Leri-Weill Dyschondrosteosis Caused by SHOX Gene Deletion: A Case Report

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Abstract

Leri-Weill dyschondrosteosis is a dominantly inherited skeletal dysplasia characterized by the classic triad of short stature, mesomelia and Madelung wrist deformity, which is caused by mutation in the *SHOX* gene. We report the case of a 14 years old girl with short stature and forearm deformity, with radiographic evidence of bilateral bowing of the radius and Madelung deformity. Multiplex Ligation Probe Amplification (MLPA) with the probe set for subtelomeric deletions showed deletion of the *SHOX* gene. The patient's mother also had short stature with limb shortening with predominant involvement of the mesomelic segments. The association of short stature with typical X ray abnormalities with *SHOX* deletion suggested the diagnosis of Leri Weill dyschondrosteosis. We recommend careful clinical and radiological evaluation and use of MLPA in the diagnostic work up of girls with short stature if the karyotype is found to be normal.

Introduction

Leri-Weill dyschondrosteosis (LWD, OMIM #127300) is a dominantly inherited skeletal dysplasia characterized by the classic triad of short stature, mesomelia and Madelung wrist deformity. The causative gene, the *SHOX* gene, is present in the pseudoautosomal region of the X chromosome and the *SHOX(Y)* gene is present in the pseudoautosomal region on the Y chromosome. Thus, there are 2 copies of the gene in both males and females. The disorder is usually more severe in females. The mesomelia, i.e. shortening of the middle segment of limbs in relation to the proximal segment, can be evident first in school-aged children and increases in severity with age. The Madelung deformity (abnormal alignment of the radius, ulna, and carpal bones at the wrist) develops in mid-to-late childhood and is more common and severe in females.

Most cases of Leri-Weill dyschondrosteosis result from mutation in the *SHOX* gene. The protein produced from this gene plays a role in bone development and is particularly important for the growth and maturation of bones in the arms and legs, by acting as a transcription factor and regulating the activity of other genes.

Figure 1 Photograph of the patient with her mother: both have short stature and Madelung deformity of the forearm.

Case report

This case, a 14 year old girl, visited the medical genetics department with short stature and deformed forearm bones (Fig 1). She had attained menarche. Her mother also had short stature. Her birth history and developmental history were normal.

Her height was 128 cm (3.5 S.D. below mean for age and sex) with the ratio of upper to lower segment being 1. Her weight was 27 kgs (3 S.D. below mean for age and sex). The forearm bones were deformed and lower ends of ulna were prominent and showed projections dorsally and distally giving a characteristic dinner-fork appearance. Her intelligence was normal.

Radiographs of the upper limbs showed bowing of the radius and Madelung deformity bilaterally. The radii on both sides were bent and the distal epiphyses of the radii were triangular. The carpals had a characteristic pyramidal configuration with the lunate bone forming the tip of the pyramid. The medial parts of the lower ends of radii showed lucent areas (Fig 2).

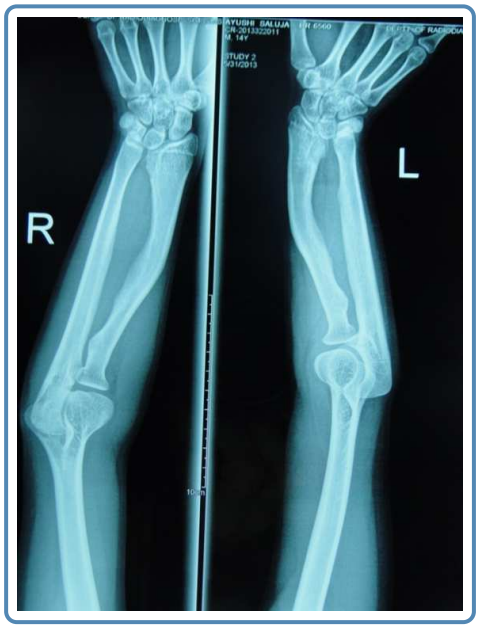

Figure 2 X ray of the upper limb showing bilateral bowing of the radius, Madelung deformity, triangular distal epiphyses of the radii, pyramidal configuration of the carpals with the lunate forming the tip of the pyramid, and lucent areas in medial parts of lower ends of radii.

Her routine hematological and biochemical investigations including serum calcium and phosphorus were normal. Her karyotype was 46, XX. Multiplex Ligation Probe Amplification (MLPA) using the probe set for subtelomeric regions (P036, MRC-Holland; https://www.mlpa.com/) was carried out which showed deletion of the *SHOX* gene in the patient (Fig 3). This confirmed the diagnosis of Leri Weill dyschondrosteosis.

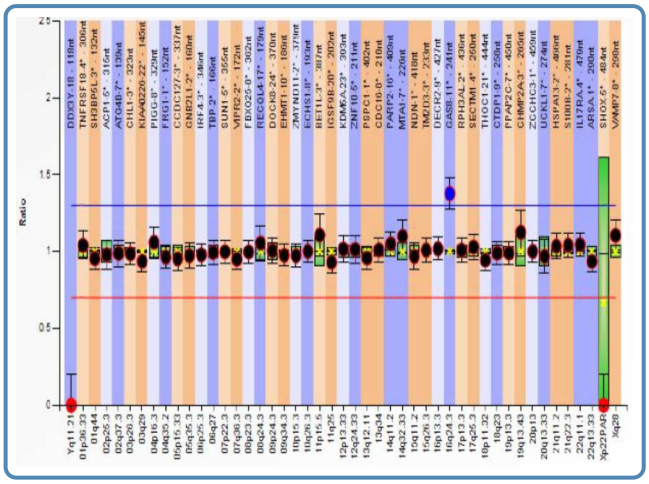

Figure 3 MLPA showing deletion of the *SHOX* gene.

Her mother also had short stature with limb shortening with predominant involvement of the mesomelic segments, but radiological and genetic evaluation could not be done for her.

Discussion

The girl in this report had characteristic clinical and radiological features of Leri-Weill dyschondrosteosis.

Seventy to 90% of cases of Leri-Weill dyschondrosteosis are caused by haploinsufficiency of the *SHOX* gene, with deletions accounting for 80% of them. Gene deletions of different sizes encompassing the gene itself or a regulatory enhancer region which is located 50-250 kb downstream of the coding region are reported. Missense and nonsense mutations, mostly located within exons 3 and 4 and also partial duplications of the gene, or heterozygous deletions upstream or downstream of the intact *SHOX* gene involving conserved non-coding cis-regulatory DNA elements that have enhancer activity are causative in the rest (Sabherwal et al.,

2007; Bunyan et al., 2015).

The diagnosis in this case was confirmed by MLPA which is a reliable, easy and less expensive technique. Point mutations in the *SHOX* gene account for some cases and need sequencing of the gene which has 6 exons (Funari et al., 2010).

SHOX deficiency leads to short stature with variable phenotypes with the main characteristics of mesomelic shortening of the limbs. Madelung deformity of the forearm develops over time and appears during the second decade of life in a proportion of cases (Choi et al., 2015). There can be great intrafamilial variability of the phenotypes as reported by Gatta et al. (2014). *SHOX* mutations are also detected in about 15% of cases with isolated short stature without any other features of Leri-Weill dyschondrosteosis and need to be tested even if there are no clinical clues (Rosilio et al., 2012). Careful evaluation of the wrist radiographs is a must, as the typical radiographic findings of the wrist provide an important clue to the diagnosis. Presence of muscular hypertrophy, cubital valgus, short neck, increased body mass index and decreased arm span height ratio are some further clues to the diagnosis (Rappold et al., 2007).

SHOX haploinsufficiency is an FDA approved indication for growth hormone therapy. However, some studies have shown limited utility of growth hormone therapy in patients with *SHOX* mutations. In contrast to many other growth disorders like growth hormone deficiency or even idiopathic short stature, in *SHOX* deficiency females outnumber males. Ascertainment bias can be one explanation as more severe phenotype is seen in females. However, female predominance was also observed in *SHOX* mutation screening studies where the only phenotype targeted was short stature. Therefore, ascertainment bias alone cannot explain gender variation in this disorder. Another explanation for this can be the fact that *SHOX* on the X chromosome is more prone to getting deleted than the *SHOX* on the Y chromosome (Binder et al., 2011).

SHOX deficiency disorders are inherited in a dominant manner, even when the gene is present on the sex chromosome. The gene is situated on the pseudoautosomal region and hence, it is one of the 15% genes on X chromosome which escape lyonization. The homozygotes with mutations on both the copies of the gene are more severely affected and the disorder is known as Langer mesomelia. An individual with Leri-Weill dyschondrosteosis has a 50% chance of transmitting the pathogenic variant to the offspring and genetic counseling should be offered.

Conclusion

Leri-Weill syndrome (LWS) is an uncommon genetic disorder caused by deletions or mutations in the *SHOX* gene or by deletions downstream of the *SHOX* gene in most of the cases. Identification of the short stature homeobox-containing gene (*SHOX*) deficiency in children, mainly females with growth problems, is vital for appropriate initiation of growth hormone therapy. *SHOX* gene evaluation by MLPA should be included in the diagnostic work up of girls with short stature if the karyotype is found to be normal.

References

1. Bunyan DJ, et al. Duplications upstream and downstream of *SHOX* identified as novel causes of Leri-Weill dyschondrosteosis or idiopathic short stature. Am J Med Genet A. 2016; 170: 949-957.
2. Choi WB, et al. A Leri-Weill dyschondrosteosis patient confirmed by mutation analysis of *SHOX* gene. Ann Pediatr Endocrinol Metab 2015; 20: 162-165.
3. Funari MF, et al. Usefulness of MLPA in the detection of *SHOX* deletions. Eur J Med Gene 2010; 53: 234-238.
4. Gatta V, et al. Spectrum of phenotypic anomalies in four families with deletion of the *SHOX* enhancer region. BMC Med Genet 2014; 15: 87.
5. Gerhard B. Short Stature due to *SHOX* Deficiency: Genotype, Phenotype, and Therapy. Horm Res Paediatr 2011;75: 81-89.
6. Gudrun R, et al. Genotypes and phenotypes in children with short stature: clinical indicators of *SHOX* haploinsufficiency. J Med Genet 2007; 44: 306-313.
7. Rosilio M, et al. Genotypes and phenotypes of children with *SHOX* deficiency in France. J Clin Endocrinol Metab 2012; 97: E1257-1265.
8. Sabherwal N, et al. Long-range conserved noncoding *SHOX* sequences regulate expression in developing chicken limb and are associated with short stature phenotypes in human patients. Hum Mol Genet 2007; 16: 210-222.