Review Article

The Current Knowledge and Treatment of SHOX Deficiency

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ABSTRACT

One of the most common genetic causes of short stature is the haploinsufficiency of the Short-stature Homeobox (SHOX) gene. In this group of SHOX-related disorders, SHOX deficiency is one of the most severe forms, resulting from the loss of function of one SHOX allele. This literature review discusses the current knowledge of SHOX deficiency, including its manifestation, diagnosis, major symptoms, and treatments. It is estimated that SHOX deficiency is responsible for about 6.8% of individuals with short stature-related diseases. The use of Recombinant Human Growth Hormones (rhGH) to alleviate growth impairment has been proven effective in treating prepubertal patients who begin therapy at a young age. An Italian study on adolescents with SHOX deficiency discovered that rhGH therapy yielded an overall height gain of +0.80 ±0.98 standard deviation score (SDS) from the start of treatment to the attainment of final height, with a duration of 5.94 ± 2.00 years. However, the often mild and complex symptoms in prepubertal patients make early diagnosis challenging, and treatment occurring after the onset of puberty can limit the positive growth effects of this therapy. This review also analyzes alternative treatment options to rhGH therapy, including the use of Gonadotropin-releasing hormone agonists (GnRHa) as a way to slow down puberty progression. However, studies on the effectiveness of GnRHa remain inconclusive. Lastly, this review evaluates the potential role of the emerging CRISPR-Cas9 gene-editing technology, and emphasizes the importance of and need for continued research into new methods for early diagnosis.

Keywords: SHOX deficiency; SHOX haploinsufficiency; Short-stature; Growth Hormones; Gonadotropin-releasing hormone agonist; CRISPR-Cas 9

INTRODUCTION

The growth and bone development of humans is a complex process controlled by hundreds of identified genes. As a result, causing a large number of possible mutations can impair this irreversible process (1). The many possible causes of short stature include genetic disorders, endocrine diseases resulting from hormone imbalances and response issues, and even simply manifesting from having early or late puberty or having a short family history (1). The most common cause of short stature from a specific gene is loss of function related to the short-stature homeobox gene, or SHOX gene. Of all SHOX-related disorders, SHOX deficiency is one of the most common and severe (2).

These numerous possible factors affecting growth and development in humans make diagnosis and, subsequently, treatment of SHOX growth disorders arduous. Furthermore, limited available treatments, the high cost of treatment, the risk of side effects, and questions looming about therapeutic efficacy make

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treating SHOX deficiency even more difficult. As such, new therapeutic options need to be uncovered urgently. The most promising of these therapies include an emerging gene-editing technology known as CRISPR, whose success in treating certain cancers in human beings and many other disorders in animals makes it a possible future theoretical option for treating SHOX deficiency.

Therefore, this literature review will mainly focus on the SHOX gene, more specifically, SHOX deficiency, how it is diagnosed, the current treatment options, and how an emerging and revolutionary therapy, CRISPR, could theoretically be used in treating SHOX deficiency.

SHOX GENE

The SHOX gene plays an essential part in human skeletal growth and in the growth and maturation of the arms and legs (3). The SHOX gene is known as a transcription factor, as its proteins are responsible for providing instructions that regulate the activities and roles of other growth-related genes. Copies of this vital gene are located in both the X and Y chromosomes of the 23rd pair in a region known as the pseudoautosomal region (Figure 1) (4). The significance of the SHOX gene can also be seen in that the most common short-stature-causing disorders arise from mutations in this transcription gene. These common disorders include Langer mesomelic dysplasia, where both copies of the SHOX allele are damaged (homozygous, more severe); Léri-Weill dyschondrosteosis (LWD), where one copy is damaged (heterozygous, less severe); Mayer-Rokitansky-Küster-Hauser syndrome; Turner syndrome; and SHOX Deficiency, less severe than LWD and also may occur when damages to one allele of the SHOX gene is observed. Most of these disorders are caused by deletions in the SHOX gene, causing a significant loss of function in growth-related cell activities. The loss of function related to this gene has been identified to cause around 12-15% of all short-stature in humans (2). While all SHOX-gene-related deficiencies have been shown to lead to a lower projected height for the infected individual, SHOX deficiency is one of the most severe of this group of mutations. The rest of this paper will focus more specifically on SHOX deficiency.

SHOX DEFICIENCY

SHOX deficiency is one of the most significant disorders associated with the haploinsufficiency of the SHOX gene, where one copy of the allele is either completely lost or is too damaged to carry out its normal function (2). Overall, SHOX deficiency most often mildly impairs prepubertal growth, sometimes causing only mild and clinically unrecognizable reductions in height. This is usually accompanied by a significant growth impairment during puberty caused by premature growth plate fusion. This growth plate closure is caused by one of the more severe skeletal abnormalities associated with SHOX deficiency, Madelung deformity, which further deteriorates during puberty (2). While a lot is still unknown, this deterioration is a condition causing earlier bone maturation in some bones in the hand and wrist. This rapid maturation is believed to be the cause of the combined effects of SHOX haploinsufficiency and increased estrogen exposure during puberty. The accelerated maturation of these bones in the hand causes a much earlier fusion of the growth plates, which, once closed, prevent any further

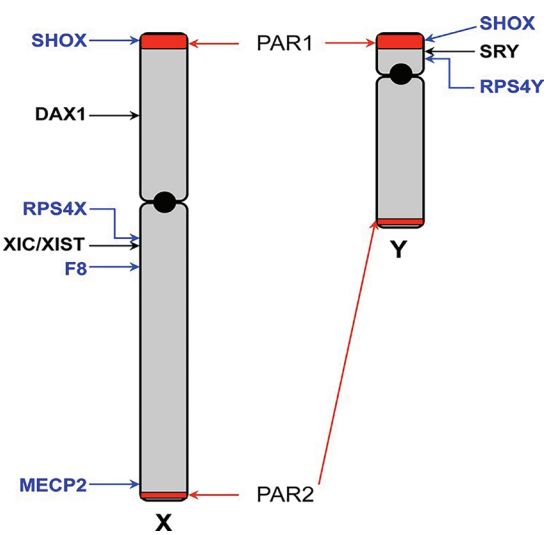

Figure 1. Schematic map of the X and Y chromosomes (4). This figure shows a schematic map of the X and Y chromosomes, highlighting the pseudoautosomal regions (PAR1 and PAR2) in red. The SHOX gene is located within PAR1 on both the X and Y chromosomes. Because PAR1 is shared between X and Y, SHOX is present in two active copies in both males and females and escapes X-inactivation. This unique positioning, where SHOX is present in both X and Y chromosomes, explains why the loss of one SHOX copy, known as SHOX haploinsufficiency, leads to disorders such as SHOX deficiency, Léri-Weill dyschondrosteosis, Langer mesomelic dysplasia, and Turner syndrome.

growth. On the other hand, growth impairment during pre-puberty is due to failures in regulating chondrocyte differentiation and proliferation, which play a major role in bone and cartilage development, a cause for impaired growth and bone age delay. As such, while patients with SHOX deficiency often have a bone age delay prior to puberty, certain bones in the wrist and hand, regions known to have uneven bone maturations, will accelerate rapidly, causing this premature growth plate fusion.

In addition, the two main types of mutations in the SHOX alleles known to cause SHOX mutations are deletions ranging from the entire gene to deletions in the enhancer regions, which make up around 80% of all mutations, and deletions in the SHOX exons, which are mostly responsible for coding proteins and make up around 5% of SHOX mutations (2). Nonetheless, the clinical spectrum of SHOX deficiency is unknown and can vary greatly; hence, it can only be narrowed down to simply short stature, as some of the other symptoms are not always present or can be unnoticeable in minor cases. The correlation between the two main types of deletions is also seemingly nonexistent, although there might be a slight difference in how specific treatments respond to them (2). SHOX deficiency is also known to cause skeletal abnormalities, including shorter arm spans and a lower sitting-down-to-standing-up ratio (5). It is estimated that SHOX deficiency is responsible for around 6.8% of all individuals with short stature-related diseases and mutations (6).

SHOX deficiency has also been shown to be significantly more prevalent and severe in females, partially due to the fact that mutations in the SHOX (X) gene have shown to be more common than deletions in the SHOX (Y) gene (5).

DIAGNOSIS

Since many of the symptoms of SHOX deficiency are at their mildest before puberty and often only become noticeable after the patient has entered puberty, diagnosing SHOX deficiency can be very challenging. However, early detection is also essential for a child to get the proper care, as once puberty begins, there is not much time left, usually a couple of years, until their growth plates permanently close. Studies have shown that a minimum of around a -1.5 standard deviation score can be used to indicate a mutation causing short stature (6). Standard deviation score (SDS) is a metric that, in terms of height, is able to combine the height of the individual, their age, and sex into one score. It is measured by actual height - average height for children of the same sex and age ÷ standard deviation of the heights for children of the same sex and age. In addition, many other clinical tests have been developed to help identify if a child should be tested for SHOX deficiency, which requires a DNA sequence analysis: usually in the form of a blood test.

These clinical tests include the presence of certain dysmorphisms and skeletal dysplasia, such as shorter arm span proportions and a lower sitting-down-to-standing-up height ratio. Specifically, a study done by Genoni et al. [2017] calculated the following scores proposing: an arm span-to-height ratio of

<96.5%, a sitting height-to-height ratio of >55.5%, muscular hypertrophy, and shorter forearms (6). However, this data can sometimes be unreliable since skeletal proportions are less noticeable and more sensitive in younger children. Even DNA sequence analysis has not shown a genotype-phenotype correlation in SHOX deficiency, where different mutations and deletions can be correlated with different symptoms. Instead, it seems the effects of SHOX haploinsufficiency vary significantly with no connections. Indeed, early diagnosis is essential for treatment to be effective, and more detailed and accurate diagnoses need to be developed.

TREATMENT

Currently, there are few clinically approved and effective therapies available for the treatment of SHOX haploinsufficiency. The most common and most widely used treatment, as approved by the Food and Drug Administration (FDA) and the European Food and Safety Authority (EFSA), is Growth Hormones (GH), which have proven to be an effective method of minimizing the growth-compromising effects of SHOX deficiency. While GH therapy has certainly been proven effective in treating SHOX deficiency patients, especially when started before puberty, its therapeutic effects can be significantly compromised by the greatly accelerated growth plate fusion many patients experience during puberty, leaving patients who were diagnosed with SHOX deficiency after the onset of puberty with few effective therapeutic options (7). To attenuate this premature growth arrest, some doctors and medical scientists have tested the use of Gonadotropin-releasing hormone agonist (GnRHa) on individuals with idiopathic short stature. The clinical

use of GnRHa in patients with SHOX deficiency is to suppress and slow down puberty, allowing for more time before growth plate closure while also using GH treatment to improve linear growth (8). However, only limited research and testing have been done on this topic, most of which have had small sample sizes, are often uncontrolled, and are often generalized on individuals with short stature rather than individual deficiencies (9). Both therapies have drawbacks though. For GnRHa, the physiological effects of postponing puberty are unknown and may include increased mood swings and anxiety. The side effects and rhGH, while milder than GnRHa, may still be linked to increase risk of cancers and diabetes for those already at high risk (10). Furthermore, both therapies are expensive, invasive, and, by nature, are not equally effective in all patients. For these reasons, studying the theoretical use of an emerging gene-editing technology known as CRISPR is necessary; its success in treating certain cancers in human beings and many other disorders in animals makes it a possible future theoretical option for treating SHOX deficiency.

Recombinant human Growth Hormones

Recombinant human Growth Hormones (rhGH) work by improving bone age delay and by stimulating growth. Many studies have shown this artificial growth hormone therapy to be both effective and safe for both short-term and long-term usage. For instance, in one Italian study, patients with SHOX deficiency and an average growth impairment of -2.37 ± 0.67 SDS and a bone age to chronological age delay of –1.07 ± 1.09 years started Growth Hormone treatment at ages 8.67 ± 3.33 years at a dose of 0.23 ± 0.04 mg/kg/week (11). With GH therapy lasting 5.94 ± 2.00 years and ranging from 1.25-11.30 years in duration, an overall height gain of + 0.80 ± 0.98 SDS from the beginning of treatment to achievement of final height. Bone age also gradually caught up to chronological age during the course of treatment for prepubertal patients, although further bone age complications will appear during puberty as a result of Madelung deformity. Furthermore, this study reiterates one of the most important factors in getting the highest overall height gain from rhGH therapy, which is the age at which the treatment is started.

Prepubertal patients treated with GH saw a much-strengthened growth, which can be partially preserved from the significant worsening during puberty that occurs in patients with untreated SHOX deficiency.

In addition, the growth velocity and height increases were most prominent during the first two years of treatment, where afterward, a higher dosage of GH was deemed necessary for many patients to maintain a high growth velocity, which otherwise slowed down for many individuals.

Interestingly, individuals with the SHOX enhancer mutation showed this reduced height increase after two years of treatment more often than individuals with the SHOX exon mutations despite the overall height increases being similar: + 0.67 ± 1.02 SDS (SHOX enhancer mutations) vs. 0.88 ± 0.96 SDS (SHOX exon mutation). Likewise, individuals with the SHOX exon mutation were shown to have significantly higher insulin-like growth factor (IGF-1) levels, which are directly correlated with GH dosage. This likely explains why a higher dosage of rhGH was deemed more necessary for individuals with the SHOX enhancer mutation after two years of treatment, as IGF-1 levels are a great indicator of what dosage a patient should be given. However, this difference may also be related to differences in puberty progression instead of a direct result of the two mutations (11). It is also important to note that IGF-1 levels still increased for both SHOX mutations and should be measured throughout treatment, as significantly higher concentrations can cause major side effect risks. While still remaining the most effective therapy for the treatment of SHOX deficiency, the decreased effectiveness when started after puberty begins, in addition to the fact on average, around 87% of growth occurs before puberty, makes these artificial growth hormones a less viable option for many patients. Further drawbacks of GH therapy include high costs and a greater risk of side effects caused by higher IGF-1 levels.

Gonadotropin-releasing Hormone Agonist

To this day, few studies have been done specifically on the combination of GH and RnGHa therapy on individuals with SHOX deficiency. Even so, in one small study of just five individuals, positive growth-related results were observed, showing an improvement in four patients with height SDS after being treated with overlapping rhGH treatment for 2 to 4.9 years and GnRHa treatment for 1.4 to 5.8 years. The final adult heights recorded in the study showed a height SDS increase from -2.3 +/- 1.3 at 11.8 +/- 2.1 years to a final height SDS of -1.7 +/- 1.6 (12). In addition, as typical with patients with SHOX deficiency, height SDS decreased in untreated patients: -1.2 +/- 0.7 SDS at 11.4 +/- 1.4 years and -2.5 +/- 0.5 SDS at final adult

height (12).

In another slightly larger study, but also uncontrolled for other possible growth factors affecting final height, the eight patients treated with combined rhGH and RnGHa saw a similar final adult height from those just treated with solely rhGH therapy despite the higher prevalence of pubertal patients and worse initial adult height prediction at the start of treatment in patients who used combined therapy (13). However, these few studies that focus only on children with SHOX deficiency are mostly unreliable due to their limited sample size and lack of patient information, which may affect the results. Even so, the results of this study do seem to match the results of a much larger study done on the combination of these treatments in children with idiomatic short stature (14). It is very important to note that the results of this study, since they are based on patients with simply short stature, do not fully reflect the results patients with SHOX deficiency would see. The large downward growth shifts patients with SHOX-related deficiencies experienced during puberty were not fully observed in this study. Furthermore, a likely inconsistency seen in this study is in the final height of the male section, where the final height SDS is lower in patients treated solely with GH during puberty than in patients treated with solely GH prior to puberty. This difference may be attributed to a higher dose being given to patients who started treatment during puberty and more aggressive actions being taken due to the limited time remaining before growth plate fusion. While this study does seemingly match the results of the prior studies mentioned, which solely test children with SHOX deficiency, more evidence is needed to see if the addition of GnRHa to GH treatment is worth the risks in patients with SHOX deficiency. GnRHa is an expensive and invasive treatment, and the risks may not outweigh the side effects. For instance, some studies have reported that bone density may be negatively affected as a result of this treatment. The results are inconsistent through different studies and may be related to whether puberty is normally timed or not (8). Lastly, these studies, while showing its effectiveness, lack control, have small sample sizes, or aren't specific to SHOX deficiency [9]. For this reason, the combination of rhGHa and rhGH is not a standard treatment for people with SHOX deficiency and has not received approval from the FDA or any other official health agency, and this likely won't change in the near future. Even so, its use may be deemed necessary in patients untreated until puberty.

Comparison of rhGH Alone Versus Combined Therapy

It is important to note that direct comparison of the studies on rhGH monotherapy and rhGH combined with GnRHa is not easily comparable due to differences in study design, small sample sizes, treatment duration, and treatment dosage. Even so, the long-term Italian study of rhGH therapy alone, and the small SHOX-specific study of five patients treated with the combined therapies resulted in a height SDS difference of just 0.2 (11, 12). The fact that the average height gain between the two studies was just a 0.2 SDS difference, despite the combined therapy group involving only peripubertal patients, who are just entering puberty, while the Italian rhGH therapy study consisted of prepubertal patients, with patients starting at an average age of just 8.33 years shows some promise to the success of the combined therapy as a real and effective therapeutic option. However, the higher dosage taken by individuals in the combined study (0.35 mg/kg/week) versus those in the rhGH study (0.23 ± 0.04 mg/kg/week) must also be taken into account. While the combined therapy shows promise in maintaining adult height even in peripubertal patients, it carries additional risks compared to rhGH therapy itself, one of the reasons GnRHa is currently rarely used as a therapeutic option, something that will likely continue until new research into the effectiveness of the combined therapy is done, and which leads to the conclusion that the benefits of potential height gain outweigh the risks.

CRSIPR

Gene editing technologies are widely known by scientists to have the potential to address many genetic diseases. While many types of gene editing technologies have been used mostly on non-human beings, they have mostly been too costly, take too long to make, and are unable to target and modify specific DNA sequences. The Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)-CRISPR associated (Cas) nuclease 9 (CRISPR-Cas9) system ideas were first introduced in 2013. Since then, the first drug using CRISPR-Cas9 technology, CASGEVY, was approved for use in the United States, European Union, and Great Britain in treating sickle-cell disease and beta-thalassemia.

CRISPR-Cas9 is also currently being tested on treating different cancers, including glioblastoma multiforme (GMB). Figure 2 shows CRISPR's theoretical use and the steps involved with treating GMB using this new gene-editing technology (15). The

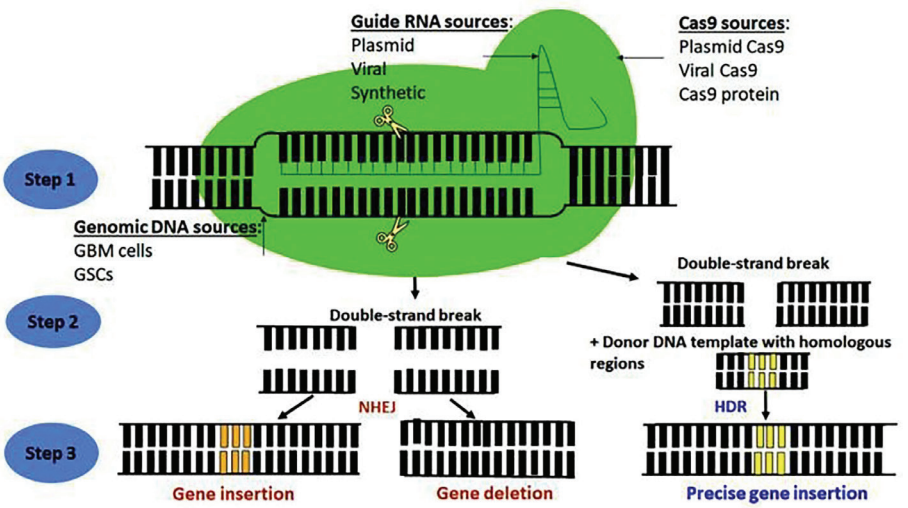

Figure 2. 3 Steps of CRISPR-Cas9 (15). This schematic illustrates the three major steps in CRISPR-Cas9 gene editing. Step 1: Guide RNA, derived from plasmid, viral, or synthetic sources, directs Cas9 (delivered as plasmid, virus, or protein) to the target genomic locus within SHOX-deficient cells. Step 2: Cas9 introduces a site-specific double-strand break (DSB) in the DNA. Step 3: The DSB can be repaired by either non-homologous end joining (NHEJ), resulting in gene insertion or deletion, or by homology-directed repair when a donor DNA template is provided, allowing for precise gene correction or insertion. This strategy holds therapeutic potential for restoring functional SHOX expression in affected individuals.

three major steps shown in Figure 2 are as follows. The Cas9 protein is guided by an RNA sequence (single strand) and binds to its complementary DNA sequence (double-stranded). The Cas9 then performs a double-strand DNA break of the targeted gene. After, the non-homologous end joining (NHEJ) mechanism repairs DNA by joining the broken ends of the DNA after the DNA sequences are inserted, deleted, or activation of homology-directed repair (HDR) mechanisms insert the targeted DNA sequence with the donor DNA template together with regions of similar nucleotide sequences to the cut ends. This allows for greater precision in the gene insertion process (15). However, unlike in GMB or sickle cell disease, which are either polygenic traits or caused by smaller mutations in more than one gene, SHOX haploinsufficiency results from the inability of at least one allele to function properly. Fortunately, successful tests on the use of CRISPR activation in mice with autism spectrum disorders, which are also mostly associated with haploinsufficiency, have opened a possible therapeutic approach in treating SHOX deficiency as well by using CRISPR technology to increase expression of the damaged SHOX allele. The success of this technology in treating other animals with autism would also likely make treating SHOX deficiency possible with this emerging gene editing technology. However, it may be many decades before this is properly tested and proven safe for use, especially since SHOX deficiency is not life-threatening, meaning it would be less urgent for scientists to develop this solution in the near future. Additionally, in order for CRISPR to be correctly used in patients with SHOX deficiency, a patient would have to have been diagnosed at a young age so that their SHOX genes could be repaired before too much time would have passed, leading to permanent lost height. As a result, similar to how GH treatment relies on an early diagnosis, a possible CRISPR treatment for SHOX deficiency would also require advances in finding easier ways to diagnose children with SHOX deficiency at an early age.

CONCLUSION

While GH has been proven to be the most effective treatment for patients with SHOX deficiency, its limitations in the treatment of pubertal patients, high cost, and risk of leading to overly high IGF-1 levels make the therapy a much less than perfect solution. One of the most important factors in increasing the effectiveness of treatment involves improving early diagnosis, as current treatment is heavily dependent on age at which it starts. Although the use of GnRHa

treatment as an add-on to GH in patients who started therapy after puberty can make up for some otherwise lost height by slowing down pubertal progression and lowering the acceleration of bone maturation, risks manifesting from Maledung deformity, the side effects are still unknown and its use if at all, is mostly limited to patients with few remaining years left of growth until further research confirms its safety and true effectiveness. Finally, the possible use of the gene-editing technology CRISPR to treat SHOX deficiency could become an easy and cheap solution, but it also has its own risks associated with gene editing technology, such as damage to other genes and cancer risks. In order for CRISPR to work, further research into finding better measurements and tests for diagnosing SHOX haploinsufficiency is needed. If successful in treating mutations like SHOX deficiency, CRISPR could address many genetic diseases.

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CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article

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