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# A Review: On Human Short Stature

**Rana Khalid Iqbal*, Nasrullah, Khizra Shoukat, Mehwish Sultana and Faiza Arif**

*Institute of molecular biology & biotechnology Bahauddin Zakariya University, Pakistan*

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***Corresponding author:** Rana Khalid Iqbal, Department of Institute of molecular biology & biotechnology Bahauddin Zakariya University, Pakistan

**Summary**

Human height is a polygenic and complex character control by numerous genes, due to these many problems are related to it one of them is short stature, in which individuals do not achieve standard height compare to others. What are the genes and other factors involved in it, to know it we go thought resent and old published available data present and research articles, review articles, short and long communication and other data related to it. By going through research and literature we came to know that Short stature may be due genes or Short Stature homeobox (SHOX) region present on the pseudo autosomal region (PAR1) of both X and Y chromosome contains and major genes for human growth defect in it ultimately results in short stature or defect in protein which have effect on height and results of protein are on hormones which is also major contributor of Short stature and also that Growth hormones and insulin like growth factors are very important for achievement of normal height and defect in any one can leads to short stature. To get rid of Short stature researchers developed Recombinant human growth hormones therapy and recombinant insulin-like growth factor to treat short stature. we conclude that genes responsible for short stature are present in SHOX region, proteins are involved as well as hormones, we can treat the short stature with the help of Recombinant Human growth hormones and insulin like growth factors.

**Keywords:** Genes; IGF; rhGH; SHOX

**Abbreviations:** SS: Short Stature; GH: growth hormones; GHD: Growth hormone deficiency; ISS; idiopathic short stature; IGF: insulin-like growth factor; CNVs: Copy number variants; GWAS: Genome-wide association studies; SNPs: Single polymorphic nucleotides as predictors;

## Introduction

Height is a heritable character which transfer from parents to offspring through genes. Due to genes involvement many problems are related to it, one of them is Short stature. Short Stature (SS) is disorder in which patients are not able to obtain his/her normal height (compare to his sex, age and people of community).

There are two types of SS, those which obtain their height in later condition known as familial SS in which growth hormones (GH) are produced in later stages and those which don't reach to their normal height are called idiopathic short stature [1]. SS can be syndromic or dis-syndromic, proportionate or disproportionate and associated or not to bone malformation. Due to large problems associated with SS, researcher are being able to find all those factors due to which SS occur i.e. heredity, mutation in extracellular matrix protein, other types of mutation, certain types of infection, hormonal dis-balance in body, malnutrition and environmental conditions [2] which are things which have effects on height.

Here point to be noted that 75% growth is effect by inherence (DNA) and 180 loci are related to height and in human growth complex genes are involved, studies show that >600 variants are related with normal height and growth in human [3-5] As DNA is responsible for normal functioning of body and defects in DNA leads to abnormities same is the case with the SS in which Growth hormone deficiency (GHD), which is responsible for 55.56% of SS case worldwide and rest include idiopathic short stature (ISS) 30% and hypothyroidism 4.07% small gestational age (SGA) 2.59% and congenital ovarian hypoplasia 2.29% [5]. Growth hormones deficiency (GHD) is a common source in all SS cases (1 out of 4000) [6]. GH is not the only thing that play its role in SS but also insulin-like growth factor (IGF) as well play significant role in gaining normal height in a linear manner and both show combined effect in the development of body parts, defect in any one of them (GH, IGF ) may leads to SS [7-9].

SS as a genetically originated case was identified as short stature homeobox (SHOX) [10,11]. SHOX is pseudo autosomal region 1 (part1) with high reproducibility present on both X and Y chromosome containing genes pairs having fundamental role in linear growth of an individual and limb development [10] When SHOX is completely/partially absent or deleted or duplication upstream or downstream results are skeletal abnormalities like SS and abnormalities in other body parts like limbs remain short

occurs [12-16]. Mutations of SHOX region occur which can either be Homozygous or heterozygous, X chromosome, hemizygous or its downstream accompaniment causing Langer mesomelic dysplasia in 75% of individuals which is the more unadorned in medical point of view, upstream/downstream Heterozygous mutations in SHOX region or its enhancer essentials are related to 2-22% of cases of ISS which is more damaging in females as compare to males [18] . Turner syndrome is also one cause of SS [20,19]. As damage of DNA is involved due to this protein and also hormones are damaged which are reveal in review and the effect of them on height and SS. In this review will look over the SS s important features and discuss them Figure 1.

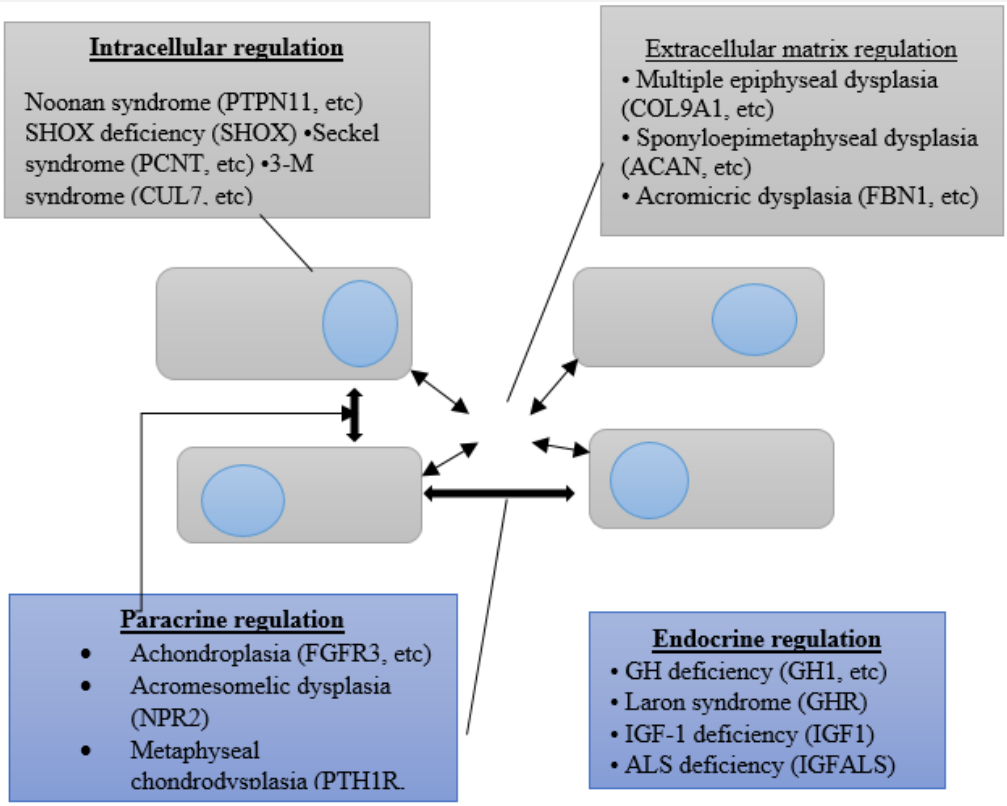


**Figure 1: Molecular mechanism of short stature:** Multiple defects at the molecular level include signaling between cells, extracellular matrix, the paracrine and endocrine parameter that cause short stature. Ovoid shapes represent the Growth plate chondrocytes. Arrows indicate the Chondrocytes regulating mechanisms. Examples under molecular mechanisms of clinical syndromes and their genetic cause are given in each box.

## Phenotype

Short stature is because of mutations which can either be homozygous, heterozygous, X chromosome, hemizygous or multipart disabling of SHOX region that results in either form of phenotype like Langer mesomelic dysplasia, milder skeletal dysplasia, Leri-Weill dyschondrosteosis which are caused by heterozygous mutations or deletions of SHOX region clinically known as ISS, Turner syndrome which is caused by heterozygous SHOX deletion also result in SS and growth failure, Mesomelia effecting the magnitudes of body [21-23] . Many other syndromes (known as rasopathies) includes Noonan, LEOPARD, Costello, cardio-facial-cutaneous, and neurofibromatosis-Noonan syndrome, all these results in SS and growth failure. Faciogenital dysplasia SS is caused by mutation in FGD1 and mutations in SOX 9 which give rise to skeletal dysplasia, campomelic dysplasia [24] and also skeletal abnormities and microcephaly [25-27] Russell-silver syndrome is also one of the phenotypes of SS and which individually don't reach to optimize height [27,28,31] SS individuals suffer from asymmetry in body (limb), having triangular faces, short arms, well known forehead, in some cases feeding problems, changes are observed in skeletal like symbol of Vickers ligament which leads the lunate to the distal lot of the radius and patients with SHOX deficiency affect the level of estrogen hormones which cause abnormalities in skeletal formation [29-30] SHOX deficiency give rise to more acute skeletal damages in adult females as compare to kids and males Females with SHOX deficiency have normal ovarian shape and function [30].

## Genes Responsible for Short Stature

The monogenic disorders normally related with short stature and bone dysmorphology and also more than 300 different monogenic disorders of bone as well. One study shows


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that deficiency of SHOX is monogenic disorders of bones but common one in many other shreds of evidence and studies is osteodysplasia [27]. The only treatment to overcome this disorder is that clinician and radiologists should recognize the phenotype of this disorder and then make the current diagnosis [28]. Two basic approaches are generally described to discover the genes involved in growth regulation. These two basic approaches include: one is GWAS (genome-wide association studies) [30] and the second is to perform genetic studies in a patient with enormously short or tall height and search for causative variations [31,32]. In the first approach, researchers found that more than 180 loci are related to adult height. Each loci contribute small amount of effect to height and contain various genes, about 10% of phenotypic variation is explained by cumulative loci [33] In an alternative of it if we use SNPs (single polymorphic nucleotides) as predictors in GWAS approach it can explain about up to 40% of the variance in height [32].

In the second approach, one can test the previously described gene defects, or genome-wide research for copy number variants (CNVs) is performed or for mutations whole-exome sequencing. A number of genes involved in monogenic defects related to short stature or tall height such as IGFI, STAT5B, IGFALS, and IGFIR are detected [33-35]. but the novel genes involved in or responsible for growth regulations are not detected or found out yet. Biochemical analysis of primary IGF-1 deficiency showed that it is usually linked with mutations in growth hormone-IGF pathway, growth hormone receptor are also included in it as well as STAT5B, IGF1, and IGFALS and also seen in the RASopathies, also faults connected to nuclear factor-κ B pathway and several disorders (e.g., 3-M) [36,37]. For SS treatment has been developed (explain later in review) and detailed analysis has a great probability to help in making treatment decisions. i.e. defect in IGFALS individuals having reasonable growth deficiency, this conclusion leads to a decision that treatment did not cure all patients, because many patients have achieved naturally normal adult height [39-41]. When there is no treatment found several factors affect the poorer height for example short stature of parents and adult age that is based on stature or bone age prediction is lower.

## The Molecular Mechanism Causing Short Stature

This following figure shows the molecular mechanism that causes short stature. This molecular mechanism includes different/ multiple molecular defects. These defects include signaling between cells, or intracellular signalling mechanism, extracellular matrix, paracrine and endocrine regulation. Different examples are shown by every molecular defect includes some clinical syndrome and theirsome genetic causes that comes underneath the molecular mechanisms. Growth plate chondrocytes are involved in this molecular mechanism which is represented by ovoid shapes. Every molecular defect and molecular mechanism directly or indirectly involved these growth plate chondrocytes through mechanisms regulating chondrocytes which are indicated by arrows [9,11] The intracellular signaling mechanism includes Noonan syndrome caused by gene PTPN11, etc, [ 12,42,43] SHOX deficiency caused by SHOX gene [27] Sickle syndrome caused by PCNT, etc [44,45] and 3-M syndrome by CUL7, etc [46]. Similarly, the extracellular matrix regulation includes multiple epiphyseal dysplasias (COL9A1, etc) [47,48], Sponyloepimetaphyseal dysplasia (ACAN, etc) [49,51] and Acromicric dysplasia [52]. The paracrine regulation includes Achondroplasia (FGFR3, etc Acromesomelic dysplasia (NPR2, etc) [53]. The endocrine regulation syndromes include GH deficiency (GH1, etc) [54,55] Laron syndrome (GHR) [56] IGF-1 deficiency by (IGF1) [54] ALS deficiency by (IGFALS) [55].

## SHOX Genes

Short arms of chromosomes (X & Y) which are identical at the distal ends also known as pseudo autosomal regions contain genes which play their role in height. PHOG (pseudo autosomal homeobox- containing osteogenic gene) is a region which is found in this area exhibits an important function in bone development and growth, and also known as SHOX genes [57,58].Studies suggested that in embryo SHOX genes regulates the body structure development predominantly and also changes in development & limb maturation [59-61]. Regulatory regions (heterozygous mutations) of SHOX gene have been identified in 17 % of patients with ISS & 50-90% with LWS where a complex of ligation-dependent probe amplification analysis & sequencing were done in some cases [27]. Leri-Weill Dyschondrosteosis is because of SHOX gene Haploinssufiency is caused which is another type of mesomelic dysplasia which has SS and associated with Madelung deformity in the forearms & short forelegs [62].Variation in patients of Turner syndrome (which is due to X chromosomes aberrations) reveals that SHOX haploinsufficiency may be responsible for SS in the first part and see that syndrome and anomalies of the connected skeletal limb [57,63,64]Dyschondrosteosis is related to Turner syndrome, so patients of Turner syndrome may have dyschondrosteosis and SS. Molecular basis for the SHOX is involved in the whole or partial gene duplications and deletions of up & downstream enhancer sequence variations [12-14] [57,58] all these are involved in SS and skeletal abnormities.

In SHOX region genes encode for transcription factor for proteins which are related to cartilage development and [28,64] and any changes in them ultimately effect on height. Two alternative transcripts (isoforms) called SHOX(a) & SHOX (b) are encoded by seven exons and its length is about 40 kb, these transcripts are same at the last exon at 5end and different at 3end [63] they are translated into 2 proteins which are isoforms of 225 & 292 amino acids. Additionally, 2 alternative promoters in SHOX is transcribed were used which generate different mRNAs that code for proteins but with variant 5 sequences UTR55, both transcripts are translated efficiently, anticipated that the amount of SHOX protein can be changed and


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control translational and transcriptional with the help of control mechanisms. Patients with LWD have been identified to have 41 mutations out of [60] , in ISS it is 10, in Langer syndrome 5 whereas 3 are not interconnected with phenotype [63] Across full coding region mutations of SHOX were spread, mutations (21) were found in exons 44.7%, 9 in 2 exons, eight in 4, and 5 exons in 6, and 3 exons in 5, and 1 intron 2, there were forty-four (44) substitutions in between them, 6 insertions and 9 deletions, 21 mutations which are linked with the homeodomain 1, 7 mutations that are in homeodomain two and 1 mutation in SHOX3 domain [17,27,65-69].

### Protein formation

The SHOX protein contains a homeodomain, a structure commonly seen in transcription factors convoluted in body modeling [70] These proteins are rare and focus on SHOX comprises 292 amino acids [71,72]. SHOX alter the presence of extracellular matrix genes with Ctgf in the developing limbs which cause the abnormal limbs. In SHOX protein domain is appropriate for nuclear translocation and for dimerization of SHOX [72] which is also translates for the C-terminal-located OAR domain that are applicable for the transactivation activity of SHOX. The SHOX mRNA is encoded by 7 exons (1-5, 6a, and 6b) surrounding about 40 kb of genomic DNA. Alternative splicing results in 2 products: SHOX (a) and its shortened version SHOX (b) which give information for the OAR domain and is consequently not active as a transcriptional activator [56,57] Specific proteases like hormones/ protein proteinase pregnancy-associated plasma protein (PAPP)-A and PAPP-A2, selectively proteolyze IGFBP-4 or IGFBP-3 and IGFBP-5, respectively release free IGF-1 to activate receptor on target tissues ("endocrine, autocrine or paracrine actions of IGF-1) are products of SHOX protein and changes in anyone of them effect on height [7,72]. PAPP-A2 is stated excessively in human placenta development, the non-pregnant mammary gland and other tissues, including the kidney, fetal brain, and pancreas [33,73] PAPPA-2 (PAPPA2) is associated with mild short stature, apparently by inadequate disposal of free IGF-I [74] Other protein 65K is part of a molecular bridge that connects U11 and U12 snRNPs with di-snRNP which are connected with human height [74]. In previous studies have operated in vitro and in vivo analysis using chick micro mass culture to recognize putative target genes of SHOX [46,71,74]. These studies recommended that SHOX applies positive and negative effects on the expression of BNP and Fgfr3, respectively [17]. In addition, SHOX interrelate with SOX5, SOX6 and SOX9 they act as main chondrogenic factor [59].

## Hormones

As Height is control by many factors in which few hormones and other factors are also involved, like GH, IGF and some other supporting hormones play a significant role in height gain. It is very vital for humans that their GH and IGF-1 and II work optimally to obtain maximum height, GH produce IGF which work on growth plats and result of which is in the form of height [75]In mammalian height hormones and IGF play central role, responsible for 70% of height do this reason rhGH and other factors are used for therapy to achieve maximum height [76]. Patients with ISS might have reduced sensation towards GH or not having enough concentration of GH or inheritance problems in GH or their receptor which in later stages results in the form of ISS (Hospital et al., 2005). Defects in JAK/STAB system which is one of downstream signaling pathway cause GH insensitivity and immunodeficiency and have lighter effect on growth which is exerted by heterozygous genetic variants at STAT5B, which support the hypothesis which says that rare pathogenic disparities expand to standard height heritability [77].GH deficiency is very important thought life that's why it is very important to understand their release as well. GHs are release in an episodic manner thought day and night, pulses are more periodic and more secretion of hormones at night time as compare to day time, generally GH level is low during day time so liver starts releasing IGF-I and IGF-III which are more stable throughout the day and better checkpoints for hormones deficiency tests, but IGF-I and III are depended on age, physical development, prepubertal and pubertal stages of patients [1]. GH measurement can take place at many points with the help of GH secretagogue, like clonidine, arginine, L-Dopa, propranolol, glucagon, or insulin, a good method to measure GH in the bloodstream is radioimmunoassay and further clarification of GH signaling and mechanism of IGF and receptors of them [37].

With the help of the availability of rhGH, which clear the roles of growth hormone and IGF as main controller of skeletal growth, and also showed that both hormones releaser and acceptor exist along a continuous pathway and mutation in either one them (GHs) and their action (receptor) may cause ISS [20,21,78] GHs are not only responsible for SS but in cases such as Laron syndrome like appearance they are responsible for immunodeficiency as a defect in receptor occur in case of some SS cases [79] Some other hormones are also responsible for SS and gain in height for example Thyroid stimulating hormone (TSH), Prolactin, Luteinizing hormone(LH), Follicle stimulating hormone (FSH), Adrenocorticotropic hormone (ACTH) have their own effect on height [79] . Patients which are resistant towards TSH have normal stature but in many cases, SS is observed because of mutations caused in THRB [80]. Mutations in GH1, GHRHR, SOX3, and BTK leads to GH deficiency and mutations in GHR and STAT5B cause resistance to GH [3,81]. Homozygosity is also responsible for growth failure and also mutation in GH1 and GHRHR leads to development of anti GH antibodies due to jumping of EXON3, which results to form isomer of GH (17.5kDa) with a strong negative effects on skeletal development and mutation in BTK and SOX show same results on skeletal [4,11,82-84]. Defects in GHR or STAT5b, are clear right after birth or in childhood those defects are in IGF1or IGF1R, results in growth failure, as IGF-I is involved in the development of CNS utero, defects often described by microcephaly, delay developmental problems with hearing [23,24].


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## Treatment

GH therapy is resourceful and safe, suitable treatment for those who are suffering from short stature and it shows good effects in both short term and long term duration [49].In 1985 the US Food and drug administration (FDA) and EMEA allow the rhGH treatment for patients with GH deficiency and SS constructed on facts which were collected after randomized controlled experiments [110-120] and the mean aim and target of rhGH is to increase the height of those who have short height as compare to standard or other living community members . In countries which are approved by FDA, treatment against SS has been started and rhDH are being used to treat individuals with IGF,I,II and GH deficiency [50] Patients when treated with rhDH indicate decant results but still results are uneven and not clear, yet and shows defects when apply on others patients (patients to patients variations) [99] The treatment of GH depends upon the age of the patient, the dosage with which the patient is being treated who much the GH deficiency, IGFs deficiency and other parts like receptors working [100]Food and drug administration in 2003 permitted GH therapy dosage (0.3-0.37mg/kg/week) for individuals with SS for those countries in which treatment can be done in control conditions [1,121-130]. Mutation can block the receptor of GH and by finding mutation rhGH can be used to overcome that mutation in shape of blockage of receptors [144]. As in case of ACAN gene a trail treatment was used to see the effect of it [85] and results were pretty good as height was increased. In case of ISS the rhGH are used to treat up to 50% kids who have normal or even more GH secretion but having low IGF, in those cases higher rhGH are required for treatment or rhIGF-1 can also be used to treat the patients [86] With rhGH gestational age SS are treated and also silver Russell syndrome in children [120] [113] Treatment is more operative when started at earlier stages/young age and concluded that to have best results and increase in height the treatment of GH should be started in earlier stages with heavy doses [60] GH therapy is more effective, and treatment is more useful when there is deletion in enhancer (anything related to growth) as compare to those who have genetic abnormalities in them [131-140].

When patients were treated with rhGH antibodies are produced during treatment, [7] and also negative effects in the form of hyperglycemia, overgrowth of organs like kidney, spleen and anabolic effects by the high concentration of IGF [80,81] in these kind of cases rhIGF1 could be used, Defects in PAPP-A2 deficiency was treated with rhGH no negative effects were observed [82].Remember that rhGH can't be apply all the time as in case of IGFALS defect the rhGH may not work and also in those in patients who obtain their height in later stages like (gestational age, blooms syndrome, Fanconi`s), and also remember that the use of rhGH treatment is conditional as risk of malignancy are involved [83]. Although rhGH show good results and increase in height was obtained but still there are many cases which show no results in height increase in GH therapy [34]. It is not easy to treat patients with GH, because GH treatment need a prepare monitoring of hormones, growth velocity and most important of all the dose of GH [141-151].

## Conclusion

Height a heritable character that is transferred to offspring from parents is controlled by several genes. Any problems related to these genes leads to height problem i.e. tall height and short staure. One of the major genes that is cause for short stature is SHOX gene. It is concluded that it is very important that human's hormone i.e. GH and IGF-1 and 2 work optimally to obtain maximum height. For short stature and height gain not only GHs are responsible but some other hormones are also responsible include thyroid stimulating hormone, prolactin, luteinizing hormone, follicle stimulating hormone, and adreno-corticotropic hormone.

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## Conflict of Interest

The authors report no conflicts of interest.

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