

CLINICAL FEATURES IN SHOX HAPLOINSUFFICIENCY: DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS

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INTRODUCTION

The distal end of Xp and Yp is composed of 2.6 Mb DNA sequences that are identical between the X and the Y chromosome.¹ This particular region is named the short arm pseudoautosomal region (PAR1), where the X and the Y chromosomes recombine during male meiosis.¹ Since Xp terminal deletions invariably result in short stature irrespective of the breakpoints,² and small Yp terminal deletions lead to short stature,³ it has been suggested that a growth gene escaping X-inactivation resides in the PAR1, and that haploinsufficiency of the growth gene causes short stature in both sexes as a dominant phenotype.²

In 1997, Rao et al⁴ successfully cloned a novel gene at the position roughly 500 kb from the Xp/Yp telomere, and named it SHOX for short stature homeobox containing gene. SHOX consists of 7 exons and produces 2 transcripts

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From The Editor's Desk

The miracle of the Internet has allowed the readership of *Growth, Genetics & Hormones* to grow very rapidly. We have recently added to our subscribers a substantial number of pediatric endocrinologists worldwide. Members of the Pediatric Endocrine Societies from Europe, Latin America, Colombia, and Japan who have email addresses will now be receiving *GGH* on an ongoing basis. It gives me great pleasure to welcome these pediatric endocrinologists to the family of *GGH*. Surely, our European, Latin American & Japanese contemporaries will help us broaden our perspectives and apprise us of advances in the field for publication in *GGH*. I am looking forward to contributions from our colleagues; an example of such is the lead article in this issue.

This second issue of 2004 contains a review of the clinical features of the short stature homeobox gene, so called SHOX. This important factor is implicated in the etiology of short stature and, in particular, features that characterize patients with this abnormality. This paper addresses a complicated subject, presents it in a clear easy-to-read manner, and brings the state of the art in the field to the readers of *GGH*. Drs. Tsutomu Ogata and Maki Fukami from Tokyo, Japan authored this lead article, emphasizing aspects of particular interest to pediatric endocrinologists and geneticists. The authors deserve our congratulations and thanks for their erudite writing.

This issue also contains abstracts of recent articles published in the literature that were considered of importance by our editorial board; each article is reviewed with editorial comments. Unfortunately, we have limited space and cannot publish all articles of importance in the field, nor do we attempt to do so. We limit our scope to bring value by publishing only articles that attract the interest of the editorial board and that meet our editorial standards. The high value that *GGH* has received from the readership indicates we have met our objectives, and we want to surpass them. The report of the December 2003 survey is posted at www.GGHjournal.com (click on survey results). We appreciate your comments so we may continue to serve your needs.

Fima Lifshitz, MD
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generated by alternative splicing of its 3' exons (SHOXa and SHOXb). SHOXa and SHOXb proteins consist of 292 and 225 amino acids, respectively. SHOXa appears to have a major biological function, although it remains to be determined whether SHOXb has some biological role.⁵ SHOX is expressed from an inactive X chromosome as well as an active X and a normal Y chromosome, indicating that SHOX exerts the dosage effect in sex chromosome aberrations.⁴ Furthermore, expression analysis in human embryos has shown that SHOX is exclusively expressed in the developing distal limbs and in the first and second pharyngeal arches where Turner skeletal features are observed postnatally.⁶

Extensive clinical and molecular studies have demonstrated that SHOX haploinsufficiency is implicated in 2% of short stature individuals and is the predominant factor in Turner skeletal features and Léri-Weill dyschondrosteosis (LWD) characterized by Madelung deformity (shortening and bowing of the radius with dorsal subluxation of the distal ulna and partial foreleg anomalies).⁷ In this paper, we summarize current knowledge about SHOX haploinsufficiency.

Table 1. Skeletal features in the distal limb region in 36 patients with SHOX haploinsufficiency

Short metacarpals and/or cubitus valgus	Madelung deformity and/or mesomelia	Prepubertal boy	Pubertal to adult male	Prepubertal girl	Pubertal to adult female
No	No	1	3	2	0
Yes	No	0	0	0	1
No	Yes	0	1	2	5
Yes	Yes	1	1	6	13

The actual number of patients is shown.

LIMB SKELETAL FEATURES

Intragenic SHOX mutations, or pseudoautosomal microdeletions involving SHOX as the sole disease gene, have been identified in a large number of patients with normal karyotype and normal gonadal function⁷ (also, Ogata, unpublished data). Skeletal features in the distal limb region of such individuals are classified into 4 groups on the basis of the combination of short 4th metacarpals and/or cubitus valgus which appears in 40-50% of Turner females, and Madelung deformity and/or mesomelia characteristic of LWD occurs in only approximately 7% of Turner females.⁸ The prevalence of these features in 36 Japanese short-stature patients is shown in Table 1 (for representative roentgenograms, see Figure 1 in reference 7). These data indicated that SHOX haploinsufficiency is implicated in short stature and in the limb skeletal features of Turner and LWD patients.

Most people with SHOX haploinsufficiency have LWD features of variable extent, although there may be an ascertainment bias since patients with LWD are preferentially identified. In addition, genu valgum and relatively short lower limbs were clinically discernible in most patients with overt LWD, and tibial or fibular exostosis was occasionally detected. For the pseudoautosomal microdeletions in the telomeric part of Xp/Yp, no other features have been identified, suggesting that haploinsufficiency of pseudoautosomal genes other than SHOX has no clinical effects.⁹

SHOX haploinsufficiency also occurs in cytogenetically discernible Xp or Yp terminal deletions. In this context,

Figure 1



Representative radiographs of the hands and forearms in 4 individuals with SHOX haploinsufficiency and normal gonadal function. The skeletal features are much more severe in the fully matured daughter with normal menses than in the father (left). The skeletal features are much more severe in the fully matured elder sister with normal menses than in the prepubertal sister with no breast development (right).

distal limb skeletal features in 43 female patients with various types of Xp deletions involving SHOX have been summarized as follows¹⁰: (1) the prevalence of the wrist abnormality suggestive of mild Madelung deformity was significantly higher in females with spontaneous puberty than in those without spontaneous puberty; (2) the severe Madelung deformity, often detected in pubertal or adult females with normal karyotype, was not identified in these patients; and (3) the prevalence of short metacarpals and cubitus valgus was similar in females with and without spontaneous puberty (Table 2).

Effect of Gonadal Estrogens

Limb skeletal features are more severe in females than in males, and become overt with puberty in patients with normal karyotype (Figure 1). The so-called idiopathic short-stature phenotype was predominantly exhibited by male patients and prepubertal girls, and LWD was predominantly manifested by pubertal and adult female patients (Table 1). In this context, two matters are noteworthy. First, SHOX appears to function as a repressor of growth plate fusion and skeletal maturation in the distal limb region, so that SHOX haploinsufficiency results in premature growth plate fusion and relatively advanced skeletal maturation in that region.^{11,12} Second, skeletal maturation in normal individuals is primarily caused by gonadal estrogens—which increase with puberty—serum estrogen levels being higher in females than in males.¹³ Thus, it is likely that gonadal estrogens exert a maturational effect on skeletal tissues that are susceptible to unbalanced premature growth plate fusion, facilitating the development of skeletal lesions in a female-dominant and in a pubertal tempo-influenced fashion.^{7,13} Furthermore, the tempo of pubertal development may also play an important role in the development of skeletal features. Severe forms manifested in early maturing girls who are exposed to gonadal estrogens from a relatively early age.¹³ This may also account for the sex differences in the severity of skeletal features in SHOX haploinsufficiency, because females enter puberty approximately 2 years earlier than males. Thus, it is inferred that, in SHOX haploinsufficiency, the amount and tempo of gonadal estrogen production in females usually cause LWD, whereas those in males usually lead to the so-called idiopathic short-stature phenotype.

This notion is consistent with the findings in female patients with cytogenetically recognizable Xp deletions. The wrist abnormality is predominantly manifested by females with spontaneous puberty, and the absence of severe Madelung deformity is compatible with a relatively small amount and slow tempo of gonadal estrogen production.⁹ Furthermore, this idea is applicable to Turner syndrome as well: (1) the prevalence of Madelung deformity is only approximately 7%,⁸ and this relatively low prevalence would be explained by the compromised gonadal estrogen of these patients (Table 3); (2) the

Table 2. The prevalence of Turner skeletal features in 43 patients with Xp deletions involving SHOX

	Lymphogenic gene(s) [¶]		Spontaneous puberty	
	Preserved	Deleted	Positive	Negative
Distal limb region [‡]	11/19	19/24	*17/20	*13/23
Short metacarpals	7/19	12/24	12/20	7/23
Cubitus valgus	9/19	18/24	15/20	12/23
Wrist abnormality [#]	*8/18	*2/23	†9/18	†1/23
Faciocervical region [‡]	4/19	10/24	6/20	8/23
High arched palate	3/18	8/23	4/18	7/23
Short neck	*1/19	*7/24	4/20	4/23

Denominators indicate the number of patients searched for each feature.

* $P < 0.05$ and † $P < 0.01$ by the Fisher's exact probability test.

‡ The ratio of patients with at least one feature of each category.

Presence of at least one of the following features: decreased carpal angle, metaphyseal lucency and/or epiphyseal hypoplasia at the ulnar side of the distal radius, and angulation of the distal radius and/or ulna.

¶ Lymphogenic gene indicates the gene involved in lymphatic development located between DMD and MAOA on Xp.

prevalence of spontaneous genital bleeding in Turner syndrome patients is higher than that of Madelung deformity (15%–20% vs 7.5%),^{8,14,15} which could be ascribed to relatively small amounts and slow tempo of gonadal estrogen production^{14,15}; and (3) estrogen treatment in Turner syndrome does not increase the prevalence of Madelung deformity because this therapy is usually started in late teens with a low dosage and for short periods.¹⁶

Of the skeletal features in the distal limb region, short metacarpals and cubitus valgus are frequently exhibited in those with Turner syndrome who have gonadal estrogen deficiency. These remain relatively infrequent in patients with SHOX haploinsufficiency who have normal gonadal function (Table 3). This may imply that such skeletal features are also caused by additional factors other than gonadal estrogens. One possibility would be a compressive effect of peripheral lymphedema resulting from haploinsufficiency of the lymphogenic gene (for lymphogenic gene, see below).¹⁷ In support of this, Noonan syndrome patients often have such skeletal features in the presence of peripheral lymphatic malformation.^{18,19}

FACIOCERVICAL SKELETAL FEATURES

Faciocervical skeletal features are occasionally manifested in patients with SHOX haploinsufficiency and normal karyotype (Table 3). In addition, short neck has been described in German subjects.^{6,13} This suggests that SHOX haploinsufficiency may also be relevant to the skeletal features in the faciocervical region of Turner syndrome patients. However, the prevalence of these features is apparently lower than that of limb skeletal features in patients with normal karyotype. Furthermore, the prevalence of faciocervical skeletal features is apparently lower in patients with normal

karyotype than in patients with Turner syndrome (Table 3). In particular, micrognathia occurs in approximately 60% of Turner syndrome females, but is rare in patients with normal karyotype.

In contrast, faciocervical skeletal features are frequently exhibited by females with Xp deletions involving SHOX. In this respect, the data are summarized as follows⁹: (1) the prevalence, especially that of short neck, is higher in females with large Xp deletions presumably missing the putative lymphogenic gene (see below) than in those with small Xp deletions presumably preserving that gene; and (2) the prevalence of high-arched palate is similar among females with and without spontaneous puberty, as is that of short neck (Table 2).

Relevance of the Lymphogenic Gene

Turner syndrome is associated with lymphatic hypoplasia.^{20,21} This postulates that a lymphogenic gene escaping X-inactivation may be shared by the X and the Y chromosome, and that haploinsufficiency of the gene results in lymphatic hypoplasia as a dominant phenotype. The lymphogenic gene has been mapped to an approximate 9-Mb region between DMD and MAOA on Xp and to an approximate 4-Mb region between PABY and DYS255 on Yp, by genotype-phenotype correlations.^{9,22}

Lymphatic hypoplasia leads to lymph fluid stasis, resulting in distension of the main and tributary lymphatic ducts and in lymphedema. Thus, a mechanical force would be exerted on tissues and organs adjacent to the lymphatic system. It is hypothesized that soft tissue and visceral stigmata are deformational consequences caused by the mechanical force of distended lymphatics and lymphedema.¹⁷ Indeed, it appears reasonable to assume that a distended cervical lymphatic system (cystic hygroma) leads to nuchal region anomalies such as webbed neck and low posterior hairline, and that peripheral lymphedema results in acral region anomalies such as puffy hands and feet and redundant skin.^{17,23} It also appears reasonable to postulate that cystic hygroma and distended thoracic and para-aortic lymphatic ducts compress the aortic arch and alter the cardiac hemodynamics, leading to cardiovascular anomalies such as aortic coarctation, and that distended

retroabdominal and iliac lymphatic ducts inhibit normal upward migration and rotation of the kidney, leading to renal malformations such as horseshoe kidney.^{17,24,25} It is notable that visceral anomalies in Turner syndrome are limited to the organs in the vicinity of the main lymphatics. Thus, characteristic soft tissue and visceral anomalies can be regarded as the result of a malformation sequence initiated by lymphatic hypoplasia.¹⁷

By analogy, it is inferred that cystic hygroma and facial edema exert a compressive effect on the developing faciocervical skeletal tissues primarily in the fetal life, facilitating the development of faciocervical skeletal features of SHOX haploinsufficiency. This notion implies that haploinsufficiency of the lymphogenic gene, rather than gonadal estrogens, is relevant to the development of faciocervical skeletal features. This hypothesis explains the difference in the prevalence of faciocervical skeletal features between patients with Turner syndrome and those with SHOX haploinsufficiency (Table 3). Furthermore, since lymphatic distension occurs in the peripheral areas including distal limb regions, this would contribute to the development of cubitus valgus and short metacarpals in Turner syndrome (Table 2).¹⁹

GROWTH PATTERNS

Patients With Normal Karyotype

Patients without overt LWD usually grow along the -2 SD growth curve throughout the growth period (Figure 2a).¹³ The magnitude of the height deficit is compatible with the previous estimation that loss of SHOX decreases the adult height by about 12 cm in the absence of overt LWD.²⁶ This difference in size approximates the magnitude of 2 SD of the adult height in the normal population. This implies that SHOX haploinsufficiency leads to short stature (<2 SD) in roughly half of patients without LWD (approximately 50% of penetrance). Indeed, normal stature has been described in several patients with SHOX haploinsufficiency.¹³ In this regard, since normal height has been observed in patients born to tall parents,¹³ this implies that statural growth in patients with SHOX haploinsufficiency is influenced by original height potential as represented by the parental height, as has been reported in Turner syndrome.²⁷ It

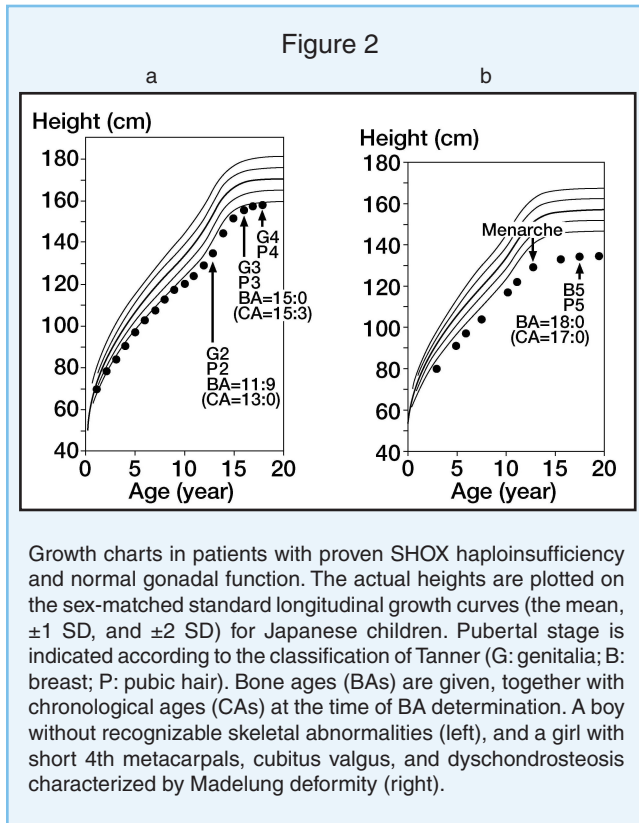
remains to be clarified, however, how SHOX haploinsufficiency causes the idiopathic short-stature phenotype.

Patients with overt LWD usually grow along the -2 SD growth curve before puberty, and show definite downward growth shift with puberty (Figure 2b).¹³ This type of growth pattern could be

Table 3. The prevalence of skeletal features

	SHOX haploinsufficiency (normal karyotype)	Turner syndrome (abnormal karyotype)
Distal limb region		
Short metacarpals, cubitus valgus	18%	40%
Madelung deformity, mesomelia	75%	7%
Faciocervical region		
Short neck	5%	40%
High arched palate	8%	35%
Micrognathia	0%	60%

Adopted from ref. 7, 8, and unpublished observations.



explained by assuming that prepubertal growth is relatively well preserved because of dormant gonadal function, whereas pubertal growth is compromised because of production of gonadal estrogens which facilitate growth plate fusion.¹³ The severely affected final height suggests that SHOX haploinsufficiency causes short adult height (< -2 SD) in most patients with overt LWD (probably approximately 70% of penetrance). Furthermore, consistent with the SHOX expression pattern, the longitudinal growth study of patients with SHOX haploinsufficiency and normal gonadal function showed that sitting height was fairly stable throughout the growth period, whereas leg length and arm span were compromised during puberty, thereby worsening mesomelic short stature.²⁸

Patients With Turner Syndrome

SHOX haploinsufficiency alone is unlikely to explain the growth failure and the growth pattern of 45,X Turner syndrome.^{2,13} In 45,X Turner syndrome, the mean adult height is about -3.2 SD below the mean of normal females, and the linear growth is associated with a reduced growth rate beginning in early childhood, in the absence of discernible LWD.^{2,29} It is noteworthy that 45,X is associated with a gross chromosome imbalance, which has been suggested to result in global developmental defects, including growth failure.^{30,31} Although 45,X Turner syndrome females usually have gonadal dysgenesis, gonadal estrogen deficiency is unlikely to influence adult height or childhood growth patterns.² Thus, the remaining

growth deficit and the reduced growth rate from early childhood in 45,X Turner syndrome appears to be due to chromosomal imbalance.

One may argue that severe short stature in Turner syndrome is contributed by loss of another growth gene(s) escaping X-inactivation. However, such a growth gene(s) other than SHOX is unlikely to exist on the X chromosome [for details, see Reference 2], although the possibility that a growth gene(s) escaping X-inactivation might exist on Xp has not been excluded.^{2,32} The adult height is similar between apparently non-mosaic Caucasian females with 45,X, those with 46,X,del(X)(p11), and those with 46,X,i(Xq);² this argues against the presence of a growth gene escaping X-inactivation on Xq.¹¹ Thus, the shorter mean adult height in patients with larger Xq deletions than in those with small Xq deletions is inexplicable without assuming the growth disadvantage of a chromosomal imbalance.² Similarly, the shorter mean adult height in patients with larger Xp deletions than in those with small Xp deletions would also be ascribed to the growth disadvantage of a chromosomal imbalance, rather than to loss of a growth gene on Xp escaping X-inactivation.² In addition, short stature in apparently non-mosaic Caucasian females with 46,X,idel(Xp) missing SHOX suggests that a growth gene escaping X-inactivation is absent from most of Xp.²

DIAGNOSTIC IMPLICATIONS

Prevalence

The prevalence of SHOX haploinsufficiency has been estimated to be approximately 2% in individuals with normal karyotype with the so-called idiopathic short-stature phenotype (< -2 SD).^{4,33,34} However, re-examination of such patients has frequently disclosed mild skeletal abnormalities such as decreased carpal angle, angulation of distal radius, tubular bone alterations, and brachymetacarpia.^{35,36} Furthermore, the prevalence should be different between sexes and ages, since normal skeletal features are predominantly exhibited in males of various ages and in prepubertal girls.^{7,13} Thus, further studies are necessary to estimate the sex- and age-specific prevalence of these alterations in the so-called idiopathic short-stature phenotype.

The prevalence of SHOX haploinsufficiency is 80% to 90% in patients with normal karyotype and LWD (reviewed in Reference 7), with the lowest value of 60%³⁷ and the highest value of 100%.³⁸ Although SHOX haploinsufficiency remains undetected in a small fraction of patients with LWD, it is unknown at this time whether LWD is a genetically heterozygous condition caused by a hitherto unknown autosomal gene(s), or if SHOX mutations reside in the unexamined regions, such as the promoter and enhancer sequences.

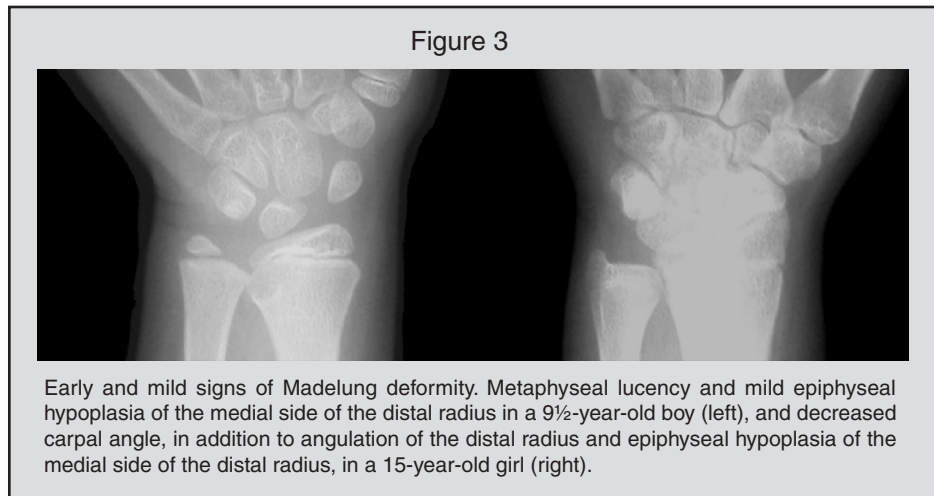
In contrast to LWD, SHOX haploinsufficiency is rarely found in normal karyotype patients with short metacarpals and/or cubitus valgus, but without LWD phenotype. To date, only 1 female has been identified with this pattern of phenotype.¹³ This would not be surprising, however, because short metacarpals and cubitus valgus appear to be highly heterogeneous conditions and could occur as a normal variant phenotype.

Clinical Indications

Phenotypic assessment in SHOX haploinsufficiency provides useful clues for the selection of normal karyotype patients to be studied for this condition. First, patients with LWD phenotype should be sought. In this context, of practical importance is to recognize the signs of Madelung deformity on hand and wrist radiographs that are almost invariably obtained for the bone age evaluation in children with short stature. For this purpose, it is recommended to carefully observe the signs of Madelung deformity, such as metaphyseal lucency and epiphyseal hypoplasia at the ulnar border of the distal radius, decreased carpal angle, angulation of the distal radius and ulna, and subluxation of the distal ulna.^{7,39,40} In our experience, the first signs of Madelung deformity are often exhibited by metaphyseal lucency and epiphyseal hypoplasia of the medial side of the distal radius in prepubertal patients, as well as by decreased carpal angle in pubertal or adult patients (Figure 3). When such findings are suspected, radiographs of the distal limbs should be obtained in order to search for characteristic features such as radial curvature and shortening. Second, SHOX haploinsufficiency should also be considered for patients with mesomelic short stature, which becomes evident in puberty. Third, familial members of a proband with SHOX haploinsufficiency should be studied irrespective of clinical phenotype. Indeed, familial studies have identified SHOX haploinsufficiency in subjects—especially males—with low-normal height alone.¹³

Molecular Diagnosis

Molecular studies are necessary to identify SHOX haploinsufficiency, especially in patients with normal karyotype. In this context, it is noteworthy that microdeletions involving SHOX are much more prevalent than intragenic SHOX mutations.⁷ The high prevalence of microdeletions would be consistent with repetitive sequences such as subtelomeric interspersed repeats being abundantly present around SHOX,⁴¹ because an unequal crossing over between homologous chromosomes or an intrachromosomal recombination is prone to occur in such a region.



Thus, it is recommended to search for a SHOX deletion first, and when SHOX deletion is excluded, an intragenic mutation should be investigated. For SHOX deletion analysis, fluorescence in situ hybridization is recommended because it unequivocally shows the presence or absence of SHOX. Microsatellite analysis for the CA repeat marker at the 3' region of SHOX is also useful because of its high heterozygosity (>90% in our experience), although parental DNA is necessary to confirm SHOX deletion. For SHOX mutational analysis, sequence analysis is essential. In this respect, denaturing high performance liquid chromatography analysis serves as a rapid and reliable screening method.

THERAPEUTIC IMPLICATIONS

Growth Hormone

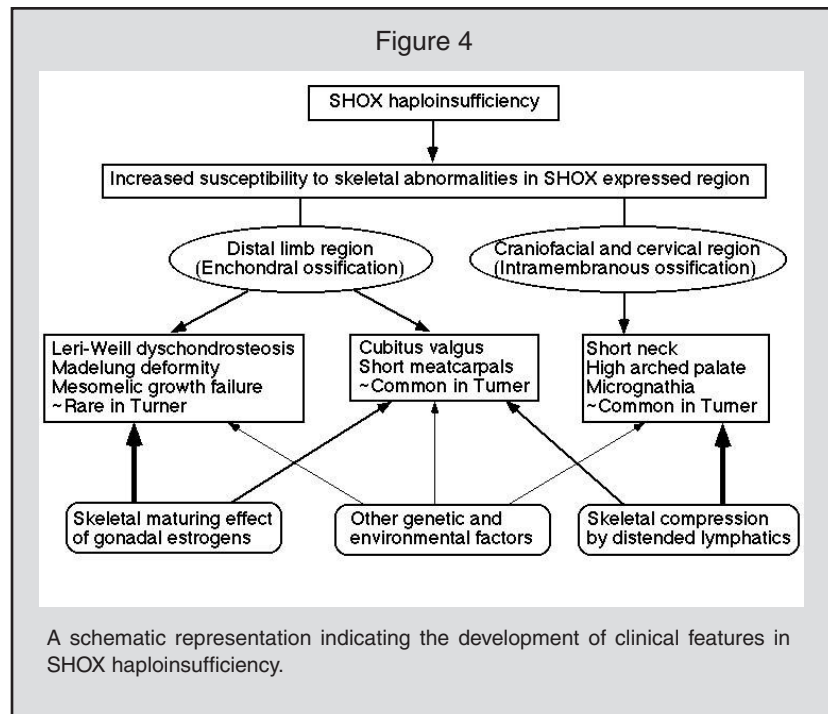
Growth hormone (GH) therapy may be advantageous in SHOX haploinsufficiency because it is effective in Turner syndrome, despite the absence of GH deficiency. Indeed, beneficial short-term effects have been reported in several patients.^{33,42,43} However, GH therapy might facilitate the development of skeletal anomalies by accelerating distorted skeletal growth resulting from unbalanced premature fusion, or by stimulating gonadal development and resultant estrogen production.⁴² Therefore, careful follow-up is required for GH therapy in SHOX haploinsufficiency.

Gonadotropin-Releasing Hormone Analog

Gonadotropin-releasing hormone analog (GnRHa) therapy is expected to serve as prevention or mitigation of the development of skeletal features by suppressing gonadal estrogen production.⁴² However, GnRHa therapy has performed poorly in SHOX haploinsufficiency, so that the adequate timing to start and stop the GnRHa therapy is unknown. At present, it may be recommended to attempt GnRHa treatment in an experimental protocol for early maturing girls or in patients with early signs of Madelung deformity, possibly in combination with GH.

SUMMARY AND SPECULATION

Clinical studies have indicated that SHOX haploinsufficiency is responsible for not only short stature but also Turner syndrome skeletal features and LWD. The expressivity of SHOX haploinsufficiency in the limb and faciocervical regions is primarily influenced by gonadal function status and the presence or absence of the lymphogenic gene, respectively (Figure 4). In this context, although phenotypic spectrum in diseases resulting from haploinsufficiency of transcription factor genes is known to range widely from nearly normal to severely affected phenotypes⁴⁴ (a list of haploinsufficiency is given in Reference 45), the underlying factor(s) for clinical diversity remains unknown in nearly all such diseases. Thus, SHOX appears to be the first gene in which modifying factors for haploinsufficient status have been identified.



Finally, two points should be made with respect to SHOX. First, a gene(s) that controls SHOX expression is unknown, as is that controlled by SHOX. Identification of such upstream and downstream genes should serve to facilitate an understanding of the molecular network of human growth. Second, it has been shown that SHOX overdose in association with gonadal dysgenesis constitutes a novel clinical entity leading to tall stature at pubertal age in normal children.⁷ Because gonadal estrogen production can be suppressed by GnRHa therapy, this may argue for the possibility of a SHOX gene therapy in patients with growth failure. Further accumulation of clinical and molecular data will provide better clues for the diagnosis and management of SHOX haploinsufficiency.

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