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Terminal Osseous Dysplasia With Pigmentary Defects (TODPD): Follow-Up of the First Reported Family, Characterization of the Radiological Phenotype, and Refinement of the Linkage Region

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Abstract

Terminal osseous dysplasia with pigmentary defects (TODPD) is an X-linked dominant syndrome with distal limb anomalies and pigmentary skin defects. We have previously described this syndrome in several females from a large, four-generation pedigree. The presentation in the affected patients included multiple anomalies, hypertelorism, iris colobomas, punched-out pigmentary abnormalities over the face and scalp, brachydactyly, and digital fibromatosis. The phenotype was highly variable thus suggesting that X-inactivation plays an important role in the expression of the disease. Following our initial description of this condition there have been reports of more cases supporting the initial phenotypic description of this disease. We report on the follow-up of this family at about 10 years from the first evaluation. A detailed clinical follow-up and a review of the skeletal surveys suggests that although the most striking features involves the hands and feet, the skeletal involvement is more generalized and affects many other areas. Our previous linkage analysis has demonstrated mapping to Xq27.3-Xq28. Using a 6,056 SNP array, we have further refined the critical region within the Xq28 region. We have also excluded two candidate genes (*FLNA* and *FAM58A*) mapping in the critical region. The identification of the gene responsible for this rare condition will shed light on the molecular pathways leading to the various congenital anomalies of TODPD and will allow a more accurate genetic counseling to the affected individuals.

Keywords

skeletal dysplasia; X-linked dominant; terminal osseous dysplasia with pigmentary defects

INTRODUCTION

Terminal osseous dysplasia with pigmentary defects (TODPD; OMIM 300244) is a disorder characterized by pigmentary anomalies of the skin, skeletal abnormalities, mainly involving the limbs, digital fibromas, multiple oral frenula, iris colobomas, cardiac, and urogenital malformations. This condition has been so far described in a total of 19 individuals from

nine distinct pedigrees [Horii et al., 1998; Bacino et al., 2000; Breuning et al., 2000; Drut et al., 2005; Baroncini et al., 2007; Kokitsu-Nakata et al., 2008]. The X-linked dominant pattern of inheritance is supported by the description of only female affected patients, paucity of males, recurrent early miscarriages, and X-inactivation studies showing a skewed pattern in the affected patients, and a random inactivation in the unaffected ones [Zhang et al., 2000; Baroncini et al., 2007]. The natural history of this disorder is largely unknown and we here present the 10-year follow-up and the radiological characterization of the original TODPD family [Bacino et al., 2000]. Moreover, we have refined the critical linkage region on Xq28 and we have excluded some candidate genes mapping in this critical region.

CLINICAL AND RADIOLOGICAL FINDINGS

The detailed clinical findings of the affected patients were previously reported [Bacino et al., 2000]. In this article we characterized more in depth the radiological phenotypes of some of the affected individuals in the family and provide some follow-up information.

Proposita

The proposita was first evaluated at the age of 4 months for short stature, dysmorphic features, pigmentary abnormalities, alopecia, multiple digital fibromas, patent foramen ovale, and atrial septal defect [Bacino et al., 2000]. At age 11 years, she was noted to have short stature, the digital fibromas resolved but she exhibits multiple hand contractures (Fig. 1). The oral exam at this age, showed the presence of pedunculated, painful lesions which were not noted at the previous evaluation at 4 months of age. She attended regular school and had normal cognitive functions like the other affected members of the family.

The skull X-rays in the proposita, as well as other family members, showed thick diploe which can also be observed as a normal variant. Hand X-rays at the age of 11 years showed symmetrical shortening of the bones and amorphous ossification. Metacarpal bones of I, II, III, IV digits were hypoplastic and abnormally ossified (amorphous). Middle phalanges of the II, III, and IV digits were either shortened or absent. Digital phalanges of digits II–V were hypoplastic with angulation deformities. Synostosis between proximal and middle phalanges was observed at least at the level of the II digit of the left hand. The carpal bones were abnormal in shape and ossification with carpal–metacarpal fusions (between II and III digits) and bridging synostosis between the several carpal bones on the right (Fig. 2). The foot X-ray also showed an amorphous architecture and shortened bones. The great toes were bilaterally disproportionally enlarged. Metatarsal, proximal phalanges, middle phalanges, and distal phalanges of the II, III, and IV digits of the right foot were short. Fusions of tarsal bones, tarsal to metatarsal, and calcaneal to cuneiform bones were also observed (Fig. 3).

The long bones showed humeral bowing and unusual bony architecture, which was more severe on the left side (Fig. 4). Ulnar bowing was also present with radial head dislocations. The radial diaphyses also had an unusual architecture. The distal radii were bilaterally shortened with large lucent defects containing sclerotic borders. The femurs showed longitudinal striation, and both tibias were S-shaped (Fig. 4).

The spine was remarkable for severe scoliosis and mild vertebral body subluxation. The pelvis showed coxa valga on the left side and coxa vara on the right.

The DXA studies in the proposita showed normal whole body BMC and BMD z-scores of +1.2 and +2.21, respectively. However, localized osteoporosis was detected at the femoral neck (BMD z-score −3.21), trochanter (BMD z-score −2.29), and spine (BMD z-score −2.4).

Proposita's Mother

The proposita's mother was the least affected in the family. The hand X-rays showed a normal left hand and on the right hand a normal thumb, shortening of the IV metacarpal, of the III and IV middle phalanges, and of III and IV distal phalanges. The carpal bones appeared to be normal (Fig. 5). The X-rays of her feet were normal. The DXA studies in the mother did not reveal reduced bone density and showed a whole body BMC z-score of -0.7 , BMD T-score of -0.9 , lumbar spine T-score of -0.4 , BMC z-score of -0.4 , left hip BMD z-score of -0.9 , and left hip BMC z-score of -0.8 .

Proposita's Maternal Aunt

Radiological evaluation of the proposita's maternal aunt showed the presence of mild pectus carinatum, scoliosis, and mild spinal stenosis with interpedunculate narrowing at L5-S1. The hand X-rays showed shortening of the IV and V metacarpals, IV and V proximal phalanges, II and V middle phalanges, and absence of the IV middle and distal phalanges. The thumbs and carpal bones were normal (Fig. 6).

X-rays of the feet showed unusually amorphous ossification and shortened bones. II and III metatarsal bone were shortened. II and III proximal, middle, and distal phalanges were also shortened. IV and V middle phalanges were absent, whereas IV and V proximal and distal phalanges were short. Some tarsal–metatarsal fusion was also noted. The great toe was proportionately enlarged (Fig. 7). The remainder of the skeletal radiographs did not show significant abnormalities.

Proposita's First Cousin

The right-hand X-rays showed shortening of the II and III meta-carpals which are irregularly shaped with bone fusion at the base. Carpal–metacarpal fusions were also noted. The proximal phalanges appeared normal but there was shortening of the II, III, and V middle phalanges. The proximal interphalangeal joints had angulation deformities. The left-hand involvement was significantly less severe with shortening of the III metacarpal, normal proximal phalanges except for mild shortening of the V middle phalanges, shortening of the II and V middle phalanges, angulation of proximal–distal interphalangeal joints of the V digit, and normal distal phalanges (Fig. 8).

The left foot showed shortening of the III and V metatarsals, shortening of the II and IV middle phalanges, absence of the III and V middle phalanges, and shortening of the III and V distal phalanges. The right foot showed similar findings although the III and IV digits were less affected (Fig. 9).

The pelvis X-ray showed narrowing of the iliac wings. The thorax X-ray revealed possible eventration of the left diaphragm. The long bones revealed abnormal structure in the intratrochanteric region and S-shaped tibiae with abnormal cystic bone texture in the proximal portions (Fig. 10). Bone density studies showed normal bone mass (whole body BMC z-score $+0.4$; whole body BMD T-score $+0.2$; left hip BMD T-score -0.7 ; left hip BMC z-score -0.7 ; lumbar spine BMD z-score -0.6 ; lumbar spine BMC z-score -0.6).

MATERIALS AND METHODS

The family members were genotyped using the Illumina linkage panel 12, which contains 6,090 SNP marker loci. To identify the possible genotyping errors, PedCheck [O'Connell and Weeks, 1998] was used to find Mendelian inconsistencies, while Merlin was utilized to detect double-recombinants [Abecasis et al., 2002]. The multi-point linkage analysis was carried out using Allegro1.2c [Gudbjartsson et al., 2000] assuming the reduced autosomal

dominant model with reduced penetrance and a disease allele frequency of 0.001. Marker allele frequencies were obtained from the Hapmap database. Genetic map distances were derived directly or through interpolation from the Rutgers combined linkage-physical map of the human genome. Physical positions of the marker loci were based on the build 36 human genome from the genome browser. The haplotype analysis was performed via Simwalk2 program [Sobel and Lange, 1996].

Intron–exon junctions and exons of filamin A (*FLNA*) and *FAM58A* were directly sequenced. Primer sequences are available upon request.

RESULTS

We have further refined the critical region within the Xq28 region between rs1860929 (147,693,062 bp) and qter (154,913,754 bp). The maximum multi-point LOD score 2.9 was observed from the marker rs1860929 to qter, and an identical haplotype was found only in affected individuals. The reduced genetic interval was refined to Xq28qter, a region including over 100 genes. Given the overlap with STAR syndrome, we screened *FAM58A* gene but it was negative for mutations. *FLNA* mutations were also ruled out by direct sequencing.

DISCUSSION

We report on the follow-up and radiological characterization of the first and largest reported family with TODPD, refinement of the linkage region, and exclusion of two candidate genes.

As noted in the original description of this condition, and as confirmed by later reports, the most striking skeletal abnormality is the involvement of the hands and the digital fibromas [Horii et al., 1998; Bacino et al., 2000; Breuning et al., 2000; Drut et al., 2005; Baroncini et al., 2007; Kokitsu-Nakata et al., 2008]. The digital fibromas appear to be prevalent in infancy and they tend to regress with age in many cases, making them an inconsistent feature in adults. This is clearly exemplified by our probanda exhibiting the fibromas only in the first years of life and not at later evaluations. The carpal and tarsal coalitions were particularly striking in the probanda of our family (Fig. 2). This feature was not noted in the early report as the carpal bones were not ossified yet [Bacino et al., 2000]. The abnormal bony texture and the localized areas of osteoporosis also point to an unusual bone process involved in the pathogenesis of the disorder.

Although the skeletal manifestations of TODPD mostly involve hands and feet, a more generalized bone involvement including bowing, mesomelic shortening, abnormal bony texture, areas of localized osteoporosis, cystic lesions, and amorphous ossification suggest a more generalized bone involvement and it may point to a defect of matrix degradation, because of similarities with the radiologic features of the osteolysis syndromes [Superti-Furga and Unger, 2007], which may be due to defects in genes involved in degradation of bone matrix [Zankl et al., 2007]. Interestingly, it also appears in our family that the degree of hand and foot involvement on the ulnar side is more severe.

Linkage analysis has indicated that the mutated gene in this disorder maps to Xq27.3-qter within a very gene-rich region [Zhang et al., 2000]. However, the genetic defect of TODPD remains unknown. In the effort to identify the gene responsible for this condition, we further defined in our family the linkage region using a high density SNP array which allowed us to restrict the linkage to Xq28qter. Because of clinical overlap between STAR syndrome (OMIM 300707), an X-linked dominant condition presenting with anogenital and renal malformations, dysmorphic facial features, normal intellect, and syndactyly of toes [Unger

et al., 2008], we sequenced the *FAM58A* gene, responsible for STAR syndrome. However, no mutations were found in the exons and intro/exon boundaries of this gene in the TODPD affected patients.

Filamin A (*FLNA*) gene, which is also included within the linkage region, is involved in signaling pathways that mediate organogenesis in multiple systems including the skeleton. Some of the generalized skeletal features of our proband and the patient's first cousin suggested Melnick–Needles syndrome (OMIM 309350) like changes, while hand and foot changes radiographically, such as the carpal and tarsal coalitions and flexion contractures [Robertson et al., 2006], suggest similarity to frontometaphyseal dysplasia (OMIM 305620). *FLNA* mutations that conserve the reading frame result in a broad range of congenital malformations observed in four X-linked human disorders: otopalatodigital syndrome types I (OMIM 311300) and II (OMIM 304120), frontometaphyseal dysplasia, and Melnick–Needles syndrome. Given the clinical similarities between some of these disorders and TODPD, we have also considered *FLNA* as a candidate gene. However, direct sequencing of this gene failed to reveal pathogenic mutations.

The development of the human skeleton is regulated by intricate signaling pathways involving secreted molecules that bind to cell surface receptors to elicit a response in the target cell. Bone morphogenetic proteins (BMPs) are an important part of this process. Their signaling capacity is regulated on several levels including the extracellular space where inhibitors such as Noggin (NOG) prevent BMPs from binding to their cognate receptors. The importance of the signaling pathway for the development of joints was shown by the identification of mutations in *GDF5*, a member of BMP family, and *NOG* in patients with symphalangism (OMIM 185800) and multiple synostosis syndrome (OMIM 186500) [Groppe et al., 2002; Seemann et al., 2005; Dawson et al., 2006]. The presence of multiple joint fusions in TODPD may lead to the hypothesis that a dysregulation of the BMP pathway may play a role in the pathogenesis in this disorder as well.

The identification of the responsible gene will allow more accurate genetic counseling to the affected families and will shed light on the molecular pathways leading to the various clinical and radiographic anomalies of TODPD, in particular this rather unique skeletal phenotype.

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FIG. 1. Proposita at the age of 11 years: note the hypertelorism, hyperpigmented punched out lesions over face and forehead, pectus excavatum, and multiple hand contractures.

FIG. 2.

Proposita's hand and wrist radiographs: bilateral, fairly symmetrical involvement with shortening of the bones, amorphous ossification and interosseous fusions. The thumbs are hypoplastic. II, III, IV metacarpals are short and abnormally ossified. The distal radii have lytic (cystic-like) lesions.

FIG. 3.
Proposita's foot radiographs: symmetrical, amorphous architecture of the shortened bones. Great toes are proportionately enlarged. Fusions between calcaneal and cuneiform bones and between metatarsal bones are evident.

FIG. 4.

Proposita's long bone radiographs: dysplastic changes including humeral bowing, unusual bony architecture more severe on the left side, ulnar bowing, radial head dislocations, unusual architecture of the radial diaphyses, large lucent defects with sclerotic borders of the distal radius, longitudinal striation of the femurs, coxa valga on the left, coxa vara on the right, and S-shaped tibias (left more severe than right).

FIG. 5. Proposita's mother hand radiographs: normal left hand and shortening of the III and IV metacarpals, middle, and distal phalanges on the right. The punctate radiopacities are due to application of a nail product.

FIG. 6.

Proposita's maternal aunt hand radiographs: relatively symmetrical involvement with shortening of the IV and V metacarpals and proximal phalanges; shortening of the II, IV, and V middle phalanges. The thumbs are intact and the carpal bones are normal.

FIG. 7.

Proposita's maternal aunt foot radiographs: some amorphously ossified short bones. Metatarsals, proximal, middle, and distal phalanges are very short. IV and V middle phalanges are absent and proximal and middle phalanges are very short. The great toe is of normal size and proportionately enlarged (hallux valgus).

FIG. 8.

Proposita's first cousin hand radiographs. Asymmetric bilateral involvement: on the right hand, shortening of the II and III metacarpals with bone fusion at the base (“picture-puzzle shape sign”). Proximal phalanges are normal while middle phalanges of the II, III, and V digits are short. Angulation deformities of the proximal interphalangeal joints. The left hand is much less severely affected, with mild shortening of III metacarpals, and shortening of the II and V middle phalanges. Angulation of the proximal–distal interphalangeal joints of the V digit.

FIG. 9. Proposita's first cousin foot hand radiographs: shortening of the III and V metatarsal, II and IV middle phalanges, III and V distal phalanges. The III and V metacarpals are absent.

FIG. 10. Proposita's first cousin thorax, pelvis, and tibia/fibula radiographs: eventration of the left diaphragm is noted. The narrow iliac wings and S-shaped tibias are very similar to the appearance of Melnick-Needles syndrome. The bone texture is abnormal in the intertrochanteric region and in the proximal tibiae.