Short stature and dysmorphology associated with defects in the SHOX gene

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ABSTRACT
Since its discovery in 1997, knowledge about the SHOX gene (Short stature HOmeoboX-containing gene) has rapidly advanced. Although originally described as causing idiopathic short stature, SHOX mutations are also responsible for growth retardation in Léri-Weill dyschondrosteosis, Langer mesomelic dysplasia and Turner syndrome. Furthermore, SHOX has a broad functional scope and leads to a variety of different morphological-skeletal stigmata associated with these syndromes. This article reviews clinical and molecular data associated SHOX gene defects. Functional ongoing studies are expected to improve our understanding of the SHOX gene as comprising part of a genetic process responsible for normal growth and bone development.

Key words: LMD, LWD, Short stature, SHOX, Turner syndrome

INTRODUCTION
Linear growth is determined by environmental, hormonal and genetic factors. The multitude of growth-affecting genetic factors has recently been supplemented by the discovery in 1997 of the SHOX gene on Xpter. Rao and colleagues1 in Germany and Ellison and colleagues2 in the United States almost simultaneously reported SHOX as a candidate gene for growth failure. Previous observations had indicated that deletions of the short arm of the human X and Y chromosomes are consistently associated with short stature.3-7

SHOX is the abbreviated designation for the Short stature HOmeoboX-containing gene and is localized in the pseudoautosomal region of both X and Y chromosomes encoding for a transcription factor of 293 and 225 amino acids (SHOXa and SHOXb, respectively). Initial data suggested an involvement of SHOX haploinsufficiency in the etiology of idiopathic short stature (ISS; OMIM# 604271) and the short stature in Turner syndrome (TS),8 while homozygous loss of the SHOX gene has been correlated with the Langer type mesomelic dysplasia (OMIM; 249700).9 Subsequently, heterozygous SHOX mutations were also shown to cause Léri-Weill dyschondrosteosis (LWD; OMIM #127300).9 The overall estimate of the incidence of
SHOX deficiency is between 1/2000-1/5000 in the general population and 1/40-1/150 among short people. In this paper, we review the current knowledge of the SHOX gene and in particular the molecular and clinical aspects.

HOMEBOX GENES AND THE SHOX GENE

A homeobox is a 180-base pair DNA sequence that codes for a 60-amino acid DNA-binding region called homeodomain. A homeodomain is the DNA-binding motif of eukaryotic transcription factors, which also mediates other key functions such as nuclear localization and protein-protein interactions. Most homeobox-containing genes are involved in developmental regulation, differentiation and organogenesis and they are expressed differentially in space and time.10,11 Several hereditary disorders, such as the Waardenburg syndrome type I (PAX 3), aniridia (PAX 6) and synpolydactyly (HOXD 13), are caused by defective homeobox genes.12-14

The SHOX gene, which has been isolated by positional cloning, covers a genomic region of 40 kb and resides in the pseudoautosomal region (PAR1) of human sex chromosomes at Xp22 and Yp11.3, within a 170-kb region, 500 kb from the telomeres.1 Because genes residing in the PAR1 region escape X-inactivation, two copies of the SHOX gene are normally expressed in males as well as in females. The SHOX gene has one non-coding and six coding exons, ranging from 58 to 1166 bp in size (Figure 1). The homeobox spans exons III and IV. Exons I-V are identical in both transcripts but exon VI is presented in two forms (VIa or VIb) with different phosphorylation sites. Exon VIa, but not VIb, has a putative site for binding to SH3 domains that are found in cytoplasmic proteins involved in signal transduction. SHOX undergoes alternative splicing to yield two mRNAs, SHOXa (4559bp) and SHOXb (1952 bp). SHOXa and SHOXb mRNA are translated into proteins of 292 (SHOXa) and 225 (SHOXb) amino acids, respectively, that differ in the C-terminal region.1,2

The SHOX protein contains three characteristic domains: a homeodomain (a member of the Q50 paired like class), an SH3 binding domain and an OAR domain, and is localized at the nucleus, acting as a transcriptional regulator. Studies on the SHOX gene in human fetal tissues at six weeks of gestation have shown that it is expressed in the distal humerus, radius, ulna, wrist and first and second pharyngeal arches. Further studies have delineated that SHOXa and SHOXb are expressed in a different array of tissues. SHOXa is expressed at low levels in many tissues, while SHOXb is expressed in a more restricted manner, their highest expression level being in bone marrow fibroblasts. Neither of these two genes is expressed in the vertebrae, phalanges, heart, CNS or genitalia.15-17 Additional evidence for a role of SHOX in bone development was provided by the recent finding that the SHOX protein is detected in hypertrophic chondrocytes of the growth plate.17,18 It was also reported that SHOX expression induces cell cycle arrest and apoptosis in osteosarcoma cells as well as in primary chondrocytes, implicating a role for SHOX in the processes regulating chondrocyte differentiation.18

MUTATIONS IN THE SHOX GENE

Deletions and, less frequently, mutations of the SHOX gene have been reported in more than 200 patients to date, excluding the many patients with Turner syndrome who have a mandatory heterozygous deletion of the SHOX gene. The high frequency of repeats within the PAR1 region make this genomic region particularly prone to recombination and this is the reason why deletions are found in more than 70% of affected subjects.19 Forty-one out
of the 59 mutations described have been detected in patients with LWD, 10 in ISS, 5 in Langer syndrome while 3 were not correlated with a specific phenotype [www.shox.uni-hd.de]. SHOX mutations were spread across the entire coding region: 21 mutations 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%). Among them there were 44 substitutions, 9 deletions and 6 insertions (nonsense, missense or frameshift); 21 mutations concerned the homeodomain 1, 7 mutations the homeodomain 2 and 1 mutation the SH3 domain.1,8,9,15,20-31 To date, no mutation residing in the OAR domain-coding region has been found. Recent data demonstrated31 that the majority of mutant SHOX alleles in sporadic cases were transmitted from the father and this phenomenon was also observed in a previous study on SHOX mutations in patients with unexplained short stature. 32 In addition, genotyping of single human sperms has shown that the recombination fraction of the pseudoautosomal interval on the Y chromosome containing SHOX is 31 times higher than the genome’s average.33 Such a high recombination fraction could explain a preferential instability of the SHOX locus during male meiosis. Most missense mutations were found to be clustered in the homeodomain. Schneider et al.34,35 have shown that a single missense mutation fundamentally impairs SHOX key functions (such as alteration of DNA binding, dimerization and nuclear translocation), thereby leading to the phenotype observed in patients with LWD and ISS. In addition, a novel class of PAR1 deletions of variable size and at least ~30-530 kb downstream of SHOX associated with LWD has been described.36 Finally, the implication of a cis-acting enhancer in the SHOX 3’region associated with skeletal phenotypes of LMD in a 45,X/46,X,r(X) infant and LWD in her 46,XX mother37 shed more light on the molecular aspects of SHOX deficiency.

IMPLICATIONS OF SHOX GENE MUTATIONS

Evidence that the SHOX gene is a critical regulator of growth was based on the following findings: 1) It is expressed during fetal life; 2) it has a highly conserved sequence in a wide variety of species; 3) loss or mutation of the SHOX gene is always associated with short stature; and 4) excess copies of the SHOX gene are associated with tall stature. It has been documented that SHOX functions as a repressor of growth plate fusion and skeletal maturation in the distal limbs and counteracts the skeletal maturing effects of estrogens.15,17 Consequently, SHOX’s expression pattern in the ulna, radius, elbow and wrist, the equivalent bones in the leg and in the first and second pharyngeal arches explains the observed clinical features of SHOX deficiency: 1) Short stature; 2) “mesomelia”, i.e. shortening of the forearms and lower legs; 3) cubitus valgus; 4) Madelung wrist deformity (Figure 2) i.e. bilateral shortening and bowing of the radius with a dorsal subluxation of the distal ulna, wedged carpal bones and premature fusion of the epiphysis; 5) short metacarpals/metatarsals; and 6) high-arched palate, abnormal auricular development, micrognathia and short neck.38

The clinical features of SHOX deficiency show a marked phenotypic variability, even among affected members of the same family. In general, females appear to be more severely affected than males and the skeletal defects tend to worsen with puberty.39,40 Radiographic features of SHOX deficiency are: coarse trabecular pattern, abnormal femoral neck, exostoses proximal tibial/fibula, abnormal tuberosity of humerus, radial/tibial bowing, short metacar-

![Figure 2. Clinical appearance of Madelung deformity (personal archive).](image-url)
Another variety of structural defects of the X chromosome. More than 90% of girls with Turner syndrome have short stature and SHOX represents the only related gene thus far recognized. It will thus be of great interest to determine which patients among mosaics will develop a less severe phenotype, with regard to short stature, depending upon the number of intact SHOX genes.

Clinical syndromes associated with SHOX deficiency are: Turner syndrome, Lédi-Weill dyschondrosteosis, Langer mesomelic dysplasia, Idiopathic short stature.

**Turner syndrome (TS)**

Patients afflicted with Turner syndrome (one in 2500 live born females) are cytogenetically characterized by a complete or partial loss of one X chromosome. About 60% have a 45,XO karyotype and the rest are either mosaics 45,XO/46,XX or have a variety of structural defects of the X chromosome. More than 90% of girls with Turner syndrome have short stature and SHOX represents the only related gene thus far recognized. It will thus be of great interest to determine which patients among mosaics will develop a less severe phenotype, with regard to short stature, depending upon the number of intact SHOX genes.

Clement-Jones and colleagues suggested a possible involvement of SHOX-related growth impairment in the expression of other Turner stigmata such as high-arched palate, abnormal auricular development, cubitus valgus, genu valgum and short metacarpals. Other clinical investigators reported that SHOX haploinsufficiency could lead to additional Turner skeletal abnormalities such as mesomelia and Madelung deformity. Ogata et al. claimed

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**Figure 3.** Radiological findings in SHOX deficiency. A. Borderline short 4th metacarpal. B. Borderline short 4th metacarpal, mildly decreased carpal angle, and slightly shortened and bowed radius. C. Short 4th metacarpal, cubitus valgus, decreased carpal angle, angulation of the distal radius, and short and curved radius. D. Borderline short 4th metacarpal, mild cubitus valgus, and deformation of the medial half of the distal radius. E. Short 4th metacarpal, cubitus valgus, decreased carpal angle, angulation of the distal radius, and short and curved radius. Reprinted with permission from the Endocrine Society.
that there must be additional factors such as an X-linked “lymphogenic” gene, located between the Duchenne muscular dystrophy (DMD) and monoamine oxidase A (MAOA) genes that could also be responsible for the development of soft tissue and skeletal abnormalities in Turner syndrome.

Léri-Weill dyschondrosteosis (LWD)

LWD is the most common form of mesomelic skeletal dysplasia with an estimated prevalence of 1/2000, Madelung deformity being a hallmark sign. As far as stature is concerned, final height in females is approximately 1.45m and in males 1.55m. The phenotype is highly variable with some patients being of normal height and showing no clinical signs of Madelung deformity.\(^2^8,3^1,4^3\) There is also great variation among patients with identical mutations belonging to the same family.\(^8,9,2^0\) Females are more frequently affected than males and growth failure as well as clinical features, such as bilateral Madelung deformity, have been described as being more severe in females than in males.\(^3^1,4^3\)

Compared to their unaffected siblings, SHOX haploinsufficient females were 2.4 SDS (14.4 cm) shorter and SHOX haploinsufficient males 0.8 SDS (5.3 cm) shorter at final height, although females and males in the SHOX haploinsufficient cohort were both –2.14 SDS at birth and –2.1 SDS through childhood.\(^4^7\) On the other hand, despite a relatively small number of LWD individuals with family data available, familial comparisons revealed that only females with LWD and a de novo SHOX mutation had a height SDS that was significantly different from their mid-parental height. According to these studies, there must exist a sex and age influence on SHOX haploinsufficiency, though pertinent data remain controversial. In a recent study among patients with LWD it was demonstrated that growth failure was observed during the first years of life with a mean height loss of 2.16 SDS in childhood, whereas pubertal growth was mildly or not affected. Furthermore, it was shown that children with a severe degree of wrist deformity were significantly shorter than those with mild deformities.\(^3^1\)

Heterozygous mutations of the SHOX gene have been reported in patients with Léri-Weill dyschondrosteosis\(^8,9,2^0,4^8\) at an estimated prevalence ranging from 60% to 100%. Among patients with Léri-Weill syndrome, SHOX defects up to 70% were SHOX gene deletions and 15% were point mutations.\(^2^4\) The absence of SHOX deficiency in almost 30% of patients with Léri-Weill syndrome may be explained by: 1) the presence of mutations in unanalyzed regions, such as the upstream, intragenic or downstream regulatory sequences of SHOX,\(^3^7,2\) the sex-chromosome-specific regulation, 3) the involvement of modifying genes, or 4) the genetic heterogeneity.\(^4^9\) In table 1 the molecular and clinical studies on SHOX deficiency associated with LWD are summarized. The differences in percentages of detected SHOX haploinsufficiency in different studies could be explained by a variable ascertainment of populations studied.

Langer mesomelic dysplasia (LMD)

LMD is characterized by severe short stature (<-2SDS) with hypoplasia or aplasia of the ulna and fibula and has been described as the most severe type of LWD.\(^5^0\) All patients with this syndrome have homozygous deficiency of the SHOX gene.\(^8,4^4\) Fukami et al.\(^3^7\) summarized the clinical and molecular data on 17 patients with LMD reported so far.\(^8,9,2^7,3^0,5^1-5^4\) The patients had a mean height deficit of –6.18 SDS and presented various degrees of SHOX deficiency associated skeletal abnormalities. One third of the above studied patients resulted from homozygous deletions, one third from homozygous point mutations while the rest were not examined. It is interesting that a severe and atypical form of dyschondrosteosis has recently been reported in a mother and her son presenting features of Léri-Weill dyschondrosteosis in the upper extremities and of Langer Mesomelic Dysplasia in the lower extremities, attributed to a heterozygous deletion of the SHOX gene in both of them.\(^5^5\) These findings broaden the phenotypic spectrum associated with SHOX gene functional haploinsufficiency.

Idiopathic short stature (ISS)

Idiopathic short stature is characterized by significant short stature (<-2SDS), a persistently low growth rate for age and no biochemical or other evidence of a specific growth retarding condition. Hence, after excluding a long list of various causes of short stature, including chronic systemic disor-
ders, skeletal, endocrine and chromosomal abnormalities, one is left with the diagnosis of idiopathic short stature (ISS). Unexplained short stature poses a dilemma for health professionals who diagnose and treat growth disorders. Less than 1% of children under the 3rd percentile for height will be found to be growth hormone deficient or have mutations involving growth hormone releasing hormone (GHRH), GH, IGF-1 genes or their respective receptors. It is, therefore, of great interest that SHOX gene mutations may explain growth failure in a proportion, albeit small, of children with ISS. In Table 2 studies on gene SHOX haploinsufficiency in children with ISS are summarized. In the majority of pertinent studies, SHOX gene deletions or mutations have been detected in about 2% of children with ISS and this prevalence would imply a population prevalence of at least 1 in 2000 children. Clas-

<table>
<thead>
<tr>
<th>Study</th>
<th>Phenotype</th>
<th>N</th>
<th>No with mut (%)</th>
<th>Height SDS Birth</th>
<th>Childhood</th>
<th>Final</th>
<th>(%)&lt;2SD</th>
<th>Morphologic Stigmata %</th>
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<tbody>
<tr>
<td>Belin et al., 1998</td>
<td>Ht&lt;-2SD and MD on X-ray</td>
<td>8</td>
<td>100</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shears et al., 1998</td>
<td>DP short stature</td>
<td>7</td>
<td>100</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kosho et al., 1999</td>
<td>Partial or total monosomy of PAR1</td>
<td>14</td>
<td>100</td>
<td>-1.1</td>
<td>-2.44</td>
<td>-2.9</td>
<td>-2.0</td>
<td>(79)</td>
</tr>
<tr>
<td>Cormier-Daire et al., 1999</td>
<td>Ht&lt;-2SDS and MD on X-ray</td>
<td>8</td>
<td>100</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiller et al., 2000</td>
<td>MD</td>
<td>18</td>
<td>56</td>
<td>-1.9</td>
<td>-2.1</td>
<td>-3.87</td>
<td>2.53</td>
<td>NR</td>
</tr>
<tr>
<td>Grigelioniene et al., 2000</td>
<td>DP short stature</td>
<td>5</td>
<td>60</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Huber et al., 2001</td>
<td>Ht&lt;-2SDS and MD on X-ray</td>
<td>16</td>
<td>100</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ross et al., 2001</td>
<td>Short or MD</td>
<td>21</td>
<td>100</td>
<td>-2.0</td>
<td>-1.9</td>
<td>-2.3</td>
<td>-3.0</td>
<td>74</td>
</tr>
<tr>
<td>Falcinelli et al., 2002</td>
<td>DP short stature and MD on X-ray</td>
<td>21</td>
<td>62</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flanagan et al., 2002</td>
<td>MD operated</td>
<td>18</td>
<td>67</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Munns et al., 2003</td>
<td>MD operated</td>
<td>10</td>
<td>100</td>
<td>-0.89</td>
<td>-2.0</td>
<td>0.0</td>
<td>-2.1</td>
<td>-2.0</td>
</tr>
<tr>
<td>Binder et al., 2004</td>
<td>MD and DP limbs</td>
<td>20</td>
<td>82</td>
<td>-0.59</td>
<td>-2.30</td>
<td>1.72</td>
<td></td>
<td>100</td>
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<tr>
<td>Schneider et al., 2005</td>
<td>DP short stature and MD</td>
<td>118</td>
<td>34</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Ross et al., 2005</td>
<td>Prepubertal children</td>
<td>34</td>
<td>100</td>
<td>-2.3</td>
<td>1.853</td>
<td></td>
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</tr>
</tbody>
</table>

Fam: families; I: individuals; NR: not reported; Ht: height; NL: normal; MD: Madelung deformity; DP: disproportionate; mut: mutations; F: females; M: males
Table 2. Summary of studies on SHOX haploinsufficiency in ISS

<table>
<thead>
<tr>
<th>Study</th>
<th>Phenotype</th>
<th>Patients N</th>
<th>Mutations (%)</th>
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<tbody>
<tr>
<td>Rao et al., 1997</td>
<td>Ht&lt;-2SDS and NL karyotype and X-rays</td>
<td>91</td>
<td>1.1</td>
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<tr>
<td>Binder et al., 2000</td>
<td>Ht&lt;-2SDS and NL X-rays</td>
<td>68</td>
<td>1.5</td>
</tr>
<tr>
<td>Musebeck et al., 2001</td>
<td>Ht&lt;-2SDS and NL family Ht and X-rays</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>Rappold et al., 2002</td>
<td>Ht&lt;-2SDS</td>
<td>900</td>
<td>2.4</td>
</tr>
<tr>
<td>Ezquieta et al., 2002</td>
<td>Short stature</td>
<td>73</td>
<td>-</td>
</tr>
<tr>
<td>Stuppia et al., 2003</td>
<td>Ht&lt;-2SDS and NL karyotype and X-rays</td>
<td>56</td>
<td>12.4</td>
</tr>
<tr>
<td>Binder et al., 2003</td>
<td>Ht&lt;-2SDS and NL karyotype</td>
<td>140</td>
<td>2</td>
</tr>
<tr>
<td>Schneider et al., 2005</td>
<td>Ht&lt;-SDS</td>
<td>&gt;1500</td>
<td>2</td>
</tr>
</tbody>
</table>

Ht: height; NL: normal; ISS: idiopathic short stature

Thus, the prevalence of short stature due to SHOX gene deletion among children with ISS appears to be analogous to or even more frequent than that of GH deficiency or Turner syndrome.\(^{25-28}\) According to Munns et al.,\(^{47}\) a candidate for SHOX deficiency investigation is the child with low birth height (but within the lower limits), stature during childhood near the lower limits (between -2.2 and -2.1 SDS for females and males, respectively) or final height well below the lower normal limits (between -2.84 and -2.36 SDS for females and males, respectively) and family history of short stature in at least one parent.

**GENOTYPE-PHENOTYPE CORRELATIONS**

SHOX deficiency appears to be a major cause of growth failure in 100% of patients with Turner or Langer syndrome, approximately 70% in Léri-Weill syndrome and about 2% in patients previously diagnosed as having “idiopathic” short stature.

Taken together, the data of some recent studies\(^{22,25,31}\) indicate that the growth deficit caused by SHOX defects in patients with Léri-Weill dyschondrosteosis is approximately 2SDS, which is not as severe as that encountered in other osteodysplasias or in Turner syndrome. This observation suggests that there may be other genes — such as the lymphogenic gene(s) mapped to a ~9 Mb region between DMD and MAOA loci on Xp chromosome— that are responsible for the impaired development of soft tissue, visceral and skeletal abnormalities and shortness.\(^{45,46}\)

The different prevalence of Madelung deformity between LWD and Turner syndrome (~75% vs. ~8%) has been attributed to loss of other X-linked, non-pseudoautosomal growth genes which masks the full phenotype of SHOX haploinsufficiency in Turner syndrome. This hypothesis however has to be proven. The modifying gene(s) could be on an autosome or on the X chromosome itself.\(^{8}\) An alternative explanation may be that girls with Turner syndrome are protected from developing Madelung deformity by their sex steroid deficiency, which does not occur in females with LWD. However, the deformity does not seem to develop even in females with Turner syndrome treated with estrogens before epiphyseal closure. Nevertheless, therapy even in these cases usually starts in the late teens and at a low dose.\(^{25}\) Unfortunately, there is no mouse or murine model for SHOX haploinsufficiency. Thus, humans represent the only prototype for studying the role of SHOX gene in normal and abnormal growth and development.

The role of estrogens, being the sole known factor influencing the phenotype in SHOX haploinsufficiency, remains controversial. In both sexes, skeletal maturation is advanced by estrogens and serum estrogen concentration is higher and begins to increase at a younger age in females.\(^{56}\) SHOX appears to function as a repressor for growth plate fusion and skeletal maturation in the distal limb region, so that SHOX haploinsufficiency results in unbalanced, premature growth plate fusion and advanced skeletal maturation. It has been suggested by some studies\(^{39,40,43,44,57}\) that the estrogenic effect could account
for the observation that females are more severely affected than males and skeletal features tend to worsen with age. On the other hand, Ross et al.,25 as well as Binder et al.,31 have made the following observations. 1) In LWD cohorts, males are just as short as females and they may go unrecognized, being diagnosed in childhood at least in part as ISS. In such cases family history could provide a clue to the diagnosis because most of the SHOX abnormalities observed in males are familial. 2) Growth failure occurs during the first years of life, whereas pubertal growth may be mildly or not affected. 3) Estrogens may have an impact on the severity of the Madelung deformity, but its antecedents are present very early in childhood both in males and females.

Two identical point mutations, c.674C>T,9,15,22,25,26 and c.599G>C [RR Project HD, GDFN HD, www.shox.uni-hd.de], have been described in patients with either ISS or LWD. This finding suggests that SHOX haploinsufficiency can lead to different clinical phenotypes. Deletions of the SHOX gene have been described as being far more frequent than point mutations among patients with LWD, but neither the size of the deletion nor the type of point mutation are correlated with the severity of the phenotype.8 This phenomenon is known as phenotypic heterogeneity and could be attributed to background genetic effects, environmental factors and chance events. This is commonly observed in haploinsufficiency syndromes, when the loss of action of the one allele results in a 50% reduction of overall activity.58 Because the underlying principle in haploinsufficiency syndromes is the disturbance of a delicately balanced temporal and spatial expression, variations in the expression level of the remaining (intact) SHOX gene copy could help explain the variable phenotypic expression of SHOX mutations. Another possible explanation for the phenotypic heterogeneity of SHOX mutations might reside in the biochemical properties of the SHOX-encoded protein. Similar phenotypic heterogeneities have been described for other “transcription factor disorders” and might be attributed to their role as master regulatory switches within one or several developmental pathways. Recent examples are PIT1 defects leading to multiple hormone defects,59 as well as mutations within the gene encoding for the transcription factor GLI3 that have been demonstrated to cause three different clinical conditions, namely the Greig cephalopolysyndactyly syndrome,60 the Pallister-Hall syndrome61 and postaxial polydactyly type A.62 In all these examples, the clinically observed phenotype is strongly dependent on the position of the mutated molecule within the specific developmental pathway.63

TREATMENT PERSPECTIVES

The presence of one or more skeletal abnormalities, known to occur in dyschondrosteosis or Turner phenotypes, should prompt the analysis for SHOX gene deletions or mutations in children and adults with short stature. It has now been well established that a thorough clinical investigation is a crucial first step in selecting patients with a likely defect in the SHOX gene. For this purpose, detailed evaluation of the x-rays of forearms and lower limbs for subtle radiographic changes should be carried out.

In general, the clinician should consider SHOX deficiency in any patient with: a) “idiopathic” short stature and especially a stature lower than expected from parental height, b) “familial short stature”, especially if there is a female predominance in the family, and c) disproportionate growth of the forearms or lower legs.24

For SHOX haploinsufficiency, two therapeutic interventions can be considered. Since growth hormone (rhGH) therapy improves the growth pattern in Turner syndrome, despite the absence of GH deficiency,64,65 it may also be advantageous in patients with SHOX haploinsufficiency. Another form of intervention could be the use of gonadotrophin releasing hormone analogue (GnRHa), which can suppress gonadal steroid production and may serve to mitigate the development of skeletal features and prolong the period of growth.39

To date, there have been five reports of rhGH therapy in individuals with SHOX haploinsufficiency. Table 3 summarizes the published data in patients with SHOX haploinsufficiency treated with rhGH.42,66-69 The data are not complete in all cases and there was a wide range of rhGH dose. No ad-
verse effects of rhGH therapy were observed. Age appropriate advancement of bone age was seen, indicating that any height advancement from rhGH therapy may result in an improvement in final height. There was only minimal radiological progression and no clinical worsening of Madelung deformity in all patients. All patients (apart from patient 3 of Ogata et al.) demonstrated short-term benefit from rhGH therapy, with a mean improvement in height SDS of 0.8 at 12 months (n=8) and 0.6 at 24 months (n=3). These data suggest that the effect of rhGH may diminish after the first 12 months of therapy, a finding also seen in other skeletal dysplasias. The overall data suggest that the higher doses of rhGH were associated with greater short-term benefit. As there are no LWD-specific growth charts to be used for the assessment of the therapeutic response to rhGH, it is important to note that the height of females with SHOX haploinsufficiency has been demonstrated to be reduced by approximately 0.7 SDS from childhood to final height. Taking this into consideration, the maintenance of the same height SDS through this period may constitute evidence of growth improvement. However, the number of reported patients with SHOX haploinsufficiency treated with rhGH is small and further studies are required before definitive conclusions can be drawn.

### Table 3. Cumulative growth data from published studies on rhGH therapy in patients with SHOX haploinsufficiency

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>rhGH dose (IU/Kg/wk)</th>
<th>Ht SDS (at months of therapy)</th>
<th>HV SDS (at months of therapy)</th>
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<td>-3.9</td>
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(Studies that analyzed the effect of rhGH in patients with clinical LWD for whom SHOX mutation analysis was not available are not included). Ht: height; HV: height velocity; NR: not reported.

### CONCLUSION

The elucidation of the respective developmental pathway of the SHOX gene and the determination of its exact position therein constitute a prerequisite for a full understanding of the variable phenotypic consequences of SHOX mutations. Understanding SHOX as part of a genetic program responsible for normal growth and bone development will also allow the identification of additional factors within this program that might modify the effects of the functional haploinsufficiency of the SHOX gene. Along these lines, SHOX might turn out to represent another example of a gene implicated in several clinical conditions formerly regarded as distinct syndromes. It is possible that SHOX haploinsufficiency is responsible not only for the ISS or the LWD but also for intermediate mild skeletal dysplasias. Taken together, the biochemical characterization of the SHOX-encoded transcription factor, the identification of upstream and downstream regulators or targets of the SHOX gene and its positioning within a specific developmental pathway are priority objectives. At present, the exact action of SHOX protein cannot be defined. Functional studies will improve our understanding of the role of the SHOX gene in skeletal and cartilage growth.
REFERENCES


Short stature, clinical syndromes, SHOX


