



Short Communication

An illustrative case of Léri-Weill dyschondrosteosis

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Abstract

We report on a girl presenting Léri-Weill dyschondrosteosis (LWD) due to deletion of the *SHOX* gene. Her family included individuals with short stature alone or with both short stature and mesomelia or Madelung's deformity. The deletion was demonstrated through detection of hemizygosity for microsatellite markers SHOX-CA repeat, DXYS10092, DXYS10093 and DXYS10091 localized around the *SHOX* gene, with retention of paternal alleles in the proband and three of her sisters who had short stature as the only clinical feature. Hemizygosity for these loci was also observed in their mother, who had short stature too. The deletion in the proband was however larger, including locus DXY10083. The proband's only sister with normal height did not carry the deletion. Family history suggests transmission of the deletion from the proband's maternal great-grandfather to her grandfather via the Y chromosome, and from the grandfather to the proband's mother via the X chromosome after crossing-over in the pseudoautosomal region proximal to the *SHOX* gene.

Key words: Léri-Weill dyschondrosteosis, Madelung's deformity, pseudoautosomal dominant inheritance, short stature, *SHOX* gene.

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Léri-Weill dyschondrosteosis (LWD, MIM 127300) is a syndrome characterized by mesomelic dwarfism, Madelung deformity of the wrist, and other skeletal malformations. The Madelung deformity is an ulnar and dorsal curvature of the distal radius due to deficient growth of the volar and ulnar aspect of the distal radius physis, increased inclination of the distal radius joint surface, triangulation of the carpus with proximal and volar migration of the lunate, and a prominent dorsal subluxation of the ulnar head (Henry and Thorburn, 1967). Recently, Zebala *et al.* (2007) described two subgroups of individuals with Madelung's deformity, one with extreme short stature and mesomelia consistent with LWD, and the other with severe involvement of the entire radius, limited range of motion of the extremity, markedly bowed appearance to the forearm, and conspicuous radiographic deformity of the forearm and distal radius.

Haploinsufficiency of the *SHOX* gene, which maps to the pseudoautosomal regions Xp22 and Yp11.3, was originally reported to be responsible for the short stature pheno-

type in Turner syndrome and also for some cases of idiopathic growth retardation (Ellison *et al.*, 1997; Rao *et al.*, 1997). An association between *SHOX* mutations and mesomelia, short stature and Madelung's deformity in LWS was demonstrated, broadening the phenotypic scope of *SHOX* mutations (Belin *et al.*, 1998; Shears *et al.*, 1998). The *SHOX* gene escapes X-inactivation, being expressed on both sex chromosomes of males and females (Rao *et al.*, 1997). In early human embryos, it is expressed in the developing limbs (particularly elbow, knee, distal ulna/radius and wrist) as well as in the first and second pharyngeal arches, and plays an important role in bone growth and development (Clement-Jones *et al.*, 2000).

The *SHOX* gene has six exons and is transcribed into two alternatively spliced mRNAs, SHOXa and SHOXb, which give rise to two proteins with different expression characteristics (Rao *et al.*, 1997). Complete gene deletions account for the majority of *SHOX* gene mutations (Rappold *et al.*, 2002), as a consequence of the presence of tandem or interspersed repeats in the pseudoautosomal region, PAR 1, which enhance the occurrence of unequal crossing-over between homologous chromosomes and intrachromosomal recombinations (Lien *et al.* 2000, Filatov and Gerrard

2003). Two major recombination hotspots were described in cases of haploinsufficiency of the *SHOX* gene due to crossing-over in the proximal PAR1 during male meiosis (Schneider *et al.*, 2005; Zinn *et al.*, 2006), although Benito-Sanz *et al.* (2006b) detected a high level of genetic heterogeneity of *SHOX* deletions. LWD due to deletions that did not include the *SHOX* gene has been recently demonstrated (Benito-Sanz *et al.*, 2005; 2006a). The finding of these pseudoautosomal region deletions mapping downstream of *SHOX* involved in the etiopathogenesis of LWD

suggests distal regulatory elements of *SHOX* transcription or another region/locus involved in skeletal development (Fukami *et al.*, 2006).

We report here on a four-generation family, with 37 members, among whom 20 individuals presented with one or more clinical features of *SHOX* haploinsufficiency (Figure 1a). Ten individuals had short stature (I.1, II.4, III.2, III.6, III.7, IV.4, IV.6, IV.12, IV.13, IV.14), eight presented short stature and mesomelia of forearms (III.1, III.3, III.4, IV.1, IV.2, IV.3, IV.5, IV.17), one had short stature and

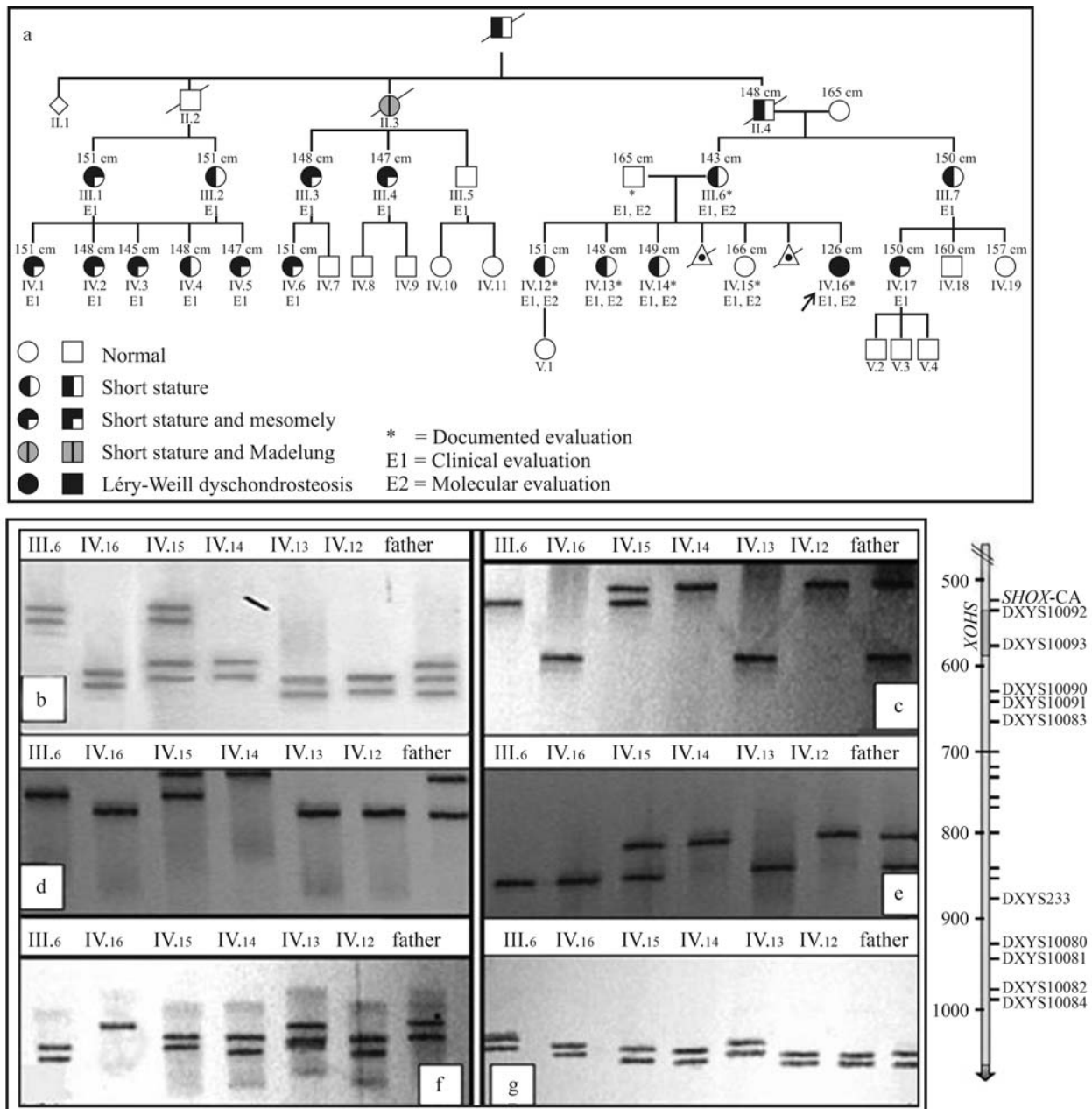


Figure 1 - (a) Genealogy of the proband; phenotypic features of members of the family not personally examined were informed by the proband's mother; (b-e) genotyping results of the *SHOX-CA* repeat (b), DXYS10092 (c), DXYS10093 (d) and DXYS10091 (e): the proband IV.16 and her sisters IV.12, IV.13 and IV.14 carry only the paternal allele in these loci; their mother (III.6) has one allele that is also present in her normal child IV.15; (f) locus DXYS10083i is deleted only in the proband IV.16; (g) locus DXYS233 is not deleted in the family.

Madelung's deformity (II.3), and the proposita (IV.16) had clinical characteristics compatible with LWD. Information regarding short stature in a relative was taken into account if body height was below the third percentile for chronological age. The study was approved by the institutional Ethics Committee (Process 81 n. 939/2001).

The proband, an 11-year-old girl, was referred to us due to short stature, mesomelia and Madelung's deformity. She was born at term by cesarean section, with a birth weight of 3,600 g and length of 45 cm. She was the youngest daughter in a sibship of five girls born to non-consanguineous parents; her mother had two miscarriages. Both the mother and three of the proband's sisters presented short stature (Figure 1a). According to the mother, the maternal great-grandfather and grandfather had severe short stature, and other members of her family had short stature and Madelung's deformity or mesomelia (recorded in the genealogy depicted on Figure 1a). The proband had a normal 46,XX karyotype.

We performed molecular analyses in the proband, her parents and her four sisters (Figure 1b-g). Genomic DNA was extracted from blood lymphocytes using standard techniques. The *SHOX-CA* repeat, a highly polymorphic microsatellite located immediately distal to *SHOX* (Fukami *et al.*, 2006), was amplified by PCR. We also genotyped DXYS10092 and DXYS10093, which map, respectively, to the 5' and 3' *SHOX* flanking regions, and the DXYS10091, DXYS10083 and DXYS233 microsatellites located 30-250 kb downstream of *SHOX*. All primer sequences and PCR conditions were those described by Benito-Sanz *et al.* (2005).

The proband and three of her sisters had only paternal alleles at the *SHOX-CA* repeat (Figure 1b), loci DXYS10093 (Figure 1c), DXYS10092 (Figure 1d) and DXYS10091 (Figure 1e); their mother also had a single allele in these loci, indicating deletion of one *SHOX* allele. The proband presented an additional deletion including the DXYS10083 locus (Figure 1f), which was not present in her mother or sisters. Heterozygosity for the microsatellite DXYS233 (Figure 1g) was observed in the proband, her mother and sisters. The proband's sister (IV.15) which did not have short stature or other clinical features did not carry the *SHOX* gene deletion.

In this family, the short stature, reported for the maternal great-grandfather and grandfather, is associated to the *SHOX* deletion in their descendants, thus suggesting the transmission of a deleted *SHOX* allele through four generations. The proband's maternal great-grandfather is assumed to have transmitted the deletion to her grandfather. The occurrence of an X-Y crossing-over proximal to *SHOX* would have transferred the *SHOX* deletion to the X-chromosome inherited by the proband's mother, who in turn transmitted it to four out of her five daughters. These features simulate an autosomal dominant pattern of inheritance, and, in fact,

LWD was until recently considered to have this mechanism of inheritance.

In the family reported here, the deletion of approximately 200 kb involving the *SHOX* gene is similar to those found in other patients with LWD (Rappold *et al.*, 2007; Jorge *et al.*, 2007). The proband, however, presented an additional deletion including the DXYS10083 locus, which was not present in her mother or sisters. Although the DXYS10083 deletion has been already described in European individuals with LWD (Benito-Sanz *et al.*, 2006b), in the context of the present family, the deletion of this locus may explain the more severe phenotype of the proband.

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Internet Resources

- Leri-Weill dyschondrosteosis; LWD (MIM 127300), <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=127300> (April 10, 2007).

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