CASE REPORT
CASO CLINICO

Leri-Weill's syndrome: clinical, radiological and genetic investigations in five patients

Discondrosteosi di Leri-Weill: valutazione clinica, radiologica e genetica in cinque pazienti

M. PICCIONE, F. PICCIONE, M. GIUFFRÈ, G. DE SIMONE, M. PERITORE, M. PIERLUIGI*, G. CORSELLO
Dipartimento Materno Infantile, Università di Palermo, Palermo; * Laboratorio di Genetica Umana, Ospedali "Galliera" di Genova, Genova

Summary

The Authors describe five patients, all females, affected by Leri-Weill dischondrosteosis, a skeletal dysplasia due to mutations of the SHOX gene. All patients showed the characteristic clinical features of dischondrosteosis: short stature, mesomelia and Madelung wrist deformity. Cytogenetic analysis showed a normal karyotype in patients 1, 2, 3 and 4, whereas in patient 5 a non-familial unbalanced X;Y translocation was evident, with deletion of the pseudoautosomal region of the X chromosome, where the SHOX gene is located. In all patients FISH analysis with cosmids for the pseudoautosomal region of the X and Y chromosomes showed the deletion of the SHOX gene. In consideration of the phenotypical heterogeneity of the clinical spectra, an accurate clinical and imaging evaluation of patients and a careful investigation of their relatives were performed in order to identify familial cases.

Riassunto

Gli Autori descrivono cinque pazienti di sesso femminile affetti da discondrosteosi di Leri-Weill, una displasia scheletrica dovuta a mutazioni del gene SHOX. Tutti i pazienti mostrano le peculiari caratteristiche cliniche della discondrosteosi: bassa statura, mesomeria e deformità del polso tipo Madelung. L'analisi citogenetica ha mostrato un cariotipo normale nei pazienti 1, 2, 3, e 4, mentre nel paziente 5 ha evidenziato una traslocazione X;Y sbilanciata non familiare, con delezione della regione pseudoautosomica del cromosoma X, dove è localizzato il gene SHOX. In tutti i pazienti l'analisi FISH con cosmici per la regione pseudoautosomica dei cromosomi X e Y ha mostrato la delezione del gene SHOX. In considerazione della eterogeneità fenotipica del quadro clinico, è necessaria una accurata valutazione clinica e strumentale dei pazienti ed un attento studio dei parenti al fine di identificare i casi familiari.

Key words

Leri-Weill syndrome • Dischondrosteosis • SHOX gene • Skeletal dysplasia

Parole chiave

Sindrome di Leri-Weill • Discondrosteosi • Gene SHOX • Displasia scheletrica

Submitted: November 19, 2004
Accepted: March 14, 2005

Correspondence:
Prof. Giovanni Corsello
Clinica Pediatrica
e Terapia Intensiva Neonatale
Dipartimento Materno Infantile
Università di Palermo
via Cardinale Rampolla,1
90142 Palermo, Italy
Tel. +39 091 6555424
Fax +39 091 6555423
E-mail: giocors@aliceposta.it

Introduction

Leri-Weill Dyschondrosteosis (DCS) is a skeletal dysplasia whose main features are Madelung wrist deformity, mesomelia and short stature [1].
Although the 4:1 female-to-male ratio [2] initially suggested a dominant X-linked inheritance, the occurrence of a male-to-male transmission in various families has supported the dominant autosomal way of inheritance with fewer signs in affected males [3].
DCS has recently been related to a haploinsufficiency on the SHOX (short stature homeobox containing gene) located on the pseudoautosomal region (PAR) of the Xp and Yp chromosomes (locus Ypter-p11.2; Xpter-p22.3) [1 4-8].
We now report on 5 new patients, 3 of them belonging to the same family in which a wide range of clinical features has been observed.

Clinical report

Patient 1: female, 13 years old, 2nd child of non-consanguineous and apparently healthy parents; from the previous pregnancy a normal male child had been born. The pregnancy had been regular with spontaneous delivery at term. The patient's birth-weight was 3,300 g, and length 50 cm.
On admission the patient weighed 46.7 kg (50th percentile) and was 144 cm tall (3rd percentile, - 2.13 SD). She had short limbs and forearms, carpal deformity more evident on the left side, and bilateral *tibia vara*.
X-rays of the upper limbs showed *homerus varus* and bilateral shortening of the antibrachial bones that were more evident on the left side. On the left side the radial diaphysis was bent on the frontal plain and the ulna on the lateral plain, with the distal extremities dorsally dislocated (Fig. 1). Hypoplasia and lateral and dorsal bowing of the radius and ulna with consecutive triangulation of the carpal bones were evident (Fig. 2), with the apex at the level of the wedged semilunar bone in the radius-ulnar space. On the right side the above-mentioned features could be found, although with milder expressivity. The X-ray of the lower limbs showed bilateral coxa valga with the angle of the cervical diaphyses at 140°, bilateral *genu varum*, esostoses on the medial metaphyseal border of the tibia (Fig. 3), hypoplasic peroneal heads and peroneal diaphysis slightly bent with back convexity. The chromosomes were normal (46,XX). FISH (fluorescence in situ hybridization) analysis using 34F5 cosmids for the pseudoautosomal region of the X and Y chromosomes showed the deletion of the SHOX locus (Fig. 4).

Fig. 1. Ventrally bent and dorsally dislocated ulna.

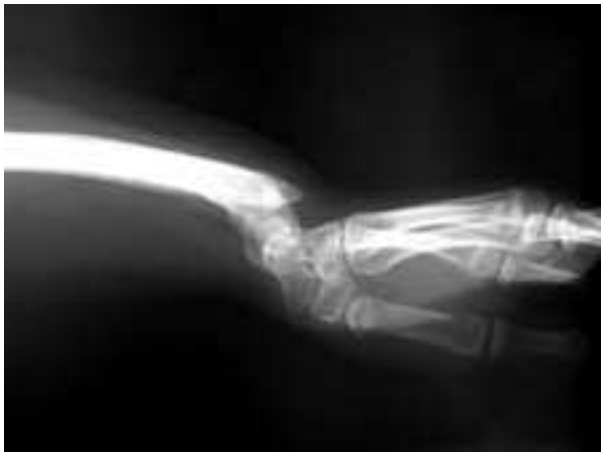


Fig. 2. Hypoplasia and lateral and dorsal bowing of the radius and ulna with triangulation of the carpal bones.

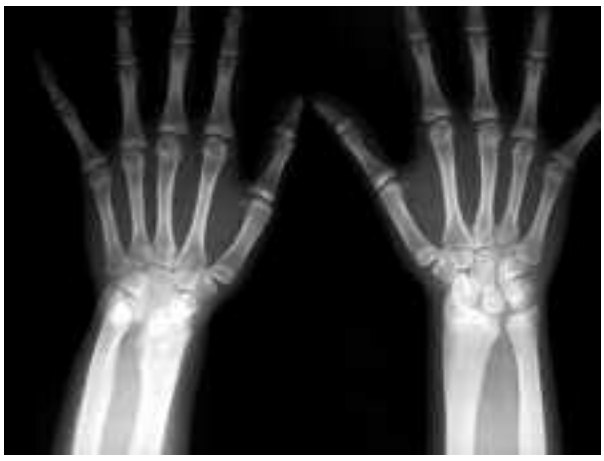


Fig. 3. Esostoses on the medial metaphyseal border of the tibia.

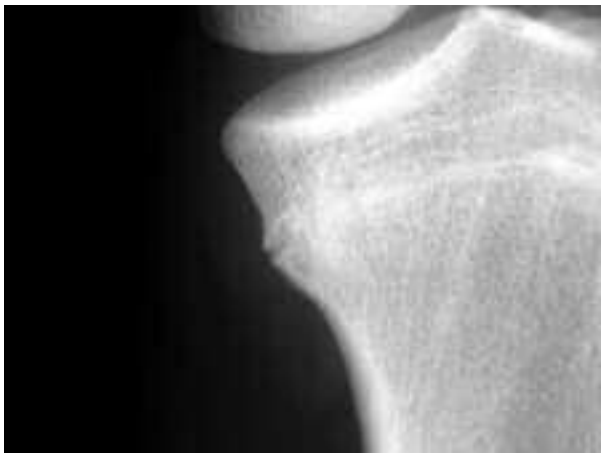
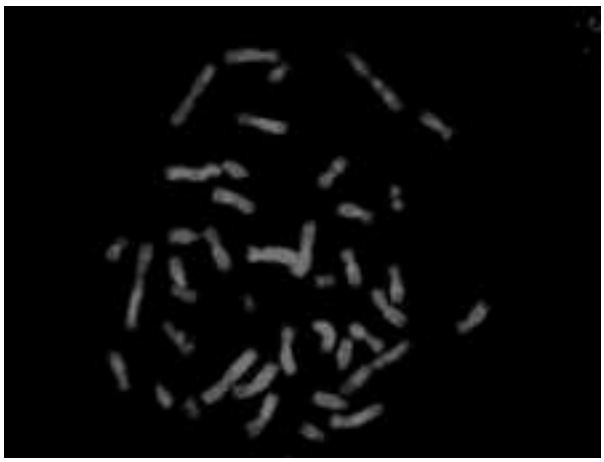


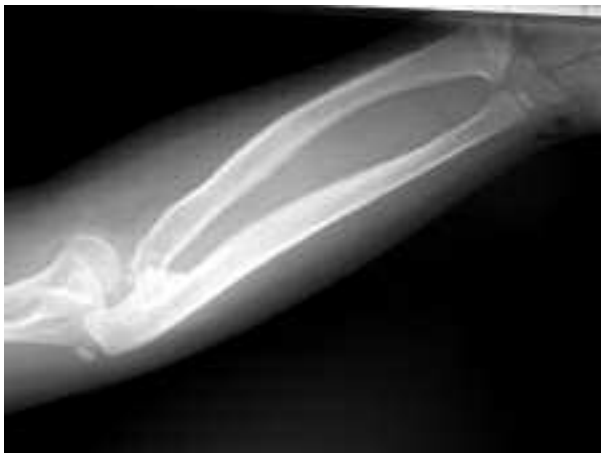
Fig. 4. FISH analysis shows only one copy of the SHOX gene on the X chromosomes.



Patients 2, 3, 4: patient 2 is an 11 year old girl. She was the second child of non-consanguineous parents; she was delivered at 36 weeks of gestation. She showed IUGR and growth retardation since the first months of

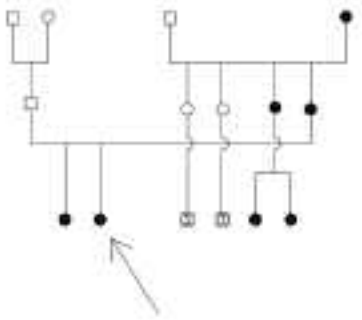
postnatal life. Her birth-weight was 1,800 g and her length 40 cm. The mother (patient 3) was 145 cm tall (< 3rd percentile, - 2.87 SD) and the sister (patient 4, 19 years old) 142 cm tall (< 3rd percentile, - 3.37 SD), both showing mesomelia and short forearms.
On admission to our institute the child weighed 25.8 kg (3rd percentile, - 2 SD) and was 123.5 cm tall (< 3rd percentile, - 3.05 SD). She showed severe discordant growth retardation and small limbs, mesomelia with a broadening of the distal epiphyses of the wrist joints, reduced extension of the elbows and limited prono-supination of the forearms.
The X-rays showed short upper limbs due to a short radius and ulna, with the diaphyses bent so as to determine a widening of the space between the bones (Fig. 5). The ulna was bent on the sagittal plain with dorsal

Fig. 5. The widening of the space between radius and ulna.



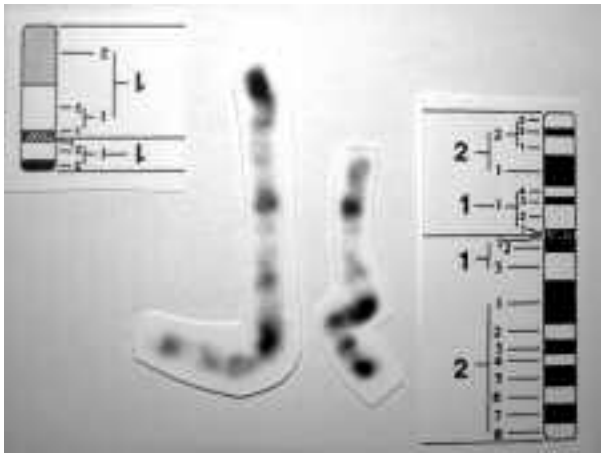
dislocation and consecutive triangulation of the carpal bones (Madelung deformation). The lower limbs showed bilateral short tibia and fibula. The chromosomes were normal (46,XX). FISH analysis using 34F5 cosmids for the pseudoautosomal region of sexual chromosomes showed the deletion of the SHOX locus. In consideration of the phenotype of both mother and sister (patients 3 and 4), X-rays were carried out on both, showing most of the features present in the proband. In addition, the FISH analysis showed in both of them the deletion of the SHOX locus.
The acquisition of an accurate anamnesis allowed us to compose the pedigree of 3 generations with a familial form of DCS (Fig. 6).
Patient 5: female child aged 1 year and 4 months at the first observation and 8 years at the second. The parents were non-consanguineous and apparently healthy. The pregnancy had been regular with spontaneous delivery at term. Birth-weight was 2,970 g; birth-length was 48 cm. On the first admission the child weighed 8.6 kg (3rd percentile, -2 SD) and was 71 cm (< 3rd percentile, - 3.17 SD) tall.

Fig. 6. Pedigree of the familial Leri-Weill Dyschondrosteosis for patient 2.



Cytogenetic investigations: the karyotype was 46,X,del(X)t(X;Y)(p22.3;q11.2) in all the metaphases examined (Fig. 7). The parents' karyotype was normal. On the second observation, when the child was 8 years old, weight was 18.5 kg (< 3rd percentile, - 3 SD) and height 107 cm (< 3rd percentile, - 3.14 SD). Her stature was short with mesomelia, hyperlordosis and bilateral *tibia vara*.

Fig. 7. Cytogenetic analysis of X/Y and X chromosomes in patient 5 with karyotype 46,X,del(X)t(X;Y)(p22.3;q11.2).



The X-rays of the upper limbs showed short radius with diaphysis bent on the frontal plain, obliquity of the distal articular extremity from top down and from the inside to the outside, with triangulation of the carpal bones. On the lower limbs there was hypoplasia of the peroneal heads more evident on the left and bilateral *tibia vara*.
FISH analysis with cosmids 34F5 for the pseudoautosomal region of Xp and Yp of X and Y chromosomes showed the deletion of the SHOX locus.

Tab. I. Phenotypical variability in the 5 patients presented.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Short stature	X	X	X	X	X
Homerus varus	X				
Mesomelia	X	X	X	X	X
Dorsal dislocation of the distal ulna	X	X	X	X	X
Triangulation of carpal bones	X	X	X	X	X
Reduced extension of the forearms		X			
Coxa valga	X				
Esostoses on the metaphyseal border of tibia	X				
Short tibia	X	X	X	X	X
Genu varus	X				X

Discussion

Mutations of the SHOX gene have recently been associated with idiopathic short stature, mild rizomelic body disproportions, and short stature in patients with Turner's syndrome and in most patients with DCS [1 4 5 7 9 10].

In 2.4% of children with short stature, mutations of SHOX gene (silent, missense, nonsense, small deletion, etc.) have been detected [11], although various studies have shown that idiopathic short stature not associated with mesomelia of the limbs does not require fluorescence in situ hybridization analysis of the SHOX gene [12].

In some subjects who clinically show DCS, the deletion of the SHOX locus is not underlined, confirming a genetic heterogeneity in DCS [13]. Different mutations in various regions of the SHOX gene can play an important role in the pathogenesis of DCS [14], confirming that haploinsufficiency is the most frequent mechanism in DCS [14 15].

DCS has been described in subjects with X;Y unbalanced translocation [6 16].

The incidence of DCS is underestimated, above all in males because of the milder clinical signs [2] associated with muscular hypertrophy [13].

Several hypotheses have been proposed to explain the varying phenotypic expressivity and the relatively low incidence (7%) of the Madelung deformity in patients with Turner's syndrome, who almost all have haploinsufficiency of the SHOX gene and short stature [2]. Recently attention has been turned to the role of estrogens [17 18].

Estrogens have been shown to accelerate the programmed senescence of the growth plate, causing earlier fusion: they may have asymmetric effects on the growth plate, interacting with specific SHOX deficient areas [19]. In patients with haploinsufficiency of the SHOX gene and normal ovarian function [20] the auxological anomalies correlated with mesomelia are evident since childhood and worsen during puberty because of the skeletal maturing effects of ovarian estrogens. This would explain why in subjects with Turner's syndrome the evidence of DCS is rare, insofar as the lack of estrogens would have a protective effect [2].

The patients described are all females and show the characteristic clinical features of DCS (short stature, mesomelia and Madelung wrist deformity) with phenotypic inter- and intra-familial heterogeneity (Tab. I) as frequently described in the literature [2 4 5 13]. Many hypotheses have been formulated to explain this clinical variability, including modifier genes, intragenic sequence alterations, long range effects, epistasis, and epigenetic interactions.

In patients 1, 2, 3, and 4, the cytogenetic analysis showed a normal karyotype, while FISH analysis showed the deletion of the SHOX locus. In patient 5, a non-familial unbalanced X;Y translocation was evident, with deletion of the pseudautosomal region of the X chromosome (Xp22.3) where the SHOX gene is mapped and correlated to DCS. The clinical features of DCS in all patients become evident during adolescence, suggesting the usefulness of a follow-up in all subjects with short stature [6]. In all the cases with chromosomal anomalies involving the pseudoautosomal regions of the sex chromosomes, even in the presence of only short idiopathic stature, FISH analysis for the SHOX gene must be carried out.

Conclusion

In consideration of the phenotypical heterogeneity of the clinical spectra due to mutations of the SHOX gene, an accurate clinical and imaging evaluation of patients is recommended along with careful familial anamnesis and investigation of the relatives in order to identify familial cases with varying clinical expressivity and elevated risk of recurrence (50%).

References

[1] Belin V, Cusin V, Viot G, Girlich D, Toutain A, Moncla A, et al. *SHOX mutations in dyschondrosteosis (Leri-Weill syndrome)*. Nat Genet 1998;19:67-9.

[2] Ross JL, Scott C Jr, Martilla P, Kowal K, Nass A, Papenhausen P, et al. *Phenotypes associated with SHOX deficiency*. J Clin End Met 2001;86:5674-80.

[3] Lichtenstein JR, Sundaram M, Burdge R. *Sex-influenced expression of Madelung's deformity in a family with dyschondrosteosis*. J Med Genet 1980;17:41-3.

[4] Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, et al. *Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome*. Nat Genet 1997;16:54-63.

[5] Shears DJ, Vassal HJ, Goodman FR, Rodger WP, Reardon W, Superti-Furga A, et al. *Mutation and deletion of the pseudoautosomal gene SHOX cause Leri-Weill dyschondrosteosis*. Nat Genet 1998;19:70-3.

[6] Calabrese G, Fishetto R, Stuppia L, Capodiferro F, Mingarelli R, Causio F, et al. *X/Y translocation in a family with Leri-Weill dyschondrosteosis*. Hum Genet 1999;105:367-8.

[7] Grigelioniene G, Eklof O, Ivarsson SA, Westphal O, Neumeyer L, Kedra D, et al. *Mutations in short stature homeobox containing gene (SHOX) in dyschondrosteosis but not in hypochondroplasia*. Hum Genet 2000;107:145-9.

[8] Ezquieta B, Cueva E, Oliver A, Gracia R. *SHOX intragenic microsatellite analysis in patients with short stature*. J Ped End Met 2002;15:139-48.

[9] Palka G, Stuppia L, Guanciali Franchi P, Chiarelli F, Fischetto R, Borrelli P, et al. *Short arm rearrangements of sex chromosomes with haploinsufficiency of the SHOX gene are associated with Leri-Weill dyschondrosteosis*. Clin Genet 2000;57:449-53.

[10] Zinn AR, Wei F, Zhang L, Elder FF, Scott CI Jr, Marttila P, et al. *Complete SHOX deficiency causes Langer mesomelic dysplasia*. Am J Med Genet 2002;110:158-63.

[11] Rappold GA, Fukami M, Niesler B, Schiller S, Zumkeller W, Bettendorf M, et al. *Deletions of the Homeobox gene SHOX (short stature homeobox) are an important cause of growth failure in children with short stature*. J Clin End Met 2002;87:1402-6.

[12] Musebeck J, Mohnike K, Beye P, Tonnies H, Neitzel H, Schnabel D, et al. *Short stature homeobox-containing gene deletion screening by fluorescence in situ hybridisation in patients with short stature*. Horm Res 2001;55:71-6.

[13] Schiller S, Spranger S, Schechinger B, Fukami M, Merker S, Drop SLS, et al. *Phenotypic variation and genetic heterogeneity in Leri-Weill syndrome*. Eur J Hum Genet 2000;8:54-62.

[14] Huber C, Cusin V, Le Merre M, Mathieu M, Sulmont V, Dagoneau N, et al. *SHOX point mutations in dyschondrosteosis*. J Med Genet 2001;38:323.

[15] Ross JL, Bellus G, Scott CI Jr, Abboudi J, Grigelioniene G, Zinn AR. *Mesomelic and rhizomelic short stature: the phenotype of combined Leri-Weill dyschondrosteosis and achondroplasia or hypochondroplasia*. Am J Med Genet 2003;116A:61-5.

[16] Stuppia L, Calabrese G, Borrelli P, Gatta V, Morizio E, Mingarelli R, et al. *Loss of the SHOX gene associated with Leri-Weill dyschondrosteosis in a 45,X male*. J Med Genet 1999;36:711-3.

[17] Ogata T, Matsuo N, Nishimura G. *SHOX haploinsufficiency and overdosage: impact of gonadal function status*. J Med Genet 2001;38:1-6.

[18] Binder G, Ranke MB, Martin DD. *Auxology is a valuable instrument for the clinical diagnosis SHOX haploinsufficiency in school-age children with uneplained short stature*. J Clin End Met 2003;88:4891-6.

[19] Weise M, De-Levi S, Barnes KM, Gafni RI, Abad V, Baron J. *Effects of estrogen on growth plate senescence and epiphyseal fusion*. Pro Natl Acad Sci USA 2001;98:6871-6.

[20] Fukami M, Matsuo N, Hasegawa T, Sato S, Ogata T. *Longitudinal auxological study in a female with SHOX (short stature homeobox containing gene) haploinsufficiency and normal ovarian function*. Eur J End 2003;149:337-41.