SHOX Haploinsufficiency as a Cause of Syndromic and Nonsyndromic Short Stature

Maki Fukami\textsuperscript{a}  Atsuhito Seki\textsuperscript{b}  Tsutomu Ogata\textsuperscript{a,c}

\textsuperscript{a}Department of Molecular Endocrinology, National Research Institute for Child Health and Development,  
\textsuperscript{b}Department of Orthopedic Surgery, National Center for Child Health and Development, Tokyo, and  
\textsuperscript{c}Department of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Japan

In 1997, \textit{SHOX} was reported as the causative gene for short stature in Turner syndrome [Rao et al., 1997]. Subsequently, heterozygous mutations of \textit{SHOX} have been identified in patients with nonsyndromic short stature (idiopathic short stature, ISS) and Léri-Weill dyschondrosteosis (LWD) [Rao et al., 1997; Belin et al., 1998; Shears et al., 1998; Rappold et al., 2002]. Furthermore, \textit{SHOX} abnormalities have been associated with various skeletal features of Turner syndrome such as scoliosis, high-arched palate, and micrognathia [Kosho et al., 1999; Binder, 2011]. Genetic defects leading to \textit{SHOX} haploinsufficiency include intragenic mutations and deletions as well as copy number variations (CNVs) in the gene-flanking regions that possibly affect \textit{cis}-regulatory machinery.

This article provides an overview of the current understanding of \textit{SHOX}.

\textbf{The \textit{SHOX} Gene}

\textit{SHOX} is located in the short arm pseudoautosomal region (PAR1) of sex chromosomes is one of the major growth genes in humans. \textit{SHOX} haploinsufficiency results in idiopathic short stature and Léri-Weill dyschondrosteosis and is associated with the short stature of patients with Turner syndrome. The \textit{SHOX} protein likely controls chondrocyte apoptosis by regulating multiple target genes including \textit{BNP}, \textit{Fgfr3}, \textit{Agc1}, and \textit{Ctgf}. \textit{SHOX} haploinsufficiency frequently results from deletions and duplications in PAR1 involving \textit{SHOX} exons and/or the \textit{cis}-acting enhancers, while exonic point mutations account for a small percentage of cases. The clinical severity of \textit{SHOX} haploinsufficiency reflects hormonal conditions rather than mutation types. Growth hormone treatment seems to be beneficial for cases with \textit{SHOX} haploinsufficiency, although the long-term outcomes of this therapy require confirmation. Future challenges in \textit{SHOX} research include elucidating its precise function in the developing limbs, identifying additional \textit{cis}-acting enhancers, and determining optimal therapeutic strategies for patients.
**Fig. 1.** Genomic structure of SHOX and its putative enhancer regions. SHOX (red box) is located in PAR1 of sex chromosomes. Previous studies identified 7 highly evolutionarily conserved noncoding DNA elements (CNEs) with cis-regulatory activity (blue boxes). These elements were designated as CNE-5, -3, -2, 4, 5, and 9 [Chen et al., 2009; Durand et al., 2010]; evolutionarily conserved region (ECR) 1 [Benito-Sanz et al., 2012b]; and evolutionarily conserved sequence (ECS) 4 [Fukami et al., 2006]. The horizontal line indicates the physical distance from the Xp/Yp telomere (hg 19, build 37).

**Fig. 2.** A, B Structural comparison among SHOXa, SHOX2a, and SHOXb. All of these proteins contain a homeodomain, while an OAR domain is present only in SHOXa and SHOX2a.
present in 2 active forms in both males and females [Rao et al., 1997]. SHOX is expressed in the developing limbs and pharyngeal arches in human embryos and likely regulates differentiation and proliferation of chondrocytes [Clement-Jones et al., 2000]. Loss-of-function mutations of SHOX affect skeletal growth in a dose-dependent manner.

SHOX haploinsufficiency underlies the short stature of Turner syndrome patients and is associated with ISS and LWD. SHOX haploinsufficiency is estimated to account for 2–3% of ISS cases and ~70% of LWD cases. Although the frequency of SHOX mutations and deletions in previously reported ISS and LWD cases varied from 1.5 to 16.9% and from 33.9 to 100%, respectively (table 1), this may reflect the differences in methods of mutation screening and inclusion criteria of participants. SHOX nullizygosity leads to Langer mesomelic dysplasia, an extremely rare condition characterized by severe short stature and skeletal deformity [Shears et al., 2002; Zinn et al., 2002]. Thus, SHOX is one of the major growth genes in humans. Although SHOX is located in the sex chromosomes, SHOX haploinsufficiency follows an autosomal dominant inheritance pattern. This phenomenon is defined as pseudoautosomal dominant inheritance [Shears et al., 2002]. Kant et al. [2011] demonstrated that heterozygous SHOX mutations can be transferred from the Y chromosome to the X chromosome and vice versa (‘the jumping SHOX gene’). Overdosage of SHOX has been implicated in the tall stature of individuals with 47,XXY (Klinefelter syndrome) or 47,XXX karyotypes (triple-X syndrome). Furthermore, trisomy of PAR1 involving SHOX was observed in a female with tall stature [Ogata et al., 2001a, Table 1. Frequency of SHOX abnormalities in patients with idiopathic short stature, bilateral Madelung deformity, or LWD

<table>
<thead>
<tr>
<th>Report</th>
<th>Methods for mutation screening</th>
<th>Ethnic origin</th>
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</thead>
<tbody>
<tr>
<td>Binder et al. [2000]</td>
<td>SSCP and microsatellite genotyping</td>
<td>not described</td>
<td>ISS</td>
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<td>Japanese, German, Greek</td>
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<td>Schneider et al. [2005]</td>
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<td>40/118 (33.9)</td>
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<td>LWD</td>
<td>42/56 (75.0)</td>
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<td>SNP/microsatellite genotyping and MLPA</td>
<td>Spanish</td>
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<td>Chen et al. [2009]</td>
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<td>ISS</td>
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BMD = Bilateral Madelung deformity; DSS = disproportionate short stature; ISS = idiopathic short stature; SSCP = single-strand conformation polymorphism. Percentages are given in parentheses.

a This patient cohort included both proportionate and disproportionate short stature. b This study focused on copy number gain of SHOX. c This study focused on SHOX downstream deletion.
the precise function of structures share significant similarity (fig. 2). Although 3 [Blaschke et al., 1998]. SHOX2 and SHOX protein manifested no remarkable phenotypes, possibly because Col2a1 SHOX [Marchini et al., 2007; Decker et al., 2011]. In addition, SHOX interacts with the SOX trio [Marchini et al., 2007; Decker et al., 2011]. Alternative- ly, SHOXb may compete with SHOXa cofactors such as SOX5 or SOX6, as suggested for SHOXa and b [Aza-Carmona et al., 2014].

**Molecular Basis of SHOX Haploinsufficiency**

Previously reported SHOX abnormalities included various missense and nonsense mutations as well as nucleotide insertions or deletions in the coding exons 2–6a [Niesler et al., 2007; Binder, 2011]. These nucleotide alterations are listed in the SHOX mutation database (http://grenada.lumc.nl/LOVD2/MR/home.php?select_db=SHOX) [Niesler et al., 2007]. Known pathogenic SHOX mutations are widely distributed in exons 2–6a without hotspots [Binder, 2011]. Although a few nucleotide changes in exon 6b have been submitted to the database, the clinical significance of these substitutions is unclear. Indeed, SHOX isoform b encoded by exons 1–6b lacks a functionally important OAR domain and is therefore likely to be a nonfunctioning protein [Rao et al., 1997]. However, it is possible that the SHOXb isoform affects skeletal growth by regulating mRNA levels of the major SHOXa isoform [Durand et al., 2011]. Alternatively, SHOXb may compete with SHOXa cofactors such as SOX5 or SOX6, as suggested for SHOXa and b [Aza-Carmona et al., 2014].

**SHOX haploinsufficiency** is more frequently caused by CNVs than point mutations [Benito-Sanz et al., 2005, 2006, 2011, 2012a, b; Fukami et al., 2008; Chen et al., 2009; Rosilio et al., 2012]. Various submicroscopic microdeletions in PAR1 involving SHOX exons and/or its flanking regions have been identified in ISS and LWD patients. In particular, microdeletions in the SHOX downstream region have been reported as the most common genetic defects in LWD patients of Spanish origin [Benito-Sanz et al., 2006]. Microdeletions in PAR1 leading to LWD and ISS are predicted to affect exons and/or cis-acting enhancer elements of SHOX. Since monoallelic SHOX expression was confirmed in the skeletal tissues of a patient with a downstream deletion [Flanagan et al., 2002], elimination of SHOX enhancers seems to be sufficient to abolish gene expression. Although the actual positions of the upstream and downstream enhancers of SHOX have yet to be determined, they are likely located within highly conserved noncoding DNA elements (CNEs) around the gene because cis-acting enhancers are usually conserved among species [Pennacchio et al., 2006]. To date, 7 CNEs with in vitro or in vivo cis-regulatory activity have been...
identified in PAR1: 3 in the SHOX upstream region and 4 in the downstream region (fig. 1) [Fukami et al., 2006; Chen et al., 2009; Durand et al., 2010; Benito-Sanz et al., 2012b]. These CNEs are predicted to contain SHOX enhancers. Indeed, physical interaction between the CNEs and SHOX has been indicated by in vitro 3C assays [Benito-Sanz et al., 2012b; Verdin et al., 2015] and by in vivo assays using zebrafish [Kenyon et al., 2011]. Furthermore, since microdeletions in the far downstream region of known CNEs have recently been identified in patients with LWD-compatible skeletal features and/or short stature [Bunyan et al., 2014; Sandoval et al., 2014; Fukami et al., 2015], there may be a hitherto unidentified cis-acting element(s) of SHOX. In vitro assays have suggested that SHOX transcription could be regulated by multiple cis-acting elements distributed in a >1-Mb region in PAR1 [Verdin et al., 2015].

Recently, a few submicroscopic PAR1 microduplications were identified in patients with ISS and LWD [Iughetti et al., 2010; Benito-Sanz et al., 2011; Fukami et al., 2015]. This finding argues against the previous notion that SHOX overdosage underlies tall stature in individuals with Klinefelter syndrome and 47,XXX females. These apparently conflicting results can be reconciled by assuming that relatively large duplications involving all SHOX exons and cis-acting enhancers result in SHOX overexpression, while small duplications encompassing only some of these components may reduce SHOX expression levels by disrupting the cis-regulatory machinery [Fukami et al., 2015]. However, since microduplications around SHOX have also been identified in several individuals with normal stature [Benito-Sanz et al., 2011; Fukami et al., 2015], the pathogenicity of these CNVs needs to be confirmed in future studies. It is possible that the clinical consequence of each PAR1-linked duplication is determined by its genomic position and structure.

Characterization of the breakpoints of some PAR1-linked deletions suggested that nonallelic homologous recombination and nonhomologous end-joining play a role in the development of these CNVs [Fukami et al., 2006; Benito-Sanz et al., 2012b]. Likewise, the breakpoints of one duplication have been characterized, showing that this CNV was a tandem duplication mediated by Alu repeats [Fukami et al., 2015]. Notably, PAR1 is enriched with Alu repeats [Blaschke and Rappold, 2006], which may underlie the high frequency of CNVs in this region. Moreover, the high recombination rate of PAR1 during spermatogenesis may also be associated with the high frequency of PAR1-linked CNVs. Indeed, the average of the recombination rate in PAR1 during male meiosis is ~17 times higher than the average of the genome [Hinch et al., 2014]. While there were no breakpoint hotspots, a 47.5-kb deletion in the SHOX downstream region was repeatedly identified in English and Scandinavian patients and ascribed to a founder effect [Bunyan et al., 2013].

SHOX abnormalities were absent in about 20% of LWD patients (table 1), and the genetic defects of these cases remained unknown until recently. Hisado-Oliva et al. [2015] demonstrated that heterozygous mutations in NPR2, a causative gene for Maroteaux-type acromesomelic dysplasia, result in LWD-like phenotypes. These findings provide the first indication of the locus heterogeneity for LWD. Thus, mutation analysis of NPR2 should be considered for ISS/LWD patients without SHOX abnormalities.

Clinical Manifestations of Patients with SHOX Haploinsufficiency

Patients with SHOX haploinsufficiency usually present with mesomelic short stature. In most cases, head circumferences and sitting height are within the normal range, while arm span is decreased and sitting height/height ratio is increased [Rappold et al., 2007; Binder, 2011; Malaquias et al., 2013]. Although apparent mesomelia can be absent in patients with SHOX haploinsufficiency, axiological examinations detect body disproportion in most patients [Rappold et al., 2007; Binder, 2011]. Longitudinal follow-up studies of female patients with SHOX haploinsufficiency showed that body disproportion often deteriorates during puberty [Fukami et al., 2003, 2004].

Growth failure in patients with SHOX haploinsufficiency usually occurs from the first years of age [Binder et al., 2004]. The mean adult height of ISS patients with SHOX haploinsufficiency and normal karyotype is around ~2.2 SD, although growth failure can be more severe in patients with LWD phenotypes [Binder, 2011]. Thus, the mean growth deficit of SHOX haploinsufficiency is estimated to be ~12 cm. This suggests that SHOX haploinsufficiency does not necessarily cause clinically discernible short stature. Consistent with this, SHOX haploinsufficiency has been identified in several individuals with normal stature. Since the mean adult height of females with Turner syndrome is about ~3.2 SD, it appears that SHOX deficiency accounts for most but not all of the short stature in Turner patients.

The most characteristic clinical feature of SHOX haploinsufficiency is Madelung deformity (fig. 3). Madelung
deformity is a combination of anatomical changes in the wrist consisting of bowing and shortening of the radius, prominence of the ulnar head, and palmar and ulnar deviation of the carpal bones (fig. 3) [Binder et al., 2001; Schmidt-Rohlfing et al., 2001]. Madelung deformity can be radiologically diagnosed by the absence or narrowing of the ulnar portion of the distal radial physis, anterior bowing of the radial shaft, and dorsal subluxation of the ulnar head (fig. 3). Histopathological analysis showed a disturbed columnar arrangement of chondrocytes in the growth plate, where tandem stacking of chondrocytes was replaced by a side-by-side arrangement [Munns et al., 2001]. Furthermore, abnormal enchondral ossification was indicated by hypertrophic osteoid in the radial metaphysis. The primary lesion of Madelung deformity appears to be the premature fusion of the distal radial epiphysis, which possibly results from an aberrant cell death process in the growth plate [Seki et al., 2014]. An aberrant ligament tethering the lunate to the distal portion of the radius was found in patients with Madelung deformity [Vickers and Nielsen, 1992; Harley et al., 2006; Steinman et al., 2013; Seki et al., 2014]. This ‘Vickers ligament’ likely compresses the distal epiphysis of the radius and further disturbs its linear growth. This ligament is predicted to develop under an aberrant mechanical force due to asymmetrical growth of the radius and ulna. Notably, although Madelung deformity is a characteristic feature of LWD, it can also occur in association with other disorders such as multiple exostoses syndrome, multiple epiphyseal dysplasia, mucopolysaccharidosis, pseudohypoparathyroidism type 1b, and injury.

The severity of skeletal changes of SHOX haploinsufficiency is variable among patients and tends to be more severe in females than in males [Kosho et al., 1999; Binder, 2011]. While adult female patients often present with LWD, adult male patients and children usually exhibit ISS or only mild Madelung deformity. Relatively severe manifestations in adult females can be explained by the effect of gonadal estrogens. Since estrogens are known to enhance the fusion of growth plates in healthy males and females, they may accelerate premature epiphyseal fusion in individuals with SHOX haploinsufficiency. A relatively low frequency of LWD in Turner patients despite SHOX deficiency is consistent with attenuated estrogen production in these individuals.

Soucek et al. [2013] investigated bone mineral density and bone geometry in prepubertal patients with SHOX haploinsufficiency. They found a significantly increased total bone area, decreased relative cortical bone area, and a thin cortex. A possible interpretation of these findings is that the total bone area was increased to maintain the bone strength under the presence of mechanical loading. Similar findings were observed in prepubertal Turner patients, suggesting that SHOX plays a major role in bone geometrical changes of Turner syndrome.

SHOX haploinsufficiency is associated with additional clinical features [Rappold et al., 2007; Binder, 2011]. Of these, muscular hypertrophy in the lower limbs is of clinical importance because it has been reported in about one-third of SHOX-deficient patients [Rappold et al., 2007]. In addition, skeletal features of Turner syndrome, such as scoliosis, high-arched palate, short metacarpals, and micrognathia, were shared by a certain percentage of patients with SHOX haploinsufficiency and a normal karyotype [Rappold et al., 2007; Binder, 2011; Rosilio et al., 2012].

Genotype-Phenotype Correlation

The phenotypic severity of individuals with SHOX haploinsufficiency does not reflect the mutation types [Binder et al., 2004]. In fact, identical SHOX abnormalities have been detected in patients with ISS and LWD and
in individuals with normal stature. Furthermore, no apparent phenotypic differences were reported between patients with missense mutations and those with nonsense or frameshift mutations [Binder et al., 2004]. Since the clinical manifestation of \textit{SHOX} haploinsufficiency is usually more severe in adult female patients than in adult male and prepubertal patients, hormonal conditions rather than mutation types seem to determine the clinical consequences of \textit{SHOX} haploinsufficiency. On the other hand, Rosilio et al. [2012] suggested that CNVs involving only the downstream enhancer regions lead to slightly milder phenotypes than mutations or deletions in the exons. \textit{SHOX} downstream deletions may be associated with a broad clinical spectrum because Chen et al. [2009] documented a prominent phenotype in patients with such deletions. Furthermore, Donze et al. [2015] reported that patients with enhancer deletions were equally short as those with \textit{SHOX} intragenic defects but were less disproportionate and showed better responses to growth hormone (GH) therapy. Benito-Sanz et al. [2011] suggested that \textit{SHOX} duplications are often associated with relatively mild phenotypes. These findings suggest that there may be some phenotypic difference between \textit{SHOX} exonic mutations/deletions and enhancer abnormalities.

\textbf{Diagnosis of \textit{SHOX} Abnormalities}

\textit{SHOX} haploinsufficiency can be diagnosed by the presence of Madelung deformity and mesomelic short stature, although these features are shared by only a certain percentage of the patients. A family history of autosomal dominant short stature supports the diagnosis of \textit{SHOX} haploinsufficiency. Malaquias et al. [2013] demonstrated that body disproportion is a useful indicator of \textit{SHOX} haploinsufficiency. Rappold et al. [2007] developed a scoring system for identification of the appropriate subjects for \textit{SHOX} genetic testing. Score items of the system included arm span/height ratio, sitting height/height ratio, body mass index, cubitus valgus, short forearm, bowing of the forearm, muscular hypertrophy, and dislocation of the ulna.

Molecular analysis is useful to confirm the diagnosis of \textit{SHOX} haploinsufficiency. Since \textit{SHOX} haploinsufficiency is more frequently caused by submicroscopic CNVs than exonic point mutations, copy number analysis should be the first approach for molecular diagnosis. Multiplex ligation-dependent probe amplification (MLPA; MRC Holland, Amsterdam, The Netherlands) is frequently used for the initial screening of \textit{SHOX} abnormalities (table 1) because it allows detection of copy number gains and losses of \textit{SHOX} exons and the CNEs in a single assay. Array CGH is frequently used to confirm and characterize the CNVs identified by MLPA. Mutation analysis of the \textit{SHOX}-coding region should be performed for patients without pathogenic CNVs. The \textit{SHOX} mutation database is useful to assess the pathogenicity of missense mutations.

\textbf{Treatment of Patients with \textit{SHOX} Abnormalities}

To date, management protocols for patients with \textit{SHOX} haploinsufficiency have not been fully established. GH treatment has successfully improved growth velocity in several patients [Blum et al., 2013; Wit and Oostdijk, 2015]. The effects of GH on stature growth were comparable between patients with \textit{SHOX} haploinsufficiency and those with Turner syndrome [Blum et al., 2013]. However, long-term outcomes of GH treatment need to be evaluated in future studies. Since Donze et al. [2015] reported that GH treatment was more effective in patients with enhancer deletions than in those with intragenic abnormalities, patients should be classified according to their mutation types. In addition, while Ogata et al. [2001b] suggested that gonadal suppression therapy may be useful to prevent the development of Madelung deformity in female patients, the outcome of this therapy remains to be investigated.

Surgical interventions have been carried out to reduce pain or improve wrist function in a few cases with severe Madelung deformity. In addition, previous studies suggested that surgical removal of the Vickers ligament in combination with dome osteotomy may benefit patients with Madelung deformity [Vickers and Nielsen, 1992; Harley et al., 2006; Steinman et al., 2013; Seki et al., 2014]. However, an optimal surgical procedure for Madelung deformity has yet to be determined.

\textbf{Conclusions}

\textit{SHOX} is one of the major growth genes in humans, and its haploinsufficiency underlies syndromic and non-syndromic short stature. \textit{SHOX} haploinsufficiency represents a unique pseudoautosomal dominant disorder that mainly results from submicroscopic CNVs in PAR1. Future challenges in \textit{SHOX} research include elucidation of its precise role in the developing limbs, identification of further \textit{cis}-acting enhancers, and the development of optimal therapeutic strategies for patients.
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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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SHOX and Short Stature

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