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Dominant Negative Mutations in the C-Propeptide of COL2A1 Cause Platyspondylic Lethal Skeletal Dysplasia, Torrance Type, and Define a Novel Subfamily Within the Type 2 Collagenopathies

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Platyspondylic lethal skeletal dysplasia (PLSD) Torrance type (PLSD-T) is a rare skeletal dysplasia characterized by platyspondyly, brachydactyly, and metaphyseal changes. Generally a perinatally lethal disease, a few long-term survivors have been reported. Recently, mutations in the carboxy-propeptide of type II collagen have been identified in two patients with PLSD-T, indicating that PLSD-T is a type 2 collagen-associated disorder. We studied eight additional cases of PLSD-T and found that all had mutations in the C-propeptide domain of COL2A1. The mutational spectrum includes missense, stop codon and frameshift mutations. All non-sense mutations were located in the last exon, where they would escape non-sense-mediated RNA-decay. We conclude that PLSD-T is caused by mutations in the C-propeptide domain of COL2A1, which lead to biosynthesis of an altered collagen chain (as opposed to a null allele). Similar mutations have recently been found to be the cause of spondyloperipheral dysplasia, a non-lethal dominant disorder whose clinical and radiographical features overlap those of the rare long-term survivors with PLSD-T. Thus, spondyloperipheral dysplasia and PLSD-T constitute a novel subfamily within the type II collagenopathies, associated with specific mutations in the C-propeptide domain and characterized by distinctive radiological features including metaphyseal changes and brachydactyly that set them apart from other type 2 collagenopathies associated with mutations in the triple-helical domain of COL2A1. The specific phenotype of C-propeptide mutations could result from a combination of diminished collagen fibril formation, toxic effects through the accumulation of unfolded collagen chains inside the chondrocytes, and alteration of a putative signaling function of the carboxy-propeptide of type 2 collagen.

KEY WORDS: spondyloperipheral dysplasia; non-sense-mediated mRNA decay; genotype–phenotype correlation

INTRODUCTION

The platyspondylic lethal skeletal dysplasias (PLSDs) are a heterogeneous group of chondrodysplasias characterized by severe platyspondyly and shortening of limbs. The most common form of PLSD is thanatophoric dysplasia (TD), with its two variants, TD1 (OMIM 187600) and TD2 (OMIM 187610), both caused by mutations in the fibroblast growth factor receptor 3 (FGFR3) [Tavormina et al., 1995]. In 1979, two similar disorders have been distinguished, PLSD San Diego type (OMIM 270230) and PLSD Torrance type (PLSD-T, OMIM 151210). Each condition was felt to have specific histologic findings, and in both, some collagen 2 abnormalities had been observed but no molecular defect was identified. Several years later, the San Diego variant was found to be caused by FGFR3 mutations identical to those found in classical TD, while no FGFR3 mutations were identified in the Torrance variant [Brodie et al., 1999].

Both radiographic and histological criteria have been used to distinguish PLSD Torrance type from similar phenotypes [Horton et al., 1979]. PLSD-T is characterized by varying platyspondyly, short ribs with anterior cupping, hypoplasia of the lower ilia with broad ischial and pubic bones, and shortening of the tubular bones with splayed and cupped metaphyses. Histology of the growth plate typically shows focal hypercellularity with slightly enlarged chondrocytes in the

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resting cartilage and relatively well-preserved columnar formation and ossification at the chondroosseous junction [Horton et al., 1979; Kaibara et al., 1983; Freisinger et al., 1996]. Though generally lethal in the perinatal period (and classified amongst the letal platyspondylyc dysplasias), a few long-term survivors with PLSD-T have been reported [Omran et al., 2000; Neumann et al., 2003].

Recently, Nishimura et al. [2004] identified mutations in the carboxy-propeptide of type II collagen in two patients with PLSD-T, suggesting that PLSD-T may in fact be yet another type 2 collagen-associated disorder. In this report, we present eight additional cases with PLSD-T and mutations in the C-propeptide region of COL2A1. Based on these observations and the two cases from Nishimura et al., and in the light of recent observations of C-propeptide mutations in spondyloperipheal dysplasia [Zankl et al., 2004], we confirm that PLSD-T is caused by specific COL2A1 mutations, review the genotype–phenotype correlations of what seems to be a novel subfamily within the type 2 collagenopathies, and discuss possible pathogenetic mechanisms specific to type 2 collagen C-propeptide mutations.

METHODS

DNA was isolated from peripheral blood lymphocytes (patients 1, 3, 4, 5), skin fibroblasts (patients 7, 8) or cultured amniocytes (patient 2). Exons 49-52 and flanking intronic sequences of COL2A1 were amplified by PCR and the resulting fragments were sequenced bidirectionally on an ABI 3100 Genetic Analyzer as described previously [Zankl et al., 2004]. Nucleotide numbering is based on RefSeq NM_001844, starting with +1 at the ATG translation initiation codon. In this system, the helical part of procollagen II extends from AA 201–1,214, the C-propeptide comprises AA 1,215–1,488.

RESULTS

Patient 1

This is the second child of healthy parents. The older sib is healthy. Mother reported rapid increase in her abdominal diameter from 31 weeks of gestation. Ultrasound examination at 33 weeks of gestation revealed polyhydramnion, generalized edema of the fetus, short arms and legs, bowed radius, narrow thorax and midface hypoplasia. Due to increasing polyhydramnios, labor was induced and the patient was stillborn at 36 weeks. Post-mortem radiographs showed wafer-thin vertebral bodies, short ribs with splayed ends, small and rounded scapulae, shortened long bones with splayed metaphyseal margins, hypoplasia of lower illia with medial spur, brachydactyly with short metacarpals and phalanges, and splayed metaphyseal margins (Fig. 1a–c). Histology of the rib revealed enlarged and vacuolized chondrocytes and slightly disturbed columnar formation (Fig. 1d–e). In this patient, we identified a 4423C > T non-sense mutation in exon 52, which introduces a premature stop codon at position 1475 (Q1475X).

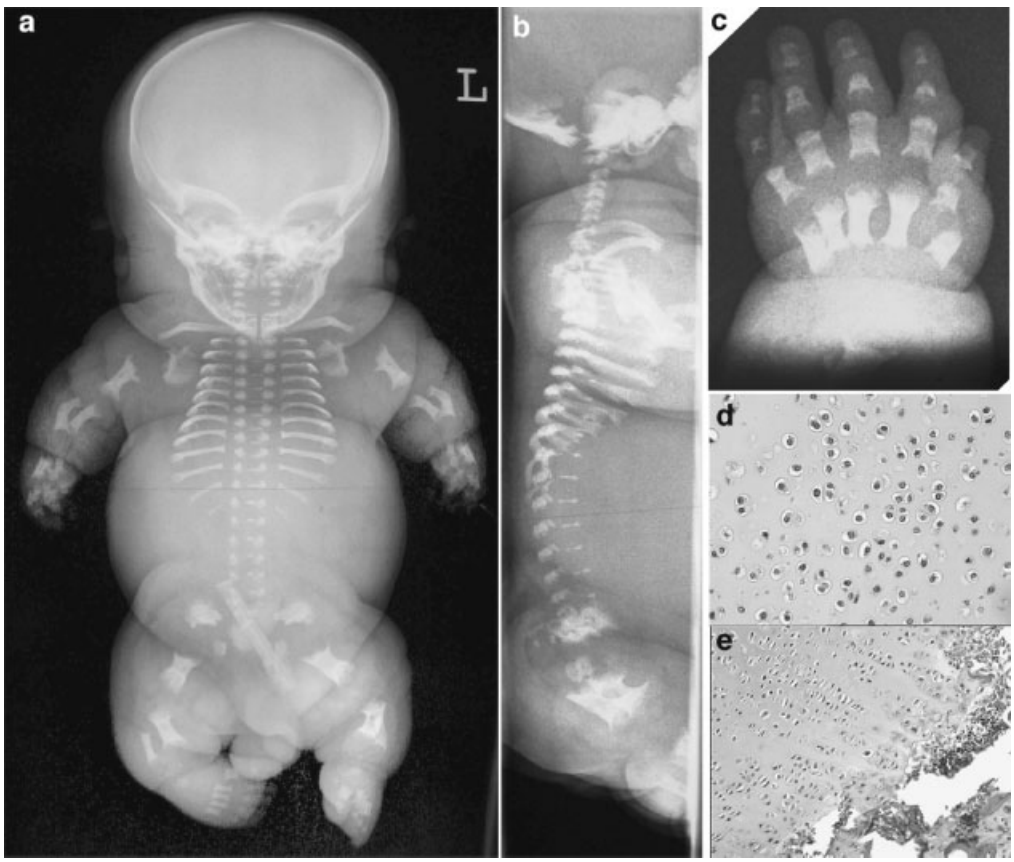

Fig. 1. **a–c**: Post-mortem radiographs of patient 1, showing wafer-thin vertebral bodies, short ribs with splayed ends, small and rounded scapulae, shortened long bones with splayed metaphyseal margins, hypoplasia of lower illia with medial spur, brachydactyly with short metacarpals and phalanges, and splayed metaphyseal margins. **d–e**: Histology of the costo-chondral junction, showing slightly disturbed columnar formation; at higher magnification, enlarged and vacuolized chondrocytes with relatively well preserved intercellular matrix.

This mutation was not present in the patient's parents and was equally absent in 50 normal control subjects.

Patient 2

This is the first child of non-consanguineous parents. Prenatal ultrasound examination revealed polyhydramnios, a small thorax with hypoplastic lungs and severe symmetrical shortening of the limbs. The child was born after 39 weeks but deceased during delivery. Pathological examination revealed a cleft palate and severe lung hypoplasia (body weight 2,753 g, crown-heel length 36 cm, head circumference 37 cm). Post-mortem radiographs (Fig. 2a,b) showed platyspondyly, short ribs with splayed ends, small and rounded scapulae, shortened long bones with splayed metaphyseal margins, hypoplasia of lower illia with medial spur, and bowed tibiae. Histology of the humeral chondroosseus junction, showed mild hypercellularity with relatively well preserved columnar formation (Fig. 2c) and vacuolization of chondrocytes (Fig. 2d). In this patient, we identified a 12 bp in-frame deletion (4441_4452del, I1481_V1484del). The mutation was not present in 50 normal control subjects. The parents were unavailable for study.

Patients 3 and 4

Clinical and radiographic features of patients 3 and 4 have been reported previously [Neumann et al., 2003]. In brief, patient 3 presented at 36 years of age with a height of 127 cm, a relatively large HC (56 cm), short fingers, lumbar lordosis and complaints of pain in the hips and lower back. Her son showed disproportionate short stature at birth with short limbs, relatively large head and a narrow chest. At age 1.5 years, he was 61.5 cm short, with a narrow chest, lumbar lordosis, genu varum, and a waddling gait. Mental development was normal. Based on radiographic findings, mother and son were diagnosed with PLSD-T. Figure 3 shows additional images, not published in the original report, illustrating brachydactyly of the hands and feet in patient 3. We have identified a missense mutation (4405G > C, D1469H) in both patients. The mutation was not found in 50 normal control subjects.

Patients 5 and 6

Patient 5 and 6 have been published previously [Omran et al., 2000; Neumann et al., 2003]. Patient 5 was born at term with disproportionate short stature (44 cm), a relatively large HC (38 cm), severe micromelia, and brachydactyly. She required supplemental oxygen but was otherwise healthy. At 26 years (127 cm), she gave birth to patient 6 who presented disproportionate short stature with a large head, a narrow chest, severe micromelia, and brachydactyly at birth. The infant suffered from lung hypoplasia and died after 22 days from respiratory insufficiency. Based on radiographic findings, both mother and son were diagnosed with PLSD-T. Figure 4 shows additional images of patient 5, not published in the original report. We have identified a missense mutation (4453T > G, C1485G) in the mother (DNA from the child was not available for testing). The mutation was not found in 50 normal control subjects.

Patient 7

This female patient is the third child of healthy, non-consanguineous parents. She was born after an uneventful pregnancy. After birth, a disproportionate short stature with short limbs and a relatively large head were noted. The face was flat with micrognathia. The thorax was small with prominent abdomen. Radiographs showed moderate platyspondyly and shortened long bones with splayed metaphyseal margins. The baby died due to respiratory insufficiency. We identified a non-sense mutation (4335G > A, W1445X) in this patient. The mutation was not found in 50 normal control subjects.

Patient 8

Patient 8 is the second child of non-consanguineous parents. The previous baby had multiple congenital abnormalities with absent thumb, lumbosacral segmentation defects, bilateral diaphragmatic defects, horseshoe kidney, and ambiguous genitalia. Long bones and ribs of this baby were normal. The

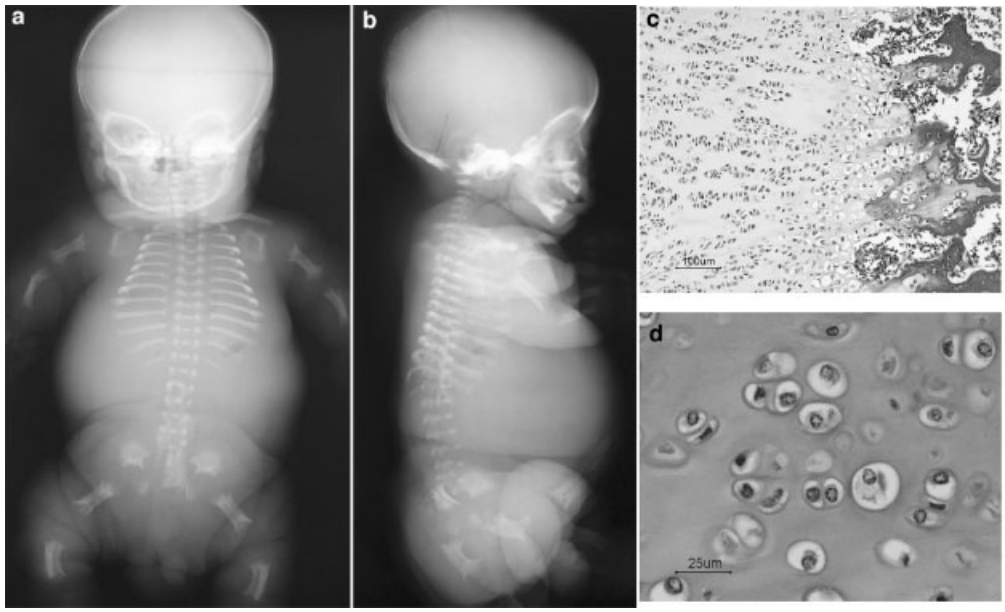

Fig. 2. **a**, **b**: Post-mortem radiographs of patient 2, with changes very similar to patient 1: platyspondyly, short ribs with splayed ends, small and rounded scapulae, shortened long bones with splayed metaphyseal margins, hypoplasia of lower illia with medial spur, bowed tibiae (**c**) histology of the humeral chondroosseus junction, showing mild hypercellularity and relatively well preserved columnar formation (**d**) vacuolization of chondrocytes.

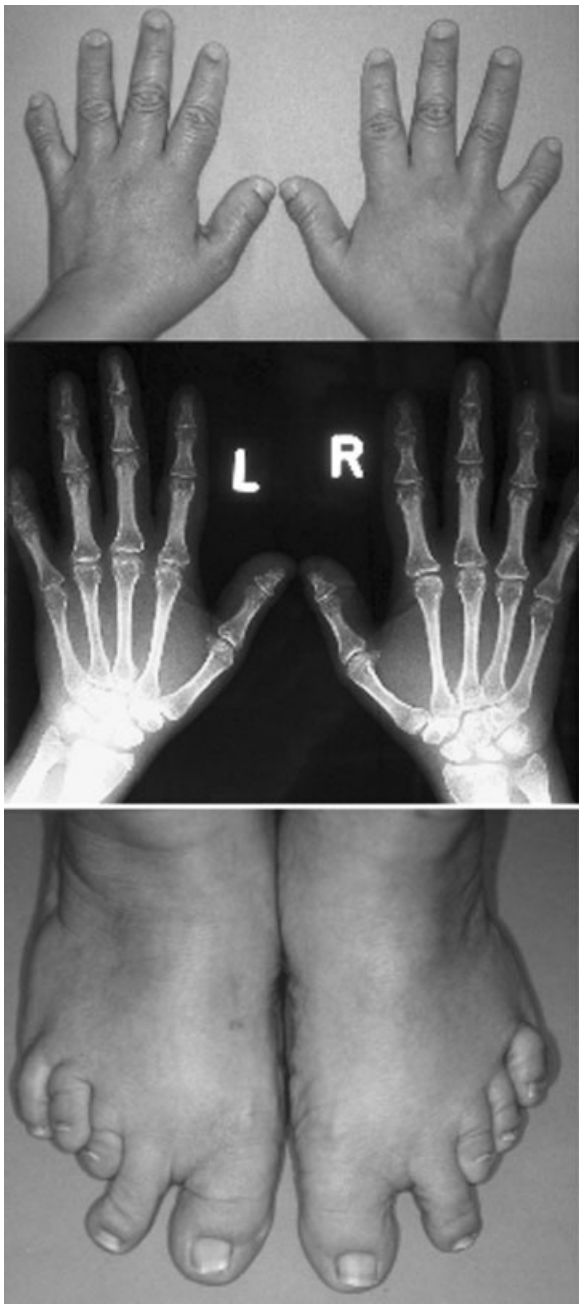

Fig. 3. Brachydactyly in patient 3 with a non-lethal variant of Platyspondylic lethal skeletal dysplasia (PLSD)-T. In the hands, the distal phalanx of digit I and the middle phalanx of digit V are particularly short. In the feet, the metatarsalia III and IV and the middle and distal phalanges are most severely affected (see radiographs in [Neumann et al., 2003]).

second pregnancy developed normally until 21 weeks of gestation, when prenatal ultrasound revealed shortening of long bones and a small chest. The parents decided to terminate the pregnancy and the fetus was born at 21 weeks of gestation. Post-mortem radiographs showed marked platyspondyly, hypoplasia of lower illia with medial spur and shortened long bones with splayed metaphyseal margins. We identified a missense mutation (4342A > C, T1448P) in this patient. The mutation was not found in 50 normal control subjects.

DISCUSSION

The identification of heterozygous mutations in the C-propeptide region of COL2A1 in all patients with PLSD-T confirms the findings of Nishimura et al. and definitively places PLSD-T among the type 2 collagenopathies. While most type 2 collagenopathies resulting in various forms of short-trunk dwarfism like Achondrogenesis type 2, Hypochondrogenesis, Kniest dysplasia, or SEDC are caused by mutations in the triple helix domain of COL2A1, mutations in the C-propeptide domain are very rare. The fact that all patients reported here have mutations in this region suggests that PLSD-T is specifically caused by mutations in this domain. This genotype–phenotype correlation is so characteristic that it allowed us to identify an additional patient from the literature who was initially considered as achondrogenesis 2/hypochondrogenesis [Mortier et al., 2000]: briefly, the patient was born at 36 weeks gestation with a birth length of 39 cm. A small thorax and shortening of long bones, especially of the hands and feet, was noted. The baby died at 13 months from pneumonia. The diagnosis of Achondrogenesis 2/Hypochondrogenesis was considered because of the presence of overmodified type 2 collagen in cartilage specimens and radiographic abnormalities suggestive for a type 2 collagen disorder. However, the phenotype of this patient was considered remarkable because of quite pronounced metaphyseal involvement and the unusual clinical course. Also, the histology did not fit well with the diagnosis, showing large chondrocytes with conspicuous inclusion bodies, but no excess number of blood vessels and no prolongation of hypertrophic chondrocytes into the primary trabeculae. Nevertheless, a COL2A1 mutation analysis was performed and revealed a missense mutation in exon 51 of COL2A1 (4169C > A, T1390N) [Mortier et al., 2000]. The finding of a mutation in the C-propeptide region was unexpected as all previously described mutations in Achondrogenesis II/Hypochondrogenesis were identified in the triple helical domain. Retrospectively, brachydactyly, metaphyseal involvement, and the histology are more compatible with a diagnosis of PLSD-T, as is the mutation in the C-propeptide domain.

The only other type 2 collagenopathy that is specifically associated with mutations in the C-propeptide domain is spondyloperipheral dysplasia (SPD) [Zabel et al., 1996; Zankl et al., 2004]. In fact, SPD and the rare adult form of PLSD-T (individuals no. 3 and 5) are remarkably similar. Both are characterized by midface hypoplasia, lumbar hyperlordosis, platyspondyly, epiphyseal dysplasia, and brachydactyly E-like changes affecting mainly the distal and middle phalanges and the metacarpalia. PLSD-T may differ from SPD by the absence of high-grade myopia and cleft palate, but these features are variable in other type 2 collagenopathies. It might well be that the rare survivors of PLSD-T are in fact examples of SPD.

Richards et al. [2002] identified a missense mutation in the C-propeptide domain of COL2A1 in a single large family with vitreoretinopathy and phalangeal epiphyseal dysplasia (VPED). Affected family members exhibited extensive lattice retinopathy and abnormal vitreal architecture, but no significant myopia. Skeletal involvement consisted of premature osteoarthritis of the hips and brachydactyly affecting the distal and middle phalanges. Spine involvement was minimal, affected persons were of normal stature and did not show midface hypoplasia.

It appears that brachydactyly, particularly of the distal and middle phalanges and of the metacarpalia, is the most consistent clinical feature of mutations in the C-propeptide domain of type 2 collagen. This observation is particularly relevant since brachydactyly is rare in the other type 2 collagenopathies, such as SEDC or Stickler syndrome, and is an important differential diagnostic criterium.

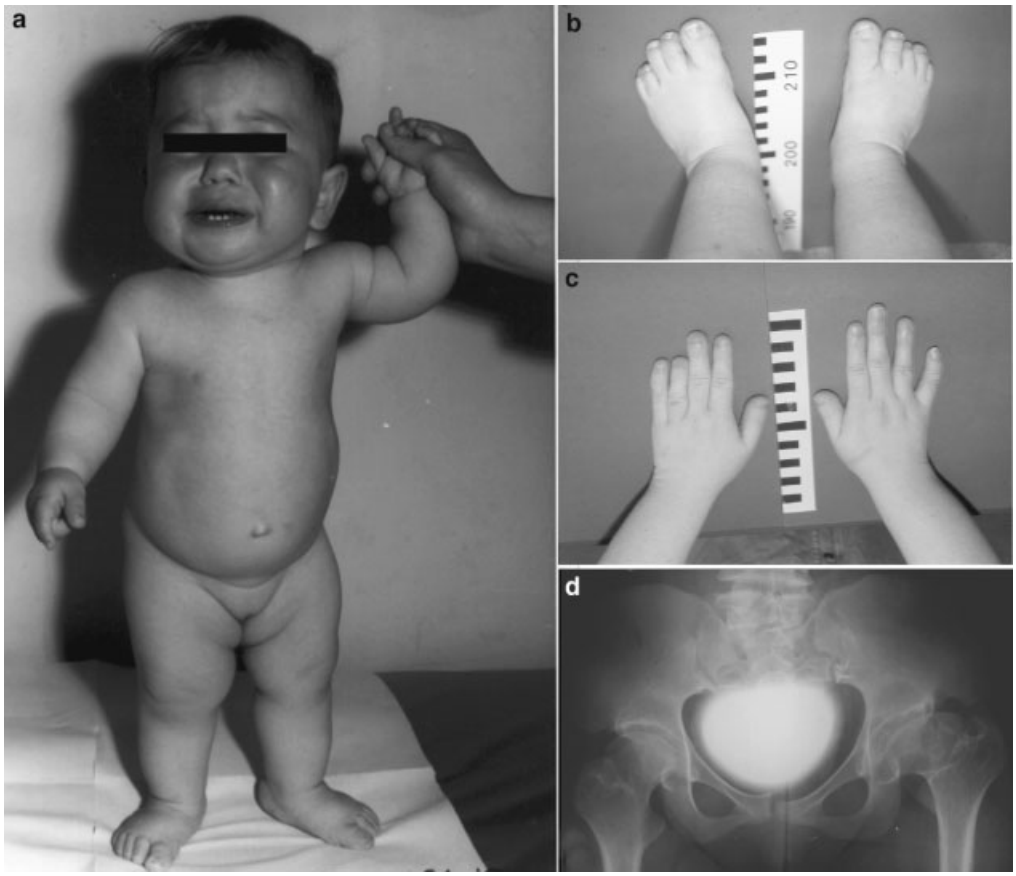

Fig. 4. Patient 5 at 3 years of age (**a**) and 24 years of age (**b**–**d**). Note brachydactyly of the hands and feet, particularly of digits 4 and 5. Pelvic radiograph shows hypoplasia of the lower ilium and dysplastic proximal femur. (see also radiographs in [Neumann et al., 2003; Omran et al., 2000]). The radiographic findings beyond the neonatal period are identical to SPD (see Discussion).

Histological studies of the growth plate in patients with PLSD-T typically show vacuolization of chondrocytes [Kaibara et al., 1983; Freisinger et al., 1996; Mortier et al., 2000] and Figure 1. Electron microscopy demonstrated chondrocytes with dilated cisternae of the rough endoplasmatic reticulum containing a granular material [Freisinger et al., 1996]. Collagen content in PLSD-T cartilage is mildly reduced, and the collagen fibrils are thin [Freisinger et al., 1996]. Freisinger and Mortier observed overmodification of type 2 collagen in fetal PLSD-T cartilage [Freisinger et al., 1996; Mortier et al., 2000]. A higher content of abnormal collagen in the salt-soluble fraction compared to the pepsin-soluble fraction suggested that the abnormal α1(II) chains were not appropriately integrated into stable cross-linked fibrils [Freisinger et al., 1996]. Freisinger et al. [1996] attributed this overmodification to a glycine substitution in the triple helix domain but failed to identify such a mutation by SSCP. The radiographic appearance that is distinct from most other type 2 collagen dysplasias, and the failure to demonstrate a COL2A1 helical mutation, lead to the interpretation of these collagen 2 findings as secondary. Based on our findings, we propose a different pathogenetic model: PLSD-T is caused by mutations, which (1) lie in the C-propeptide region of COL2A1 and (2) result in the biosynthesis of an altered collagen chain (as opposed to mutations that result in unstable mRNA and thus are functional null alleles). The majority of mutations identified so far are missense mutations that should result in the production of an altered collagen chain (Fig. 5). Two of the mutations introduce premature stop codons, but since both lie in the last exon of COL2A1 they should escape non-sense mediated mRNA decay [Schell et al., 2002; Zankl et al., 2004] and result in the production of a truncated protein. As the C-propeptide plays an important role in triple-helix formation, assembly of the altered α1(II) chains into trimeric collagen molecules is likely to be impaired, as demonstrated by overmodification of the resulting molecules. In addition, some of the mutated α1(II) chains might not be integrated into collagen fibrils at all and accumulate in the chondrocytes as free chains. The latter would explain (1) the presence of granules in the dilated rough endoplasmatic reticulum, (2) the higher content of abnormal collagen in the salt-soluble fraction compared to the pepsin-soluble fraction, and (3) the decreased collagen content and small collagen fibril diameter in the extracellular matrix. We have proposed a similar model to explain the pathogenetic mechanisms underlying SPD [Zankl et al., 2004] and the concept would also be compatible with the missense mutation observed in the family with VEPD [Richards et al., 2002].

Since all three conditions share the unique feature of brachydactyly, we could further speculate that the accumulation of altered collagen chains in the chondrocytes somehow causes slow proliferation of chondrocytes and/or premature closure of specific growth plates resulting in abnormally short tubular bones. Alternatively, the peculiar phenotype might be related to a specific function of the C-propeptide that becomes altered through a mutation in this region. The C-propeptide of type 2 collagen is also known as chondrocalcin [Poole and Rosenberg, 1986]. Chondrocalcin accumulates in the hypertrophic zones of the growth plate and seems to promote

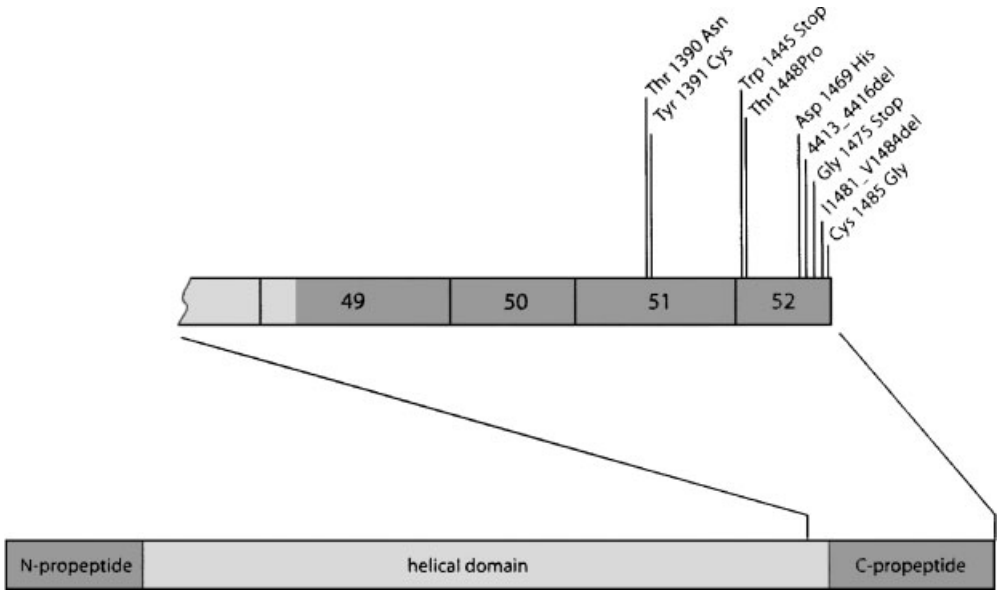

Fig. 5. Schematic view of type II collagen with all known mutations associated with PLSD-T. The C-propeptide domain is enlarged, numbers indicate exons.

mineralization in this zone, but little else is known about this protein. Mutations in HOXD13 have recently been identified in patients with brachydactyly type E [Johnson et al., 2003], which shows some resemblance to the brachydactyly observed in SPD and PLSD-T, but the relation to SPD and PLSD-T is unclear. Maybe HOXD13 and Chondrocalcin act in a common pathway.

Support for a specific function of the C-propeptide comes from collagen I. Most known mutations of collagen I lie within the triple-helical region and produce osteogenesis imperfecta (OI) in its remarkably wide phenotypic spectrum. Only a few mutations have been identified within the C-propeptide, and in some cases, these mutations have resulted in a peculiar and very rare variant, OI type IIC, characterized by fragile but dense bones [Pace et al., 2002]. Pace et al. hypothesized that the collagen I C-propeptide acts as a signaling molecule in the extracellular matrix and that alteration of this activity contributes to the unique features of OI IIC. In support of this theory, the collagen I C-propeptide has been shown to suppress collagen synthesis in preosteoblasts [Mizuno et al., 2000] and initiate growth arrest and differentiation in cultured Schwann cells [Rushton et al., 1999].

In summary, our findings confirm and reinforce the original observation by Nishimura et al. that PLSD-T is part of the spectrum of disorders associated with COL2A1 mutations, and suggest that PLSD-T and SPD constitute a novel subfamily within the type 2 collagenopathies, associated with specific mutations in the C-propeptide domain and characterized phenotypically by metaphyseal involvement and brachydactyly in addition to the commonly observed spondyloepiphyseal changes.

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