

MUTATIONS IN SHOX, GHR AND IGFALS GENES AMONG INDIAN CHILDREN WITH 'IDIOPATHIC SHORT STATURE'



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Background

- The term "idiopathic short stature" (ISS) is applied to short children in whom no definite etiology for short stature is found after extensive evaluation.
- A proportion of these children have a monogenic basis of short stature. Mutations in genes that regulate components of GH-IGF axis or bone/ cartilage or extracellular matrix can cause ISS in heterozygous state and more severe phenotype in homozygous state.
- In previous studies, heterozygous mutations in SHOX and GHR, and pathogenic variants in IGFALS gene have been reported in about 15, 5 and 6.5%, respectively, in children with ISS.

Objective

- To study the prevalence of mutations or pathogenic variants in SHOX, GHR and IGFALS genes among Indian children with ISS.

Subjects and methods

Setting: Pediatric Endocrinology Clinic, AIIMS, Delhi

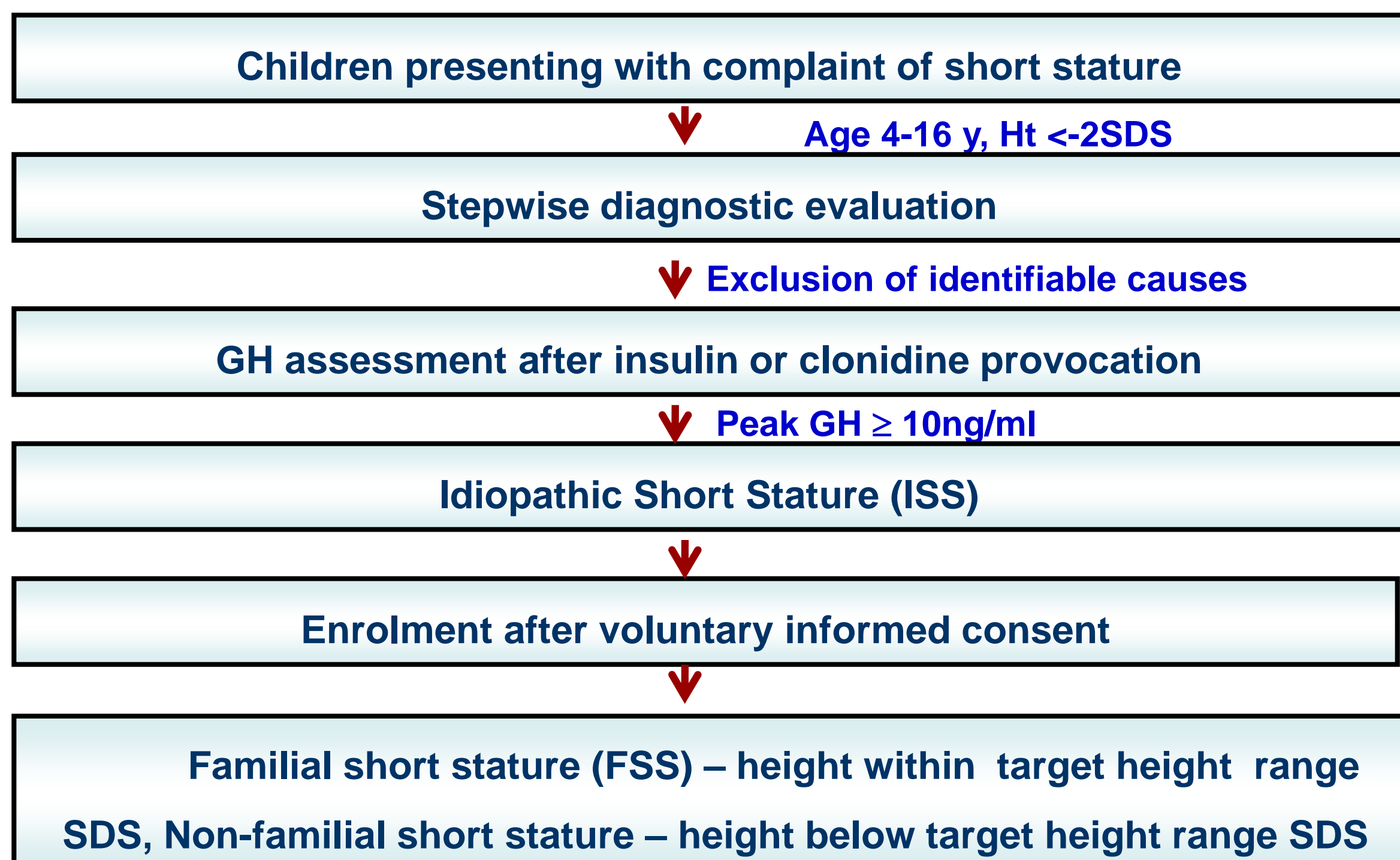
Inclusion criteria

- Age 4 to 16 years
- Height <-2 SDS or (3rd centile) according to IAP growth charts

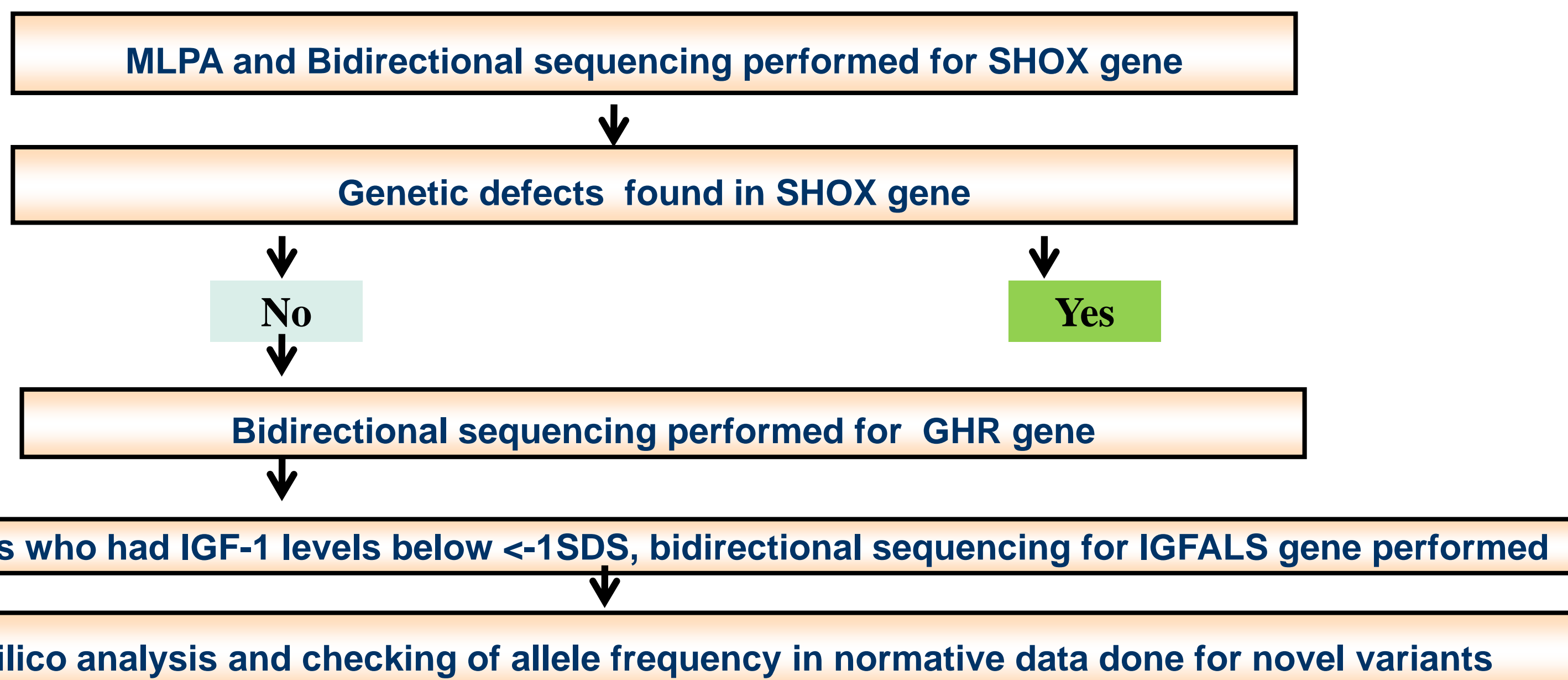
Exclusion Criteria

- Any chronic systemic illness
- Peak GH level after pharmacologic stimulation < 10 ng/ml
- Obvious dysmorphism or disproportion
- Low birth weight
- Turner Syndrome, other genetic syndromes associated with short stature
- Abnormal thyroid function

Screening of patients



Enrolled children with ISS



Results

Table 1. Etiological profile of short stature (n= 394, boys= 195, girls = 199)

Etiology of short stature	Subjects n (%)	Boys n (%)	Girls n (%)	Age Mean ± SD (yrs)	Height SDS Mean ± SD	BMI SDS Mean ± SD
Hypothyroidism	76 (19.3)	30 (15.4)	46(23.1)	10.5 ± 2.9	-3.5 ± 1.5	-0.2 ± 1.2
ISS	61 (15.5)	26 (13.3)	35(17.6)	11.0 ± 2.5	-3.3 ± 0.8	-0.6 ± 0.7
GHD	56 (14.2)	34 (17.4)	22(11.1)	10.1 ± 3.1	-4.1 ± 1.3	-0.1 ± 1.1
SGA	54 (13.7)	29 (14.9)	25(12.6)	9.5 ± 3.1	-3.2 ± 1.6	-1.1 ± 1.4
Skeletal dysplasia or dysmorphic syndrome	44 (11.2)	30(15.4)	14(7.04)	8.9 ± 3.1	-4.0 ± 1.5	-0.2 ± 1.6
Undernutrition	34 (8.6)	13(6.7)	21(10.6)	9.5 ± 3.3	-2.7 ± 0.9	-1.1 ± 0.5
Chronic systemic illness	34 (8.6)	24(12.3)	10(5.0)	10.6 ± 2.9	-3.2 ± 1.6	-0.2 ± 1.2
Celiac disease	15 (3.8)	6(3.1)	9(4.5)	11.3 ± 3.1	-2.6 ± 1.4	-0.2 ± 1.0
Turner syndrome	12(3.0)		12(6.03)	11.4 ± 3.3	-3.5 ± 1.2	-0.4 ± 1.2
Rickets	8 (2.0)	3(1.5)	5(2.5)	8.3 ± 2.4	-2.8 ± 1.3	-0.3 ± 1.0

Table 2. Summary of clinical parameters in patients with ISS (n=61)

Parameter	All subjects (n = 61)	FSS (n = 20)	NFSS (n = 41)	p-value*
Age (Years)	11.4 ± 2.5	12 ± 2.5	11.1 ± 2.5	0.186
Gender (M/F)	26/35	8/12	18/23	0.612
Height SDS	-3.2 ± 0.8	-2.7 ± 0.5	-3.3 ± 0.8	<0.001
TH SDS	-1.1 ± 0.7	-1.4 ± 0.5	-0.9 ± 0.7	0.006
Peak GH (ng/ml)	22.3 ± 12	23.3 ± 12.8	21.8 ± 11.6	0.843
IGF-1 (ng/ml)	196 (23.9 – 575.2)	232 (64.1 – 421)	167.7 (23.9 -575.2)	0.048
IGF-1 SDS	-1.2 ± 1.0	-0.9 ± 0.9	-1.3 ± 1.0	0.167
Children with IGF-1 ≤-2SDS	13 (21%)	4 (20%)	10 (24%)	0.54
IGFBP-3 (ng/ml)	3338 (407 – 7508)	3402 (407– 7333)	3313 (412 – 7508)	0.534
IGFBP-3 SDS	-0.8 ± 1.2	-0.8 ± 1.4	-0.8 ± 1.1	0.882
Children with IGFBP-3 ≤2SDS	12 (19.6%)	4 (20%)	8 (19.5%)	0.912

Molecular genetic results

SHOX gene

- SHOX gene mutations were found in 4 of 61 children with ISS (6.5%).
- The clinical details of these four children including the presence or absence of clinical pointers to SHOX haploinsufficiency are summarized in Table 1.

Table 1: Clinical details of the four patients with mutations in SHOX gene

	ISS 19	ISS 20	ISS 23	ISS 58
Mutation	Duplication of exon 5	c.278-1G>C	Partial deletion	Complete deletion
Gender	F	F	F	F
Age (years)	12	9.8	14.6	13.1
Height (cm) (SDS)**	126 (-3.2)	109 (-3.6)	142 (-2.1)	126 (-3.8)
Inheritance pattern	Paternal	Maternal	Maternal	Maternal
Father's height (cm) (SDS)	158.5 (-2.2)	164.0 (-1.2)	164.0 (-1.2)	158 (-2.3)
Mother's height (cm) (SDS)	155 (-0.4)	127 (-4.7)	137.0 (-3.2)	135 (-3.5)
Subcategory	NFSS	FSS	FSS	NFSS
Peak GH (ng/ml)	31.1	22.9	48.3	24.2
Baseline IGF-1 (ng/ml) (SDS)	323 (-0.5)	166 (-1.4)	379 (-0.3)	279.2 (-1.1)
IGFBP-3 (ng/ml) (SDS)	5835.2 (0.9)	2000.7 (-1.9)	3302.3 (-1.5)	5206 (-0.1)
Arm span/ height ratio (%)*	95.4	96.4	106.6	99.9
BMI>50 th percentile*	No	Yes	Yes	Yes

* Arm span/ ht ratio < 96.5%, and BMI> 50th centile are subtle dysmorphic features reported to be common in SHOX haploinsufficiency.

GHR gene

- None of the patients had mutation in GHR gene

IGFALS gene

- Heterozygous frameshift or missense variants likely to be pathogenic were found in 3 out of 39 (7.8%) patients.
- The clinical details of the patients with heterozygous variations in the IGFALS gene are listed in Table 2.

Table 4: Clinical details of the four patients with mutations in IGFALS gene

	ISS 3	ISS 10	ISS 27
Description of the variants	Frameshift variant (c.764_765insT, p.A265G fs*114)	Missense variant c.1756 C>T, p.R586W,	Missense variant c.1793 G>A, p.R598H
Gender	F	M	M
Age (years)	8.0	10.0	13.6
Bone age (years)	6	4	8.5
Height (cm) (SDS)	105 (-3.3)	116 (-3.1)	132 (-2.4)
Inheritance pattern	Paternal	Maternal	Paternal
Father's height (cm) (SDS)	155.0 (-2.7)	170.0 (-0.5)	159.5 (-2.0)
Mother's height (cm) (SDS)	143.0 (-2.2)	143.5 (-2.1)	155.5 (-0.3)
Sub-category	FSS	NFSS	FSS
Peak GH (ng/ml)	26.6	23.0	13.3
IGF-1 (ng/ml) (SDS)	122.7 (-1.1)	48 (-2.5)	140.7 (-2.4)
IGFBP-3 (ng/ml) (SDS)	931.3 (-2.5)	1146.2 (-2.0)	3104 (-1.3)

Conclusions

- Mutations in SHOX and likely pathogenic variants in IGFALS genes account for about 6.5 and 7.5% of ISS in Indian children.
- In children with ISS, with short stature in one or both parents, mutational analysis for SHOX should be undertaken if GH-IGF axis is unimpaired, and for IGFALS, if IGF-1 and IGFBP-3 are low and there is significant delay in bone age.

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