8). These findings consisted of anemia (12%), low MCV (9%), neutropenia (9%), and elevated hemoglobin A2 (7%). Two cases [69, 76] of anemia were due to iron deficiency. Eight TTD patients [111] with XPD mutations were reported as having “hematologic features of beta-thalassemia trait, and reduced levels of beta-globin synthesis and beta-globin mRNA”. The cause of anemia in the remaining 3 patients [38, 54, 72] was Coombs-positive hemolytic anemia, sideroblastic anemia and unspecified. Twenty-one percent of patients had either a normal CBC or routine blood analysis.

**Table 8- Hematologic abnormalities reported (N = 24) in TTD patients.**

	<b>PATIENTS, NO. (%)</b>
<b>HEMATOLOGIC ABNORMALITY</b>	24 (21%)
Anemia <sup>a</sup>	13 (12%)
Low MCV	10 (9%)
Neutropenia	10 (9%)
Elevated Hemoglobin A2	8 (7%)
<b>NORMAL; NOT REPORTED</b>	24 (21%); 64 (57%)
<b>TOTAL</b>	112 (100%)

<sup>a</sup> 2 patients reported with iron deficiency

### DNA REPAIR ABNORMALITIES AND GENE DEFECTS

DNA repair abnormalities or gene defects were reported in 41 patients. Thirty-two patients were reported as having mutations in *XPD*, 2 in *XPB* and 2 in *TTDA* (Table 3 and Figure 4). Five patients [59, 80, 100, 108], were reported to have cellular UV hypersensitivity, with no specific gene defect determined. Six additional patients [7] were reported as having mutations in the newly discovered *TTDN1* gene with unknown function. Eleven patients were reported to not have a DNA repair abnormality [37, 57, 67, 72, 75, 85, 90, 107]. Of the 32 patients with mutations in *XPD*, 27 were reported to have photosensitivity. While most of the cases with a DNA repair abnormality were from patients with photosensitivity, this might be due to ascertainment bias in that photosensitivity is a reason to suspect a DNA repair abnormality. Genotype-phenotype correlation is best studied on a group of patients who are studied in the same manner. It may not be valid to compare phenotypes from reports with different extents of clinical information provided.



## DISCUSSION

### **Birth abnormalities, pregnancy complications and increased mortality in TTD**

TTD has substantial morbidity and mortality in the neonatal and childhood years. There was an approximately 20-fold increase in the probability of death in reported TTD children 10 years of age or less compared to the US general population. This increased mortality in TTD is neither widely recognized nor well understood. However, there may be bias in reporting more severe cases thereby suggesting a worse prognosis for TTD.

This study documents the wide spectrum of severity within TTD. The high frequencies of reported abnormal characteristics at birth and pregnancy abnormalities suggest that childhood and neonatal morbidity can begin in the prenatal period. Fifty-three percent of reported patients had abnormal characteristics at birth and 28% of pregnancies were abnormal. The relatively young median parental ages (maternal: 25 years; paternal: 27 years) at birth of TTD patients indicates that advanced parental age was not a factor in the frequency of pregnancy abnormalities or in the development of TTD. This surprisingly large number of reports of pregnancy abnormalities suggests that the pathophysiology of TTD involves a developmental abnormality directly affecting the pregnancy. This adds a complex dimension to understanding the clinical phenotype of TTD. Some of the clinical features may be due to the effect of TTD on the affected patient and in addition, some of the clinical disease may be secondary to compromise resulting from maternal pregnancy abnormality.

Different mutations in the *XPD* or *XPB* genes can lead to TTD, XP or a clinical overlap of both, the XP/TTD complex. Genes that are defective in TTD, *XPB*, *XPD* and *TTDA*, are components of the basal transcription factor, TFIIF, as well as the nucleotide excision repair pathway [5, 6, 120, 121]. A current theory suggests that mutations in these genes in patients with XP predominately impede DNA repair, while mutations in the same genes in TTD patients predominately affect transcription [1, 121]. Thus XP is a disease of progressive sunlight induced degeneration of the skin [2, 11]. In contrast to XP, TTD is primarily a disorder of development which may be the consequence of transcriptional anomalies resulting from different defects in the same DNA repair genes [11, 120]. Thus the finding of elevated hemoglobin A2 and low RBC mean corpuscular volume that mimic thalassemia without a defect in a hemoglobin gene was interpreted as a transcription defect in TTD patients with mutations in *XPD* gene [111]. The other developmental features of TTD may represent abnormalities in transcription of genes that are essential for normal pregnancy and fetal development. The high frequency of reported fetal abnormalities and maternal pregnancy complications in mothers of TTD patients suggests a role of the DNA repair/ transcription genes in normal pregnancy and fetal development. CS, another rare genetic disease with defective DNA repair, shares some of the same clinical features as TTD including photosensitivity, short stature, developmental delay, intrauterine growth retardation, dysmyelination of the brain, and an outgoing social personality [2, 6, 122]. CS is caused by *CSA* and *CSB* genes, which have a role in repair of actively transcribing genes.

### **Classification**

Trichothiodystrophy is a rare multi-system disorder with a wide spectrum of clinical involvement. We were able to identify only 112 patients reported in the world's literature

who fit our criteria for inclusion into this study of TTD reports. These criteria allowed us to capture a large number of TTD cases from the literature where limited information was available on each patient. These criteria were not intended to be used for diagnosis of new patients where more extensive evaluation should be possible [3, 4]. The goal of this study was to assess the frequency of clinical features in order to better understand the spectrum of manifestations of TTD [1, 123]. The most common clinical features were brittle hair or hair shaft abnormalities (96%), intellectual impairment or developmental delay (86%), short stature (73%) and ichthyosis (65%). While it is useful to look at the frequency of different features across the broad population of patients, it is also important to know how often a set of clinical features occurs together (Figure 4). Sixty-four percent of patients had the clinical features to fit into the category of either PIBI(D)S, IBI(D)S or BI(D)S, however, the others (36%) did not. Almost all of the patients who had clinical features sufficient to fit into these designations had additional clinical manifestations not specified by the acronyms. In addition, even the broadest acronym, PIBIDS, does not include several major clinical features found to be more common than photosensitivity (42%) and decreased fertility, including abnormal characteristics at birth (53%), ocular abnormalities (51%), and infections (46%), which should be considered major clinical features of TTD. So these acronyms are poor descriptors of TTD patients' clinical manifestations.

Van Neste [115] suggested a classification system in 1989 based on increasing severity beginning with only hair defects. While this schema takes into account additional features of TTD beyond PIBIDS, it intrinsically implies a sequential pattern to the progression of disease severity. As seen in Figure 4, not all patients fit into a uniform sequence. For example, although the Van Neste classification lists photosensitivity as a more severe case of TTD, some patients may have photosensitivity without ichthyosis or short stature. Van Neste's classification was later expanded to include more features, such as chronic neutropenia or immunoglobulin deficiency, severe IUGR and basal ganglia calcifications [1].

### **Multiple reported abnormalities in TTD**

Surveys of reported clinical features have several weaknesses. These include ascertainment bias, leading to the reporting of patients who are more interesting and severe and the under-representation of more mildly affected patients. Reports vary with respect to thoroughness of clinical evaluation, leading to the probable underreporting of many features that may not have been evaluated. This suggests that the prevalence of many clinical features summarized here may under-represent their true frequencies. In addition, since we would expect milder phenotypes to be less likely to be reported, TTD may be much more common than the number of reported cases implies.

Neurologic abnormalities (86%) were frequently reported in TTD cases, manifesting most commonly as developmental delay, intellectual impairment, microcephaly, impaired motor control or psychomotor retardation. This high frequency may be an underestimate, since 11 of the 16 patients who were not reported to have developmental delay or intellectual impairment were less than 5 years old. In general, these findings were not found to be deteriorations in neurologic status, but rather were more suggestive of a chronic non-progressive condition. Two exceptions were reported. One patient [63] had progressive encephalopathy and ataxia and a second

patient [70] had developmental regression after an episode of measles. This further supports an early developmental abnormality being a key factor leading to TTD neurologic involvement. In contrast, about 20% of XP patients, who have different mutations in many of the same genes as TTD patients [121], have neurological abnormalities which manifest as progressive degeneration [2, 9]. Recent studies have looked at the relationship between DNA repair defects and impaired neurologic development [11]. The presence of ichthyosis may be a marker of a systemic developmental abnormality since more than 90% of the TTD patients reported to have ichthyosis also have developmental delay.

Infections were commonly (46%) reported and were often recurrent (36%). Sixty five percent of the 20 reported deaths were related to infections. This frequency and severity of infections suggests that the pathophysiology of TTD includes an immunologic abnormality. However, no consistent laboratory abnormality in the immune system has been identified in TTD patients.

### **TTD involves many medical specialties**

Effective management of the multisystem abnormalities of TTD involves a multidisciplinary approach involving many medical specialties. Seventy-seven percent of patients were less than or equal to 14 years old, and thus it is important for pediatricians to be aware of this disease. Sixty-three percent of patients had abnormal characteristics at birth, signaling importance for the neonatologist. Twenty-three percent were from abnormal pregnancies, which would bring these mothers to the attention of obstetricians. Twenty-nine percent of patients had cataracts (median age 7.5 years), including 8 with congenital cataracts, which, if undetected, can lead to vision impairment and interference with early childhood development and learning. The oldest TTD patient in the literature (47 years old) was first seen by those researchers at age 17 with pruritis and urticaria. She also had symptoms in her first year of life, consisting of collodion baby, congenital hip subluxation, and psychomotor developmental delay [56].

These patients may present to specialists in obstetrics, neonatology, pediatrics, ophthalmology, neurology, orthopedics, internal medicine, rehabilitation medicine, immunology, infectious disease, hematology, genetics, or radiology in addition to dermatology. If properly aware, any of these specialists can make the diagnosis. Since prenatal diagnosis is possible, establishment of a diagnosis can identify the risk to future pregnancies. It is surprising that a disorder with such a broad range of multisystem abnormalities can be unified by the simple finding of tiger tailed banding under polarized microscopy. This very simple and inexpensive test can reliably establish a diagnosis in both the healthy adult with learning disabilities and the severely ill, collodion baby in the neonatal intensive care unit. This review characterizes the wide spectrum of TTD and reinforces the importance of this simple screening test for patients with these multisystem findings. Greater recognition among a broad range of specialists can facilitate early diagnosis and treatment and identification of risk to future pregnancies.

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**COMPETING INTERESTS:** None reported

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## FIGURE LEGENDS

### Figure 1. Microscopic diagnosis of trichothiodystrophy.

(Left) Routine microscopic examination of hair from a patient with TTD shows shaft abnormalities of trichoschisis (\*) and trichorrhexis nodosa-like fraying (<). (Right) Under polarizing microscopy the hair shafts show a striking alternating dark and light (tiger-tail) banding pattern.

### Figure 2. Age at last report in TTD patients (N = 110).

The number in each bar indicates the number of patients reported in the indicated age group among the 90 reported living TTD patients. The shaded portion of the bar indicates the number of patients who died in the indicated age range among the 20 reported deceased TTD patients.

### Figure 3. Infections reported (N = 51) in TTD patients.

The number in each bar indicates the number of patients reported with the indicated type of infection among the 51 reported patients. A patient may have more than one reported infection. The shaded portion of the bar indicates the number of patients with the indicated type of infection as the cause of death among the 13 cases who died of infection. Etiologies of infections included bacterial, fungal and viral.

### Figure 4. A clinical array of features reported in the literature on 112 TTD patients.

Each column of rectangles represents clinical features of one reported patient. Presence or absence of each feature is indicated in each rectangle of a column. Abnormal clinical features reported are indicated by "1" in a colored rectangle. Normal reported features are indicated by "0" in a tan rectangle. Unreported features are blank. The rows represent P (yellow) – photosensitivity (n=47 cases); I (orange) – ichthyosis (n=73 cases); B (powder blue) – brittle hair or hair shaft abnormality (n=108); II (pink) – intellectual impairment (n=96 cases); GD (gray) – gonadal dysgenesis (n=16 cases); BC (light green) – abnormal birth characteristics (n=62 cases); PC (dark green) – pregnancy complications (n=31 pregnancies); O (maroon) – ocular abnormality (n=57 cases); IN (royal blue) – infections (n=51 patients); D (red) – DNA repair abnormality (N=41) [D in red rectangle – XPD (N=32 cases), B in striped red rectangle – XPB (N=2 cases), A in striped red rectangle – TTDA (n=2), N in striped pink rectangle – TTDN1 (N=6 cases), I in red rectangle – cellular UV hypersensitivity, gene not determined (N=5); G – gender (N=105 patients), [Blue rectangles – males (N=54 cases), Pink rectangles – females (N=51 cases).] Patients whose clinical features fulfill the criteria for PIBIDS (28%), IBIDS (20%), BIDS (16%) and those that do not (OTHER)(36%), are grouped by bold outline (Decreased fertility is ignored in this grouping due to inability to assess in children.)

### Figure 5. Abnormal characteristics at birth reported (N = 62) in TTD patients.

The number in each bar indicates the number of patients reported with the indicated birth characteristic among the 62 reported patients. A patient may have more than one abnormal birth characteristic. The inset shows the proportion of the 112 cases reporting abnormal birth characteristics, pregnancy complications or both.

### Figure 6. Reported course of pregnancy in mothers delivering TTD patients (N = 60). The number in each bar indicates the number of TTD pregnancies reported with the

indicated pregnancy complication among the 60 pregnancies detailed in the reports. The pregnancies with complications are indicated with shaded bars. A pregnancy may have more than one complication reported. The inset shows the proportion of the 112 cases reporting pregnancy complications. The bar labeled "Other" refers to bleeding (2 patients), oligohydramnios (1), placental abnormalities (1).

**Figure 7. Ocular abnormalities reported (N = 57) in TTD patients.**

The number in each bar indicates the number of TTD cases reported with the indicated ocular abnormality among the 57 patients detailed in the reports. "NOS" – cataracts not otherwise specified; "Bilat" in shaded bar – bilateral cataracts; Of the 32 patients with cataracts, 20 were reported as bilateral and 8 as congenital. "Other" refers to dry eyes (1 patient) and retinal pigmentation (1). A patient may have more than one ocular abnormality reported.



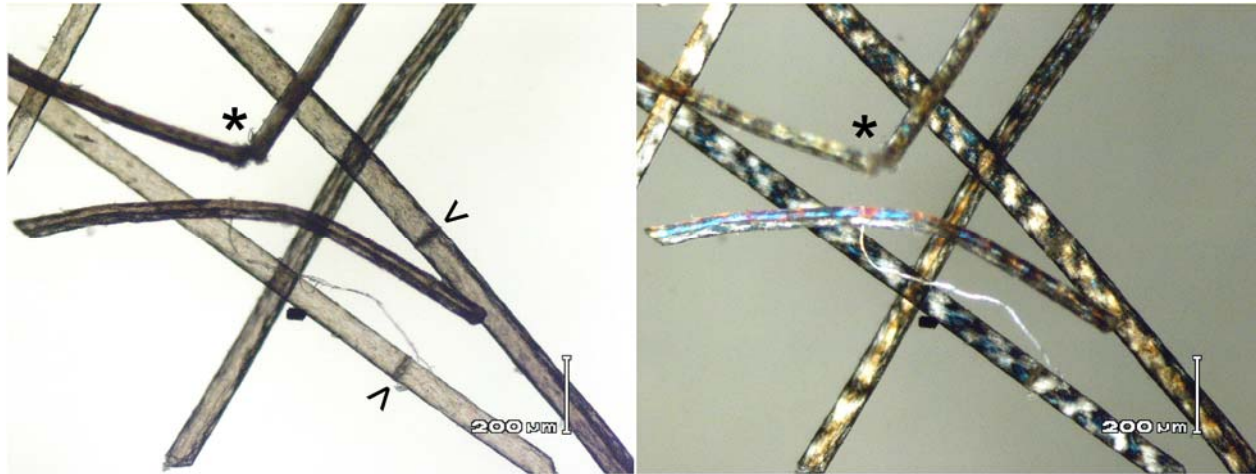


Figure 1

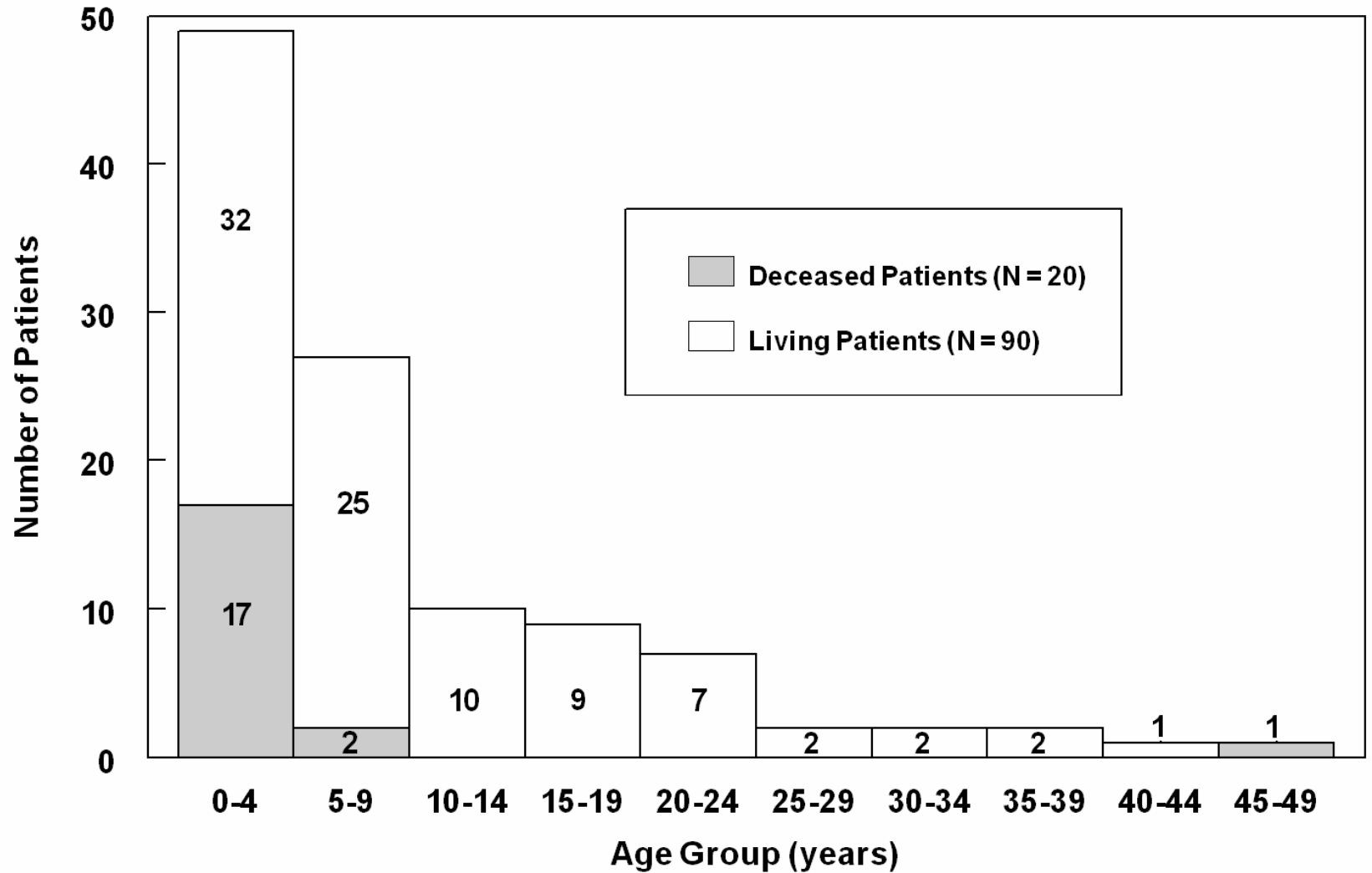


Figure 2

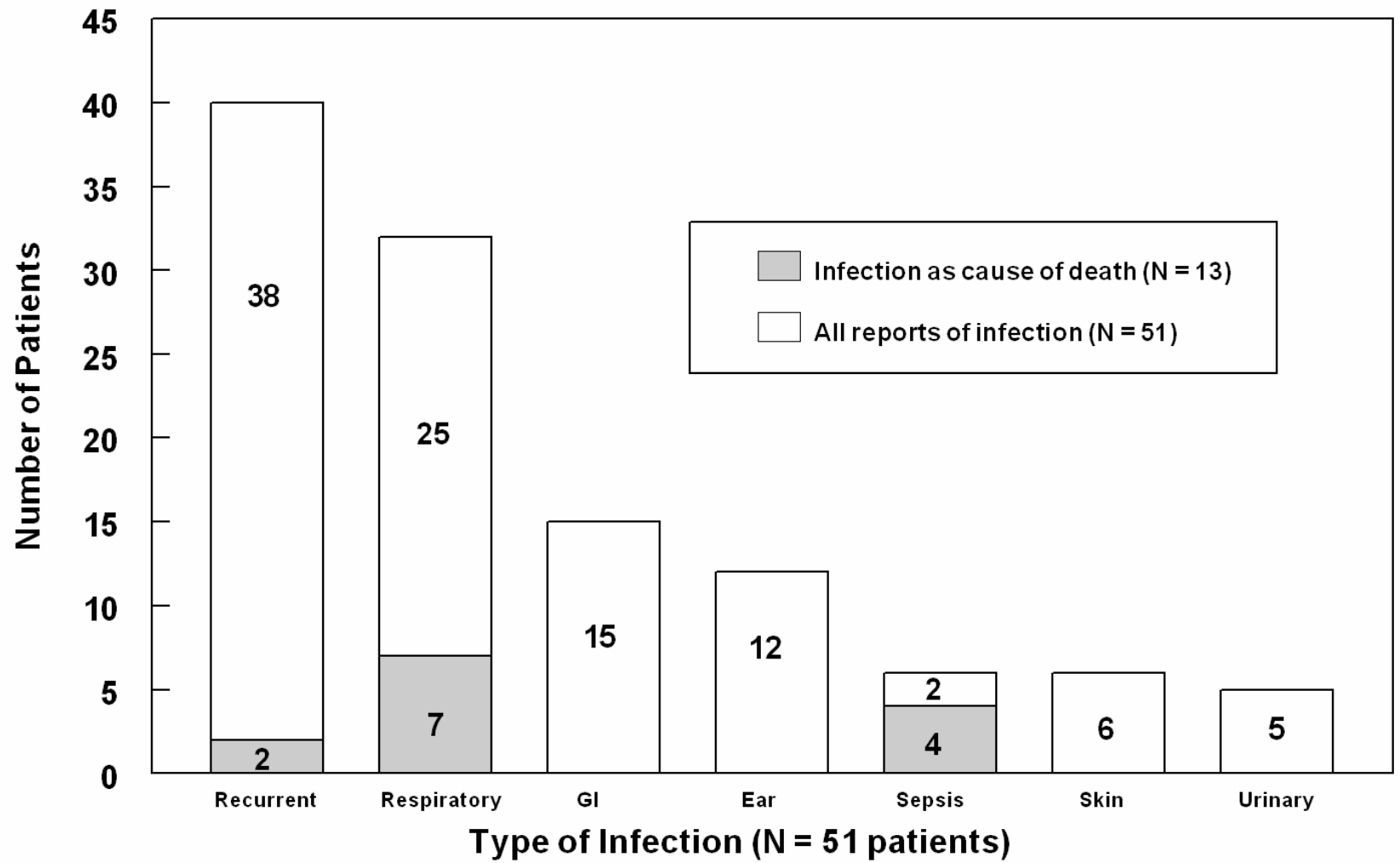


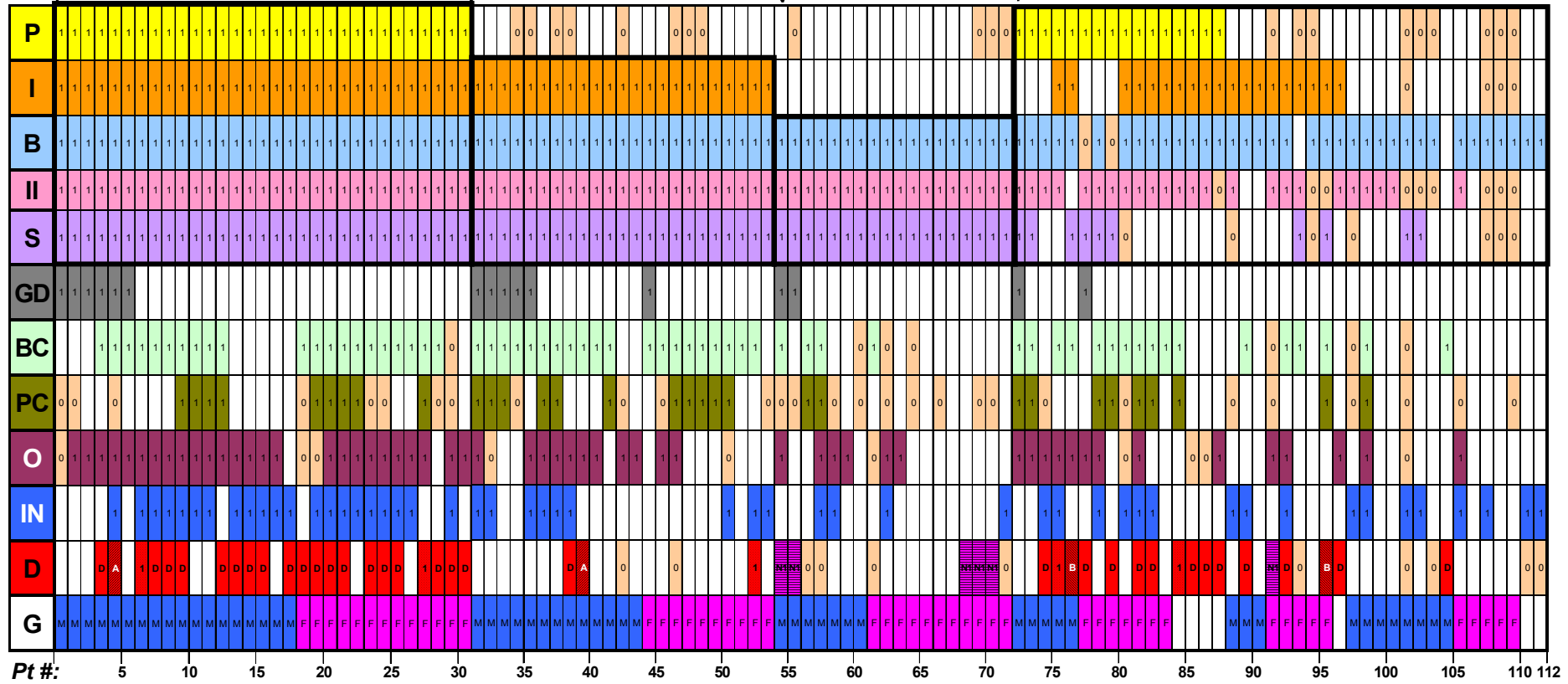
Figure 3

**PIBIDS**  
31 pts; 28%

**IBIDS**  
23 pts; 20%

**BIDS**  
18 pts; 16%

**OTHER**  
40 pts; 36%



<b>P</b>	<b>PHOTOSENSITIVITY (N = 47)</b>
<b>I</b>	<b>ICHTHYOSIS (N = 73)</b>
<b>B</b>	<b>BRITTLE HAIR OR HAIR SHAFT ABNORMALITY (N = 108)</b>
<b>II</b>	<b>INTELLECTUAL IMPAIRMENT / DEVELOPMENTAL DELAY (N = 96)</b>
<b>S</b>	<b>SHORT STATURE (N = 82)</b>
<b>GD</b>	<b>GONADAL DYSGENESIS (N=16)</b>

<b>BC</b>	<b>ABNORMAL CHARACTERISTICS AT BIRTH (N = 62)</b>
<b>PC</b>	<b>PREGNANCY COMPLICATION (N = 31)</b>
<b>O</b>	<b>OCULAR ABNORMALITY (N = 57)</b>
<b>IN</b>	<b>INFECTIONS (N = 51)</b>
<b>G</b>	<b>GENDER (N = 105)</b>

<b>D</b>	<b>DNA REPAIR ABNORMALITY (N = 41)</b>
<b>D</b>	<b>XPD (N=32)</b>
<b>B</b>	<b>XPB (N=2)</b>
<b>A</b>	<b>TTDA (N=2)</b>
<b>N1</b>	<b>TTDN1 (N=6)</b>
<b>t</b>	<b>CELLULAR UV SENSITIVITY, GENE DEFECT NOT DETERMINED (N=5)</b>

Figure 4

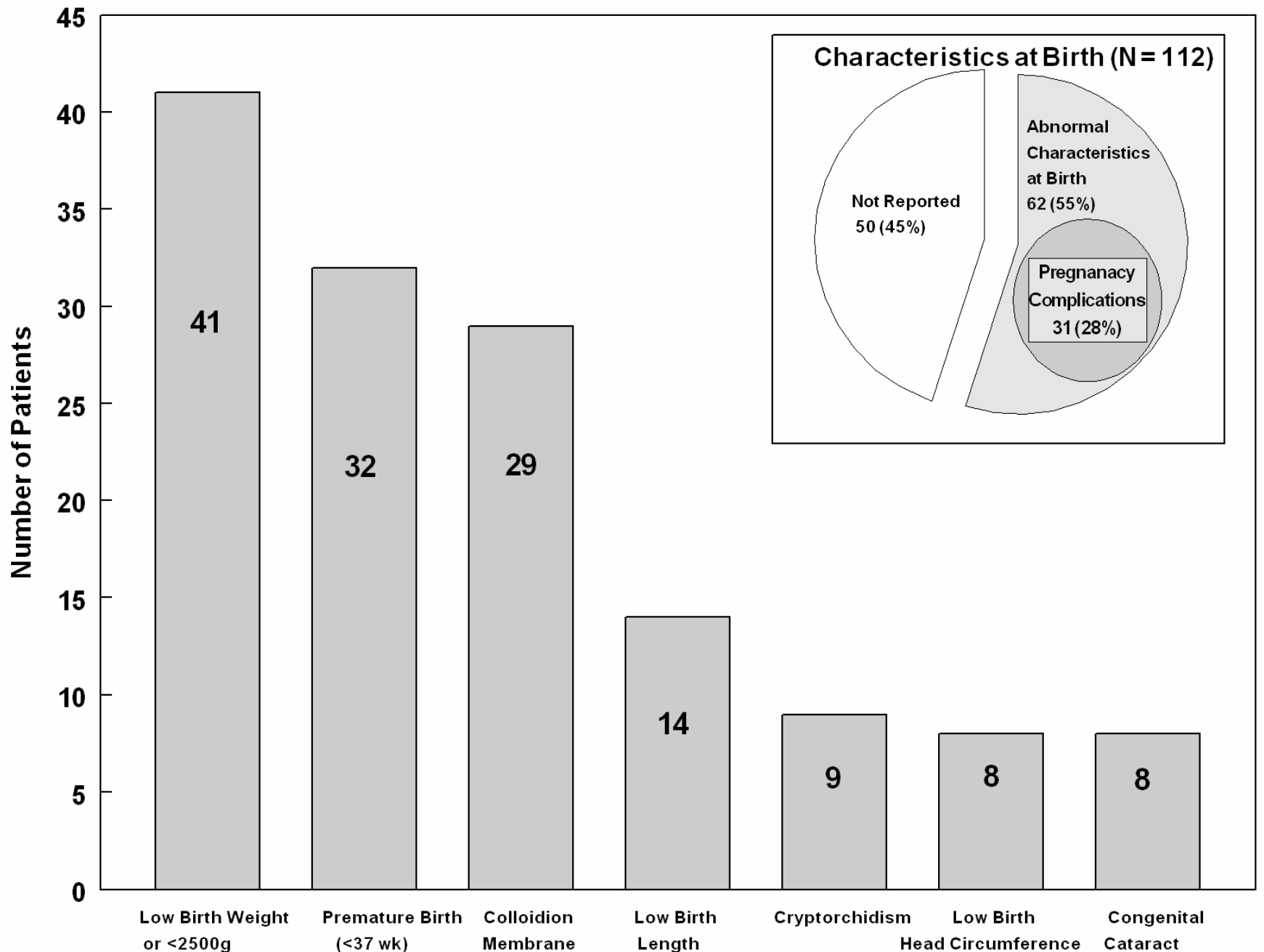


Figure 5

Abnormal Birth Characteristic (N = 62 patients)

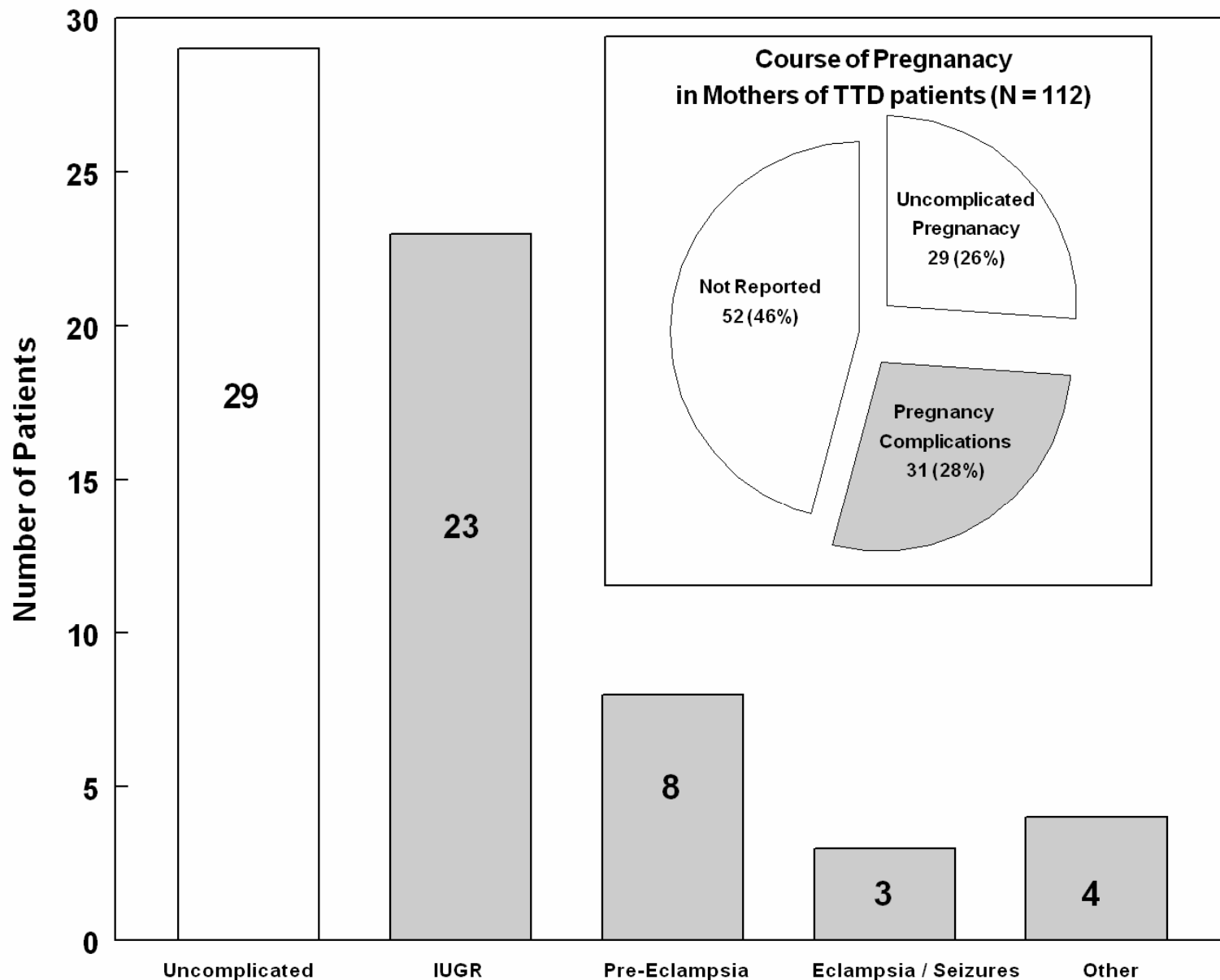


Figure 6

Pregnancy Complications (N = 60 pregnancies)

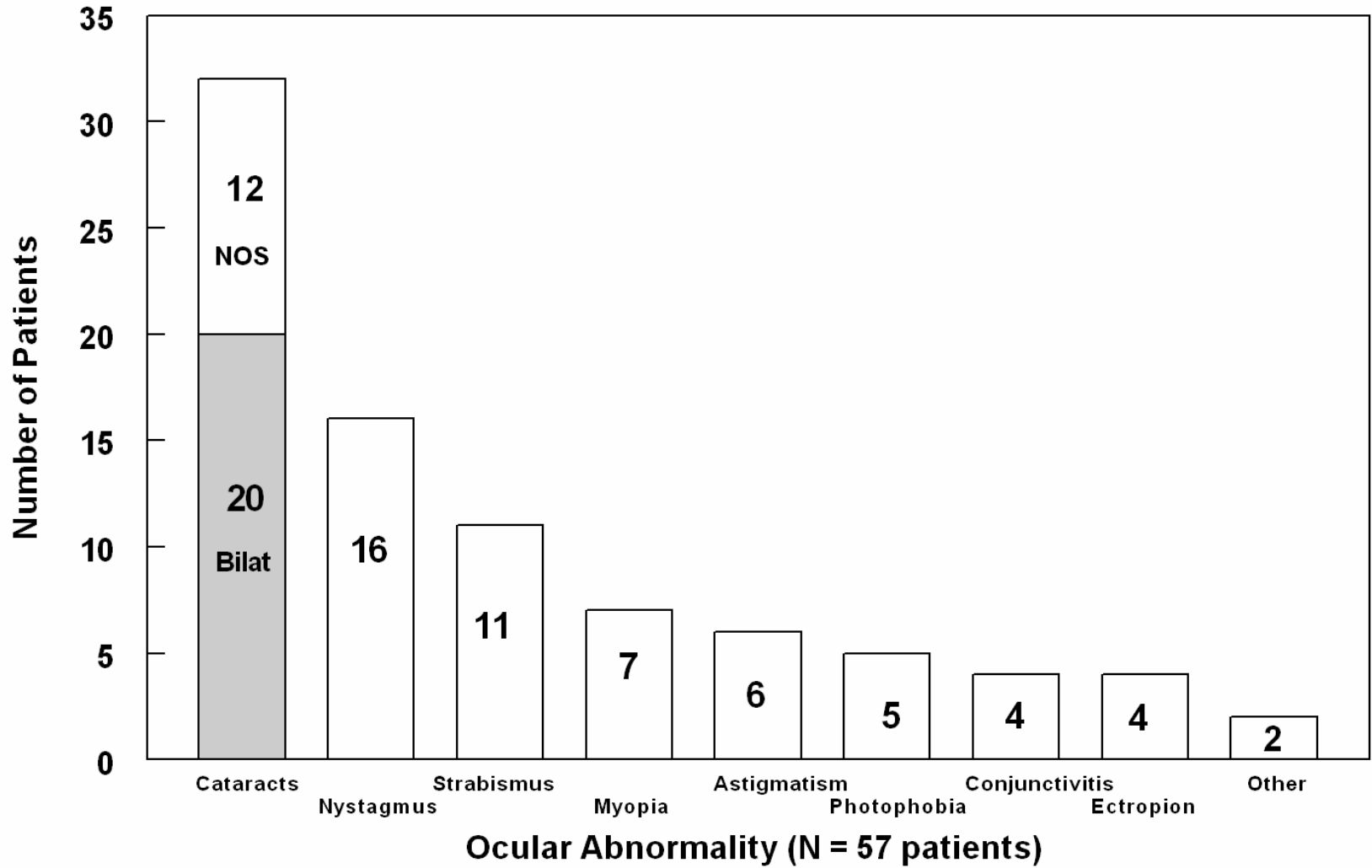


Figure 7