The SHOX Gene and The Short Stature. Roundtable On Diagnosis and Treatment of Short Stature Due To SHOX Haploinsufficiency: How Genetics, Radiology And Anthropometry Can Help The Pediatrician in The Diagnostic Process Padova

(April 20th, 2011)

Vincenzo De Sanctis[1],MD, Ilaria Tosetto[2] MD, Lorenzo Iughetti[3], MD, Franco Antoniazzi[4] MD, Maurizio Clementi[5] MD, TizianaToffolutti[6] MD, Paola Facchin[7], MD, Elena Monti[4], MD, Lorena Pisanello[8], MD, Giorgio Tonini[9], MD, Nella A. Greggio[2], MD

\[1]Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital Ferrara - Italy, [2]Pediatric Endocrinology and Adolescence Unit, Department of Pediatrics, Hospital - University of Padova, Padova- Italy, [3]Department of Pediatrics, Hospital - University of Modena, Modena- Italy, [4]Pediatric Endocrinology, Department of Pediatrics, Hospital - University of Verona, Verona- Italy, [5]Genetics Unit, Department of Pediatrics, Hospital - University of Padova, Padova- Italy, [6]Pediatric Radiology Unit, Department of Pediatrics, Hospital - University of Padova, Padova- Italy, [7]Epidemiology Unit, Department of Pediatrics, Hospital - University of Padova, Padova- Italy, [8]Family Pediatrician, Padova, [9]Pediatric Endocrinology Unit, IRCSS Burgo-Garofalo of Trieste- Italy

Corresponding Author: Nella A. Greggio MD, Paediatric Endocrinology and Adolescence Unit, Department of Paediatrics, Hospital - University of Padova, 35128 Padova, Italy. Email: greggio@pediatria.unipd.it , Tel: +39.049.8211408, Fax: +39.049.8211664

Abstract

The growth of the human body depends from a complex interaction between nutritional, environmental and hormonal factors and by a large number of different genes. One of these genes, short stature homeobox (SHOX), is believed to play a major role in growth. SHOX haploinsufficiency is associated with a wide spectrum of conditions, all characterized growth failure such as Leri-Weill dyschondrosteosis , Turner syndrome, short stature with subtle auxological and radiological findings and the so called "idiopathic short stature" (short stature with no specific findings other than growth failure). The document was prepared by a multidisciplinary team (paediatric endocrinologists, paediatrician, radiologist, geneticist and epidemiologist) to focus on the investigation of children with suspected SHOX- deficiency (SHOX-D) for an early identification and a correct diagnostic work - up of this genetic disorder. On the basis of a number of screening studies, SHOX-D appears to be a relatively frequent cause of short stature. The following recommendations were suggested by our multidisciplinary team: (i) a careful family history, measurements of body proportions and detection of any dysmorphic features are important for the suspect of a genetic disorder ,(ii)the presence of any combination of the following physical findings, such as reduced arm span/ height ratio, increased sitting height/height ratio, above average BMI, Madelung deformity, cubitus valgus, short or bowed forearm, dislocation of the ulna at the elbow, or the appearance of muscular hypertrophy, should prompt the clinician to obtain a molecular analysis of the SHOX region, (iii) it is of practical importance to recognise early or mild signs of Madelung deformity on hand and wrist radiographs, (iv) growth hormone ,after stimulation test, is usually normal . However, treatment with rhGH may improve final adult height; the efficacy of treatment is similar to that observed in those treated for Turner syndrome.

Ref: Ped. Endocrinol. Rev. 2012;9(4)

Key words: SHOX- gene, idiopathic short stature, short stature with and without dysmorphic features, Madelung's deformity, guidelines, primary and secondary health care services

Introduction (Nella A. Greggio, Vincenzo De Sanctis)

The short stature term describes a subject's height that is significantly below the average for age, sex and racial group.

The large number of clinical conditions associated with short stature can make the task of identifying a specific diagnosis particularly challenging (1).

The human growth depends from a complex interaction among nutritional, environmental and hormonal factors and by a large number of different genes. One of these genes, *short stature homeobox (SHOX)*, is believed to play a major role in growth (2, 3).

The mechanism by which *SHOX*, a homeodomain transcription factor, regulates linear growth and why deficiency of this factor results in short stature is not completely understood. The protein is expressed during pre- and postnatal skeletal development and regulates aspects of chondrocyte differentiation in the growth plate (4-6).

It appears that two functional copies of this gene are required for attainment of normal stature since it has been established that haploinsufficiency for the gene is associated with a wide spectrum of conditions. All conditions are characterized by growth failure such as Leri-Weill dyschondrosteosis (LWD), Turner syndrome (TS), short stature with subtle auxological and radiological findings and the so called "idiopathic short stature" (short stature with no specific findings other than growth failure-ISS).

Finally homozygosity for the *SHOX* deficiency is associated with the more severe phenotype of Langer mesomelic dysplasia (LMD) (2, 3).

Aims and methods (Vincenzo De Sanctis, Nella A. Greggio)

This document has been prepared by a multidisciplinary team (paediatric endocrinologists, paediatrician, radiologist, geneticist and epidemiologist) in order to focus on the investigation of children with suspected *SHOX*- deficiency for an early identification and a correct diagnostic workup of this genetic disorder. All this to give an aid to clinicians working in primary and secondary health care services.

In the development of recommendations the Committee reviewed more than 180 original articles and selected reviews on *SHOX*- gene and its mutation, ISS, short stature with and without dysmorphic features and Madelung's deformity.

All Members of the Panel participated in the preparation of manuscript.

The document does not intend to substitute physician judgement with respect to particular patients or special clinical situation.

The SHOX Gene and Its Mutations (Nella A. Greggio, Maurizio Clementi)

The *SHOX* gene is present in two identical copies in all individuals and is a located in the pseudoautosomal region 1 (PAR 1) on the distal end of X and Y chromosomes at Xp22.3 and Yp11.3. *SHOX* also spans approximately 40 kb in the PAR1 and consists of seven exons. The PAR1 region escapes from X-inactivation process and recombines during male meiosis.

Two copies of the *SHOX* gene are normally expressed in males as well in females (3).

SHOX encodes two differentially spliced mRNA, *SHOX*a and *SHOXb*. The two isoforms are differently expressed in tissues. *SHOXa* is expressed in skeletal muscle, placenta, pancreas and heart. *SHOX*b is a transcriptional modulator of *SHOX*a and is expressed in foetal kidney and skeletal muscle. In addition both are particularly expressed in bone marrow fibroblasts (3).

The *SHOX* gene encodes a homeodomain transcription factor expressed during early foetal life in developing skeletal tissue of the radius and ulna, the tibia and distal femur, and the first and second pharyngeal arches (3). *SHOX* functions as a repressor for growth plate fusion and skeletal maturation in the distal limbs, so that *SHOX* haploinsufficiency results in premature growth plate fusion and relatively advanced skeletal maturation in such regions (3). The protein is specifically expressed in the growth plate in hypertrophic chondrocytes undergoing apoptosis and appears to play an important role in regulating chondrocyte differentiation and proliferation (5, 6).

Recently, a strong positive effect of *SHOX* on the expression of the fibroblast growth factor receptor gene FGFR3, a well known factor for limb development, has been recently reported by Decker et al (6). These findings offers a possible explanation for the phenotypes seen in patients with FGFR3 (e.g. achondroplasia) and *SHOX* defects (e.g. LWD).

Insufficient amount or abnormal function of *SHOX* protein due to a mutation in one copy of *SHOX* compromises normal growth. Mutations include deletions, missense and nonsense mutations in both genes or in its regulatory elements (7-10).

Deletions are the main cause of *SHOX* mutation (70% are interstitial deletions and 30% are terminal). Mutations in the regions of *SHOX* are less frequent than deletions, with a prevalence of exons 3 and 4 coding for the homeodomains .The majority of point mutations are missense mutations (9, www.shox.uni-hd.de).

SHOX- related haploinsufficiency disorders (*SHOX*-D) are inherited in a pseudoautosomal dominant manner. Absence or malfunction of one copy of the two *SHOX* genes suffices to cause the phenotype. The mutated copy can be derived from either the father or the mother. *SHOX* deficiency frequently occurs in several members of a family. No phenotypic differences have been noted between individuals with a deletion in *SHOX* and those with point mutation (8, 9).

Prevalence of SHOX-D (Paola Facchin, Lorena Pisanello)

SHOX-D accounts for at least 50%-90% of patients with LWS and in almost 100% of TS subjects (11-14).

On the basis of a number of screening studies, *SHOX*-D appears to be a relatively frequent cause of short stature. A recent study conducted in 1534 ISS children without clear or significant or recognized body disproportion detected a *SHOX* mutation in 3%-5% of ISS children (2), the percentage increased to 22% when children with disproportionate short stature were included in the selection criteria (13).

Therefore, we can expect a population prevalence of *SHOX*-D at least of 1 in 2000, higher than that of TS, which occurs in 1 in 2500 live female births and of growth hormone deficiency (1: 3.500) (11,14).

Molecular Genetic Testing and Diagnostic Implications of SHOX-D (Maurizio Clementi)

Several techniques have been applied to identify these abundant deletions, including fluorescence *in situ* hybridization, microsatellite analysis, quantitative PCR (qPCR) with amplicons restricted to the *SHOX* gene and more recently multiplex ligation-dependent probe amplification (MLPA) (9, 13-16).

Essentially, laboratory diagnosis involves three steps.

At first chromosome analysis is performed to search for a deletion of the PAR1 pseudautosomal region. Second, using MLPA (multiplex ligation dependent probe amplification), presence / absence of the *SHOX* gene is tested. Third, provided no deletion of *SHOX* is found, the entire gene is sequenced. Sequencing detects alterations in the building blocks of the DNA (point mutations) (9).

The deletion/point mutations ratio is 4:1 the sporadic/familiar form ratio is 1: 2,5 (13). Of the 59 mutation reported in the literature, 41 have been detected in patients with LWD, 10 in ISS, 5 in Langer syndrome and 3 were not correlated with a specific phenotype (3).

The *SHOX* mutations are spread across the entire coding region. In particular,

21 were located in exon 3 (44.7%), 9 mutations in exon 2 (19.1%), 8 in exon 4 (17%), 5 in exon 6a (10.6%), 3 in exon 5 (6.4%), 1 in intron 2 (2.1%) (3).

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from foetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed (17).

SHOX Deficiency Phenotype: Clinical Diagnosis (Nella A. Greggio, Lorenzo Iughetti, Franco Antoniazzi, Giorgio Tonini, Ilaria Tosetto, Elena Monti)

Mutations or deletions of the *SHOX* gene are associated with a broad spectrum of phenotypic effects, even among affected

members of the same family, ranging from short stature without evident dysmorphic signs to profound mesomelic skeletal dysplasia, a form of short stature characterized by disproportionate shortening of the middle (mesial) segments of the upper and lower limbs (i.e. the forearms and lower legs) (8, 18-22).

Clinical signs are more frequent and more severe in girls, probably because the *SHOX*(X) is more prone to be deleted compared to *SHOX*(Y) (13,14)

The **LWD** phenotype is highly variable with some patients being of normal height and showing no clinical signs of Madelung deformity. As far as stature concerned, usually they grow along the -2 SD growth curves before puberty, show a downward growth shift with puberty, reaching a final height approximately of 145 cm in females and 155 cm in males (3, 13, 18-22).

It is likely that prepubertal growth is relatively well preserved because of dormant gonadal function, whereas pubertal growth is compromised because of gonadal oestrogens production that facilitate growth plate fusion (21,22).

The **TS** patients exhibit a complete or partial absence of one of the X chromosomes and among other clinical features, they present skeletal abnormalities such as short stature (95%), stature disproportion, neck webbing, lymphedema, high-arched palate, short metacarpals, scoliosis, Madelung deformity (7%), hearing difficulties, cardiac and renal anomalies, primary amenorrhea (1,23,24). The phenotype is variable; some females manifest only short stature or primary amenorrhea. The final adult height of women with Turner syndrome who have not received any growth-promoting therapy is reduced by approximately 20 cm or 3.0 SD below the mean (23, 24).

LMD is a rare homozygous or compound heterozygous form of *SHOX*-D (incidence of 1:1.000.000) and is characterized by extreme dwarfism, profound mesomelia, and severe limb deformity (3).

In **ISS** subjects with *SHOX* haploinsufficiency the prenatal growth appears to be compromised. Postnatal growth is along the -2 SD growth curve throughout the growth period in absence of biochemical and hormonal alterations. The final height deficit is about 2 SD below the mean of normal population (3, 13, 18-22).

Finally *SHOX* haploinsufficiency is quite unlikely in patients with no evidence of Madelung deformity or mesomelia, especially in those with severe short stature (< 3 SD) accompanied by a reduced height velocity (21).

In summary a *SHOX* deficiency should be taken into consideration on the basis of a number of physical features, such as:

1. short stature
2. increased upper/lower segment ratio (sitting height/ standing height)
3. reduction of ratio between arm SPAN / forearm length
4. cubitus valgus (carrying angle)
5. Madelung wrist deformity
6. bowing of forearms
7. short metacarpals/metatarsals
8. apparent muscular hypertrophy
9. increased body mass index (BMI)
10. high-arched palate, abnormal auricular development, micrognathia and short neck

Analyzing the literature there are several possibilities for identifying patients candidate for *SHOX*-D analysis and below we have listed a series of scores that could be considered independently, on the basis of the above mentioned physical characteristics.

We have therefore taken into account as proposed by Munns et al (8), Rappold et al (2) and Binder et al (14)which have suggested helpful parameters to individuate the most eligible candidates for the molecular analysis of the *SHOX* gene.

For Munns (8) a candidate for *SHOX* deficiency investigation is a subject with:

1. Low birth weight and short stature through childhood
2. A final height consistently shorter than normal siblings
3. A family history of short stature at least in one parent

Whilst Rappold (2) reported a scoring approach based on the evaluation of 3 anthropometric measurements:

1 .arm SPAN/height ratio <96.5% (2 points)
2. sitting height/standing height ratio > 55.5% (2 points)
3. BMI > 50th percentile (4 points)

Plus five clinical variables:

1. cubitus valgus (2 points)
2. short forearm (3 points)
3. bowing of forearm (3 points)
4. muscular hypertrophy (3 points)
5. dislocation of ulna (or elbow) (5 points)

Importantly, the limit given in percentage by this score are only valid in school children (7).The graphs for normative assessment of SH/SH are available in : www.growth analyzer.org

The Rappold's score was based on the data of 1,608 short individuals including 68 individuals with *SHOX* deficiency.(2) Testing for *SHOX*-D is recommended for subject with a score greater than 7 of a total possible score of 24. At a cut-off of 7 points the positive predictive value is 19% (2).

Finally, Binder *et al.* (14) defined as diagnostic criteria the integration of 3 parameters: leg length + arm span/sitting height. A ratio more than 1 SD below the mean for school age children is suggestive for *SHOX*-D (14).

Skeletal Abnormalities: Diagnostic Implications (Tiziana Toffolutti, Franco Antoniazzi)

Several skeletal radiological abnormalities have been described in patients with *SHOX* defects. In particular , it is of practical importance to recognise early or mild signs of Madelung deformity on hand and wrist radiographs that are almost invariably obtained for the evaluation of bone age in children with short stature, such as : metaphyseal lucency and epiphyseal hypoplasia at the ulnar border of the distal radius, radial curvature ,decreased carpal angle, angulation of the distal radius and ulna, subluxation of the distal ulna , short fourth metacarpals, true shortening of the total length of the radius, exostosis at the distal ulnar border of the radius, lateral and dorsal curvature of the radius and exostosis at the distal ulnar border of the radius (3,21, 24 - 26).

Children with a severe degree of wrist deformity are significantly shorter than those with mild deformities.

When such findings are suspected, a radiograph of the distal limbs should be requested for curvature ,shortening and/or deformity of tibia (21).

It is important to note that (3, 4, 14, 24- 26):

1. Madelung deformity may not be apparent until mid-childhood and is usually preceded by radiological signs
2. the presence of a clear radiological lucency (brightness) of the distal radius and the severe degree of triangulated of the distal radial epiphysis result in a poorer prognosis in comparison with individuals who have only mild radiological signs
3. the skeletal changes of dyschondrosteosis and are less common in males.
4. skeletal features tended to be more severe in females than in males and became more obvious after puberty .

Non-Skeletal Abnormalities

Up to now, *SHOX* expression has not detected in cardiac, renal or vascular organogenesis (17).

Treatment of Manifestations (Lorenzo Iughetti, Nella A. Greggio, Giorgio Tonini)

Short Stature

The molecular diagnosis of *SHOX*-D in children with ISS or LWD has therapeutic implications. Treatment with recombinant human growth hormone (rhGH) augments the growth of individuals with LWD and may improve final adult height (26). Untreated patients show a height loss from - 1.2 SDS at 11 years to - 2.4 SDS at final height, whereas treated children improve their height from - 2.3 SDS at 11 years to -1.7SDS at final height (+ 0.6 SD) (26-29).

The concurrent use of rhGH and gonadotropin-releasing hormone agonist to delay pubertal onset in females with LWD may be of benefit when onset of puberty is early or Madelung deformity is present (30).

Bilateral Madelung deformity

Conservative management consists of wrist splints and supports during periods of increased discomfort and the use of ergonomic devices (17,31-33).

Surgery have been attempted to decrease pain, improve cosmetics, and restore wrist function in patients with severe wrist deformity.

The rationale for an early intervention is to alter the natural history of the deformity by excising the area of dyschondrosteosis in the distal radius, thus restoring growth in the distal radius (17, 34-38).

Conclusions (Vincenzo De Sanctis, Nella A. Greggio)

This document was intended to provide guidelines for the investigation of children with *SHOX*- related short stature for a correct diagnostic work - up to help clinicians in primary and secondary health care services.

In fact the challenge for the paediatrician is to perform an early identification of short children who shows one or more abnormalities at physical examination, particularly dysmorphic features (39). For few syndromes diagnostic criteria have been developed (40, 41). A relatively frequent genetic disorder associated to short stature is *SHOX*-D (3). Deletions or mutations of the *SHOX* gene have been reported in approximately 70% of patients with LWS and 3-22% of children with the clinical phenotype of ISS. Overall, the prevalence of *SHOX*-D (1:2000) appears to be higher of TS (1: 2500 live female births) and growth hormone deficiency (1: 3.500) (13).

The skeletal defects are present in a large phenotypic variation, according to the severity of expression and bone involvement, and tends to worsen with puberty. The *SHOX* gene is expressed neither in the axial skeleton development nor in the skull.

The following recommendations were suggested by our multidisciplinary team:

(i) a careful family history, measurements of body proportions and detection of any dysmorphic features are important for the identification of a genetic disorder ,(ii)the presence of any combination of the following physical findings, such as reduced arm span/height ratio, increased sitting height/height ratio, above average BMI, Madelung deformity, cubitus valgus, short

or bowed forearm, dislocation of the ulna at the elbow, or the appearance of muscular hypertrophy, should prompt the clinician to obtain a molecular analysis of the *SHOX* region, (iii) it is of practical importance to recognise early or mild signs of Madelung deformity on hand and wrist radiographs that are almost invariably obtained for the evaluation of bone age in children with short stature, (iv) growth hormone, after stimulation test, is usually normal. However, treatment with rhGH may improve final adult height .The efficacy of treatment is similar to that observed in those treated for TS.

Disclosure

F. Antoniazzi , N.A. Greggio, and **L. Iughetti** are involved in the study "The Genetics and Neuroendocrinology of Short Stature International Study-Genesis" sponsored by Eli Lilly Italia - SpA.

The other Authors declare no conflict of interest.

Vincenzo De Sanctis MD
Ilaria Tosetto, MD
Maurizio Clementi, MD
TizianaToffolutti, MD
Paola Facchin, MD
Elena Monti, MD
Lorena Pisanello, MD
Giorgio Tonini, MD

References

1. Rose SR, Vogiatzi MG , Copeland KC. A general pediatric approach to evaluating a short child Pediatr Ann. 2005;34:686-697
2. Rappold G, Blum WF, Shavrikova EP, Crowe BJ, Roeth R, Quigley CA, Ross JL, Niesler B. Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. J Med Genet. 2007;44:306-313
3. Leka SK, Kitsiou-Tzeli S, Kalpini-Mavrou A, Kanavakis E. Short stature and dysmorphology associated with defects in the SHOX gene. Hormones. 2006;5:107-118
4. Marchini A, Marttila T, Winter A, Caldeira S, Malanchi I, Blaschke RJ, Hacker B, Rao E, Karperien M, Wit JM, Richter W, Tommasino M, Rappold GA, The short stature homeodomain protein SHOX induces cellular growth arrest and apoptosis and is expressed in human growth plate chondrocytes. J Biol Chem 2004;279:37103-37114
5. Munns CJF, Haase HR, Crowther LM, Hayes MT, Blaschke R, Rappold G, Glass IA, Batch JA Expression of SHOX in human fetal and childhood growth plate. J Clin Endocrinol Metab 2004 ;89:4130-4135
6. Decker E, Durand C, Bender S, Rödelsperger C, Glaser A, Hecht J, Schneider KU, Rappold G. FGFR3 is a target of the homeobox transcription factor SHOX in limb development. Hum Mol Genet. 2011;15;20:1524-1535
7. Jorge AA, Souza SC, Nishi MY, Billerbeck AE, Libório DC, Kim CA, Arnhold IJ, Mendonca BB.SHOX mutations in idiopathic short stature and Leri-Weill dyschondrosteosis: frequency and phenotypic variability. Clin Endocrinol (Oxf). 2007;66:130-135
8. Munns C, Glass I, Flanagan S, Hayes M, Williams B, Berry M, Vickers D, O'Rourke P, Rao E, Rappold GA, Hyland VJ, Batch JA.Familial growth and skeletal features associated with SHOX haploinsufficiency. J Pediatr Endocrinol Metab 2003;16:987-996
9. Steinberger D, Wildhardt G,Trübenbach J, Müller U, Post M. Molecular genetic diagnosis of the gene SHOX (short stature homeobox) in patients with suspected SHOX deficiency. http://bio.logisDX.com
10. Durand C, Bangs F, Signolet J, Decker E, Tickle C, Rappold G. Enhancer elements upstream of the SHOX gene are active in the developing limb. Eur J Hum Genet. 2010;18:527-532
11. Jorge AA, Souza SC, Nishi MY,Billerbeck AE, Liborio DC,KimCA, Arnhold IJ, Mendonca BB SHOX mutations in idiopathic short stature and Leri-Weill dyschondrosteosis: frequency and phenotypic variability. Clin Endocrinol (Oxf) 2007;66:130-135
12. Huber C, Rosilio M, Munnich A, Cormier-Daire V . High incidence of SHOX anomalies in individuals with short stature. J Med Genet 2006;43:735-739
13. Nicolosi A, Caruso Nicoletti M Epidemiology of SHOX deficiency J Endocrinol Invest 2010;33(Suppl.6):7-10
14. Binder G Short stature due to SHOX deficiency: genotype,phenotype,and therapy Horm Res Pediatr 2011;75:81-89
15. Ross JL, Scott Jr C, Marttila P, Kowal K, Nass A, Papenhausen P, Abboudi J, Osterman L, Kushner H, Carter P, Ezaki M, Elder F, Wei F, Chen H, Zinn AR Phenotypes associated with SHOX deficiency. J Clin Endocrinol Metab 2001;86:5674-5680
16. D'haene B, Hellemans J, Craen M, De Schepper J, Devriendt K, Fryns JP, Keymolen K, Debals E, de Klein A, de Jong EM, Segers K, De Paepe A, Mortier G, Vandesompele J, De Baere E.Improved molecular diagnostics of idiopathic short stature and allied disorders: quantitative polymerase chain reaction-based copy number profiling of SHOX and pseudoautosomal region. J Clin Endocrinol Metab. 2010;95:3010-3018
17. Munns C, Glass I. SHOX-related haploinsufficiency disorders. Online Gene Rev Bookshelf ID: NBK1215- PMID: 20301394, 2008
18. Mazzanti L,Matteucci C,Scarano E, Tamburrini F, Ragni MC, Cicognani A. Auxological and antropometric evaluation in skeletal dysplasias . J Endocrinol Invest 2010;33:(Suppl.6):19-25
19. Binder G, Ranke MB , Martin DD. Auxology is a valuable instrument for the clinical diagnosis of SHOX haploinsufficiency in school-age children with unexplained short stature J Clin Endocrinol Metab 2003;88:4891-4896
20. Hintz R. SHOX mutations. Rev Endocr Metab Disord. 2002;3:363-367
21. Ogata T, Matsuo N , Nishimura G. SHOX haploinsufficiency and overdosage: impact of gonadal function status J Med Genet 2001;38:1-6
22. Huber C, Rosilio M, Munnich A, Cormier-Daire V, French SHOX, GeNeSIS Module. High incidence of SHOX anomalies in individuals with short stature. J Med Gen 2006;43:735-739
23. Saenger P, Wikland KA, Conway GS, Davenport M, Gravholt CH, Hintz R, Hovatta O, Hultcrantz M, Landin-Wilhelmsen K, Lin A, Lippe B, Pasquino AM, Ranke MB, Rosenfeld R, Silberbach M. Recommendations for the diagnosis and management of Turner syndrome. J Clin Endocrinol Metab. 2001;86:3061-3069
24. Kosho T, Muroya K, Nagai T, Fujimoto M, Yokoya S, Sakamoto H, Hirano T, Terasaki H, Ohashi H, Nishimura G, Sato S, Matsuo N, Ogata T Skeletal features and growth patterns in 14 patients with haploinsufficiency of SHOX: implications for the development of Turner syndrome. J Clin Endocrinol Metab 1999;84:4613-4621
25. Binder G, Fritsch H, Schweizer R, Ranke MB. Radiological signs of Leri-Weill dyschondrosteosis in Turner syndrome. Horm Res 2001;55:71-76
26. Munns CF, Berry M, Vickers D, Rappold GA, Hyland VJ, Glass IA, Batch JA. Effect of 24 months of recombinant growth hormone on height and body proportions in SHOX haploinsufficiency. J Pediatr Endocrinol Metab. 2003;16:997-1004
27. Cicognani A, Pirazzoli P, Nicoletti A,Baronio F, Conti V, Bonetti S. The SHOX gene:A new indication for GH treatment . J Endocrinol Invest 2010;33 (Suppl 6)15-18

28. Blum WF, Cao D, Hesse V, Fricke-Otto S, Ross JL, Jones C, Quigley CA, Binder G. Height gains in response to growth hormone treatment to final height are similar in patients with SHOX deficiency and Turner syndrome. Horm Res. 2009;71:167-172
29. Blum WF, Crowe BJ, Quigley CA, Jung H, Cao D, Ross JL, Braun L, Rappold G; SHOX Study Group. Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: Two-year results of a randomized, controlled, multicenter trial. J Clin Endocrinol Metab. 2007;92:219-228
30. Ogata T, Onigata K, Hotsubo T, Matsuo N, Rappold G. Growth hormone and gonadotropin-releasing hormone analog therapy in haploinsufficiency of SHOX.Endocr J. 2001;48:317-322
31. Fagg PS. Wrist pain in the Madelung's deformity of dyschondrosteosis. J Hand Surg [Br] 1988;13:11-15
32. Schmidt-Rohlfing B, Schwobel B, Pauschert R, Niethard FU. Madelung deformity: clinical features, therapy and results. J Pediatr Orthop B. 2001;10:344-348
33. Villeco J. Case report and review of the literature: Madelung's deformity. J Hand Ther. 2002;15:355-362
34. dos Reis FB, Katchburian MV, Faloppa F, Albertoni WM, Laredo Filho J Jr.Osteotomy of the radius and ulna for the Madelung deformity. J Bone Joint Surg Br. 1998;80:817-824
35. Vickers D, Nielsen G. Madelung deformity: surgical prophylaxis (physiolysis) during the late growth period by resection of the dyschondrosteosis lesion. J Hand Surg [Br] 1992;17:401-407
36. Angelini LC, Leite VM, Faloppa F.Surgical treatment of Madelung disease by the Sauvé-Kapandji technique. Ann Chir Main Memb Super. 1996;15:257-264
37. Salon A, Serra M, Pouliquen JC. Long-term follow-up of surgical correction of Madelung's deformity with conservation of the distal radioulnar joint in teenagers. J Hand Surg Br. 2000;25:22-25
38. Glard Y, Gay A, Launay F, Guinard D, Legré R..Isolated wedge osteotomy of the ulna for mild Madelung's deformity. J Hand Surg Am. 2007;32:1037-1042
39. Wit JM, Kiess W, Mullis P. Genetic evaluation of short stature. Best Pract Res Clin Endocrinol Metab. 2011;25:1-17
40. Kant SG, Wit JM ,Breuning MH. Genetic analysis of short stature. Horm Res 2003;60:157-165
41. Seaver LH, Irons M, American College of Medical Genetics (ACMG) Professional Practice and Guidelines Committee. ACMG practice guideline: genetic evaluation of short stature. Genet Med. 2009;11:465-470