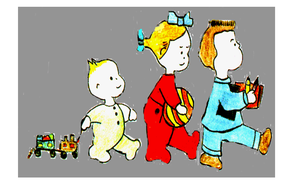
Haploinsufficiency of short stature homeobox containing gene (SHOX): clinical signs and anthropometric measurements in children.



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Background:

Haploinsufficiency of short stature homeobox containing gene (SHOX) is one of the main monogenic causes of short stature. The phenotype of SHOX deficiency (SHOX-D) is often mild, making difficult to identify which short-statured children should be screened.

Objective and hypotheses:

To estimate the prevalence of SHOX-D in Italian short-statured children and to analyse their phenotype and the sensitivity of various scores and anthropometric measurements in identifying SHOX-D.

Method:

SHOX gene analyses was performed by MLPA (multiplex ligation-dependent probe amplification) in 281 subjects, aged 2-18 years (mean age 8.6 ± 4.0 years, 50.7% females, 70.8% prepubertal, mean height SDS -2.0 ± 0.5) referred for short stature to our Endocrinology Unit. SHOX-D patients were compared to 117 age-, gender- and pubertal status matched children without SHOX mutations (mean age 8.0 ± 3.7 years, 55.3% females, 78.1% prepubertal, mean height SDS -2.0 ± 0.6) for clinical features.

Results:

SHOX mutations were identified in 15 subjects (5.3%). SHOX-D patients showed significantly higher prevalence of micrognathia (66.7% vs. 26.5%, p <0.01), short forearm (26.7% vs. 3.4%, p <0.01), muscular hypertrophy (40.0% vs. 14.5%, p <0.05) and Madelung deformity (13.3% vs. 1.7%, p <0.01). No difference was found between SHOX-D and non SHOX-D patients for ear's anomalies, short neck, scoliosis, bowing of forearm and cubitus valgus prevalences. The arm span, the sitting height and the ratios of arm span to height and sitting height to height were similar in the two groups. Using a Rappold score >7 points and >4 points, as screening criterion to perform the genetic analyses of SHOX gene, out of 15 children with SHOX mutations, 11 and 9 subjects would be missed, respectively.

Conclusion:

The phenotype of children with SHOX-D is highly variable and a positive Rappold score as criterion to screen for SHOX mutations would miss most of SHOX-D subjects.

References

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	Non-SHOXD	SHOX D	p
Number	117	15	
Age (years)	7.9 ± 3.8	8.7 ± 3.4	n.s.
Females	64 (54.7)	9 (60.0)	n.s.
Prepubertal	89 (76.1)	14 (93.3)	n.s.
Target height (cm)	163.3 ± 8.6	161.9 ± 10.7	n.s.
Target height (SDS)	-0.77 ± 0.86	-0.91 ± 0.89	n.s.
Height (cm)	114.4 ± 22.6	120.3 ± 20.9	n.s.
Height (SDS)	-2.02 ±0.59	-2.09 ± 0.65	n.s.
Weight (kg)	21.9 ± 10.6	23.8 ± 12.1	n.s.
Weight (SDS)	-1.98 ± 0.98	-1.98 ± 1.24	n.s.
BMI (kg/m^2)	15.7 ± 2.4	16.4 ± 4.9	n.s.
BMI (SDS)	-0.92 ± 1.13	-0.46 ± 1.68	n.s.
Growth velocity (cm/year)	5.7 ± 2.9	4.1 ± 1.4	p<0.05
Growth velocity (SDS)	-0.77 ± 2.00	-1.86 ± 0.93	p<0.05

Tab.1 Anthropometric data of subjects with (SHOX D) and without (Non-SHOXD) SHOX mutations. Values are expressed as numbers (%) or mean ± SD.
n.s.: not significant.

	Non-SHOXD (n=117)	SHOXD (n=15)	p
Arm span (cm)	127.3 ± 23.8	127.6 ± 20.3	n.s.
Arm span/height	1.12 ± 0.17	1.06 ± 0.09	n.s.
Sitting height (cm)	68.8 ± 11.4	70.4 ± 10.1	n.s.
Sitting height/height	0.54 ± 0.04	0.55 ± 0.01	n.s.
Micrognathia	31 (26.5)	10 (66.7)	<0.01
Anomalies of the ear	11 (9.4)	1 (6.7)	n.s.
Short neck	19 (16.2)	2 (13.3)	n.s.
Scoliosis	35 (29.9)	4 (26.7)	n.s.
Short forearm	4 (3.4)	4 (26.7)	<0.01
Bowing of forearm	3 (2.6)	0	n.s.
Cubitus valgus	34 (29.1)	5 (33.3)	n.s.
Muscular hypertrophy	17 (14.5)	6 (40.0)	<0.05
Madelung deformity	2 (1.7)	2 (13.3)	<0.01
Rappold score > 7	6 (5.1)	4 (26.7)	<0.01
Rappold score > 4	19 (16.2)	6 (40.0)	<0.05
Rappold score	2.47 ± 2.71	4.53 ± 4.34	<0.05

Tab.2 Anthropometric measurements and dysmorphic signs in children with (SHOX D) and without (Non-SHOXD) SHOX mutations. Values are expressed as numbers (%) or mean ± SD.
n.s.: not significant.

	Sensitivity	Specificity	PPV	NPV
Rappold score > 4	40.0	83.8	24.0	91.6
Rappold score > 7	26.7	94.9	40.0	91.0
Arm span/height < 96.5%	14.3	95.7	28.6	90.3
Sitting height/height > 55.5%	28.6	77.8	14.3	89.4
Growth velocity ≤-1.5 SDS or RS >4	86.7	44.4	16.7	96.3
Growth velocity ≤-1.5 SDS or RS >7	86.7	58.1	21.0	97.1

Tab.3 Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) (%) of the proposed screening criteria for SHOX deficiency and of growth velocity or Rappold score > 7/4 points.
RS: Rappold score

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